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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

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1. A Qualitative Study Evaluating Perception of the Community Pharmacist Towards ADR Reporting in Northern Malaysia

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Introduction: Most pharmacovigilance systems around the world adopted spontaneous reporting system as main method for collecting data about adverse drug reactions. In Malaysia currently reporting of adverse drug reactions is mandatory for drug registration holders and voluntary for health care professionals. As one of the important of health care professionals, community pharmacists play a major role in patient medication safety. Based on the data available from Malaysia national pharmacovigilance center, the involvement of community pharmacists in adverse drug reactions reporting remains low.
Aim: To ascertain the perceptions of the practicing community pharmacists towards Adverse drug Reactions (ADRs) reporting and to identify barrier to reporting ADR's among community pharmacists in Northern Malaysia.
Methods: A qualitative study was carried out utilizing face to face interviews using a semi-structured interview guide with a sample of sixteen community pharmacists.
Results: Sixteen community pharmacists were interviewed and thematic content analysis of the interviews revealed four major themes: familiarity with the reporting system, attitude and behavior towards ADR reporting, and barriers associated with reporting adverse drug reactions. In terms of the familiarity with the pharmacovigilance scheme (PVS) and ADR reporting, majority of the pharmacists were not aware that the PVS system was already in place in Malaysia.
The assessments of transcripts revealed that the community pharmacists generally had a positive attitude towards ADRs reporting and relay ADR reporting as a part of their professional duties. The major factors influencing the reporting rate of ADRs were the behaviour of the patients, type of practice, work overload and lack of time.
The study identified the major barriers for ADR reporting to be lack of knowledge in determining the types of ADRs occurred, lack of understanding about the available mechanisms of reporting and lack of communications from the regulatory authorities even if a report has been sent. In the present study, the respondents highlighted a few suggestions to improve the current reporting rates. These suggestions are: to incorporate formal education on ADR reporting in the pharmacy curriculum, and promote ADR reporting via CPD programs by important stake holders like the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC).
Conclusions: The majority of the pharmacists surveyed were very confused in regards to ADR reporting and had very little knowledge about ADR reporting as a whole. The results emphasized the importance of establishing and continuing efforts to promote the ADR reporting scheme in Malaysia and to overcome the barriers identified by the study.

2. The Gravity and Consequence of Adverse Drug Reaction Duration in Patients Treated in the Palia Institute-Jalisco, Mexico

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Introduction: Several studies have demonstrated that Adverse Drug Reactions (ADRs) account for 5% of total hospitalization cost. One or more ADR incidences occur in 10–20% hospitalized patients (worldwide), from which 7% are serious and 0.32% lethal, representing a significant problem for public health.[1-3] Therefore, we considered important to determine the consequences and gravity of ADR duration in our patient population to better assess and prevent ADRs occurrences in the Palia Institute-Jalisco, Mexico.
Aim: To identify the gravity and consequences of ADR duration in patients treated in the Palia Institute-Jalisco, Mexico.
Methods: We performed a retrospective observational study of ADRs reported to the Pharmacovigilance Institutional Center (Jalisco, Mexico) from January to December 2008. All ADR reports were evaluated according to the Mexican Official Norm 220-SSA1-2002. Descriptive statistics were undertaken and a crossed analysis between gravity versus duration, gravity versus consequence, and duration versus consequences of the occurrence was made using the statistical software Dyane.
Results: The most frequent therapeutic groups reported in this study are: (n = 159) antineoplastics (37.1%) analgesics (17.6%), antibiotics (11.3%). The main ADRs were: (n = 220) tiredness (13.8%), rash (13.2%) and bone pain (10.1%). ADRs classified as minor (35.8%) lasted 15 days or more (17.5%), moderate ADRs (49.7%) also lasted 15 days or more (29.6%) and finally serious ADRs (13.8%) only lasted 1 day (90.9%). In sequels of the consequence event we found only 3.8% of cases related to ADRs. Finally, we found that more sequels were found in the longest ADR occurrences: 4-14 days long (33.3%), and >15 days long (50%).
Conclusions: Based on this retrospective study we conclude that the longer the ADR lasts, the risks of consequences to occur are greater. Moreover, minor to moderate ADRs are not overseen as strictly as severe ADRs. Hence, minor to moderate ADRs duration is longer than severe ADRs. Thus, our study indicates that attention needs to be addressed in ADRs duration, and not only to ADR severity.

References

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279: 1200-5

2. Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993; 27: 832-40

3. Alesso L. Farmacovigilancia. Hacia una mayor seguridad en el uso de medicamentos. 1st ed. Cordoba, Argentina, 2007

3. Strategies for Increasing Spontaneous Adverse Drug Reaction Reporting Rates Among Portuguese Health Professionals

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Background: It is well known worldwide, that Adverse Drug Reactions (ADR) are an important cause of morbidity and mortality in developed countries. In Portugal, as in many other countries, ADR reporting rate is rather low,[1-3] and as a consequence there is a lack of information being transmitted to the Medicines Regulatory Authority, which does not effectively represent the real number of adverse events.
Objective: Our aim was to increase the number and relevance of ADR reporting among pharmacists and physicians, with workshops and telephone interviews.

Method: We conducted a cluster-randomized controlled trial, among pharmacists and physicians working in the Northern region of Portugal.
Results: This abstract refers only to the results of the pharmacists' group. The ADR reporting rate increased 3-fold as a result of this action (RR = 3.22; 95% CI 95%: 1.33, 7.80) compared to the control group, during the studied period. Besides, the relevance of ADR reported was also increased. In fact, serious ADR reports increased 4-fold (RR = 3.87; 95% CI: 1.29, 11.61) and unexpected ADR reports increased 5-fold (RR = 5.02; 95% CI: 1.33, 18.93), compared with the control group.
Conclusions: Educational interventions are efficient in increasing the ADR spontaneous reporting rate, among Portuguese health professionals. Among the pharmacists, *workshops* are as efficient as telephone interview to improve ADR spontaneous reporting.

References

1. McGettigan P, et al. Reporting of adverse drug reactions by hospital doctors and the response to intervention. Br J Clin Pharmacol 1997; 44 (1): 98-100

2. Smith CC, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol 1996; 42 (4): 423-9

3. Bégaud B, et al. Rates of Spontaneous Reporting of Adverse Drug Reactions in France. JAMA 2002; 288 (13): 1588

4. Drug-Induced Hepatotoxicity in Hospitalized Patients

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Introduction: Drug induced hepatotoxicity is a common Adverse Drug Reaction and the most relevant cause of drug withdrawal from the market. Hospitalized patients are more prone to this ADR because they have frequently another situation that can injure the liver. The aim of this study was to determine the real incidence of drug induced hepatotoxicity in hospitalized patients.
Material and Methods: This study was performed within the pharmacovigilance system of a tertiary care hospital in Buenos Aires, Argentina (Argerich Hospital). This system is functional in all departments except for the emergency room. The study took place between June 2008 and April 2009. We consider hepatotoxicity when transaminases elevated three times the upper limits and when the Direct Bilirubin increase two times the upper limit. We applied the Naranjo score to assess the causality of an ADRs.
Results: In this period we reported 96 cases of drug induced hepatotoxicity, and represented 10% of the total ADRs reported by the Pharmacovigilance Department. More than 80% of the cases occurred in men. The average age was 53.06 years (CI 95%, ±3.53 years). The pattern of hepatotoxicity was hepatocelular in 46 cases, cholestatic in 30 and mixed in 20 cases. The drugs most offently associated with hepatotoxicity were ampicillin – sulbactam 9 cases, ceftriaxone 8, piperacillin – tazobactam 6, atorvastatin 5, phenytoin, ibuprofen and ciprofloxacin 4 cases, carbamazepine and tms – smx three cases. Multiple other drugs were involved in 50 more cases. There were four cases of serious hepatotoxicity, two of them were fatal. The fatal cases were caused by cyproterone in one case and the combination of ciprofloxacin and clindamycin in other case. The departments in which the ADRs were reported were Internal Medicine 27 cases, Critical Care Unit 22, neurosurgery 9 and general surgery in 4 cases.
Conclusions: The drugs involved in hepatotoxicity were similar than reported in international bibliography[1] being anti-infectious, NSAID, antiepileptic and hipolipemiant drugs the most frequently involved. Ampicillin – sulbactam caused more cases than expected according to other studies.[2]

References

1. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a population-based study. Hepatology 2002; 36 (2): 451-5

2. Lee M. Drug-Induced Hepatotoxicity. N Engl J Med 2003; 349: 474-85

5. Drug Induced Nephrotoxicity in Hospitalized Patients

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Introduction: Kidney is an organ usually affected by multiple drugs and frequently increase the morbimortality in hospitalized patients. Cardiovascular drugs as ACE or diuretics, several antibiotics and NSAIDs that are highly consumed in hospitalization are frequently involved. The aim of this study was to determine the true incidence of nephrotoxicity in hospitalized patients in a tertiary care hospital of a developing country.
Material and Methods: We realized this study within the pharmacovigilance system of Argerich Hospital (Buenos Aires, Argentina), a tertiary care hospital. The time considered for this study was between June 2008 until April 2009. We considered nephrotoxicity the elevation of the creatinine more than 50% of the basal value or a decrease in the glomerular filtration more than 30% of the basal. We applied the Naranjo Score to assess the causality of ADR.
Results: We found 97 cases of nephrotoxicity in this period and represented 10.10% of the total Adverse Drug Reactions described in this period for the whole hospital. The average age was 64.69 years (CI 95%: ±2.95 years). 67% of the cases appeared in males and 33% in females. 6 cases of nephrotoxicity were serious: 4 cases prolonged the hospital stay requiring dialysis, 1 case provoked hospital admission and one other compromised seriously the life and required dialysis too. The drugs most frequently involved were enalapril 19 cases, colystin 14 cases, vancomycin 10 cases, furosemide and amphotericin 9 cases, losartan 6, contrasts 5, rifampicin, diclofenac and gentamycin 4 cases. Other different drugs caused 14 other cases. Colistin and amphotericin nephrotoxicities appeared in some cases as tubulopathy with concomitant polyuria and electrolyte disturbances (mainly as renal tubular acidosis). Cardiology (21 cases), cardiovascular surgery (15) and intensive care units (14) were the departments with most cases of nephrotoxicity.
Conclusions: The frequency of drug induced nephrotoxicity was similar as the reported in other studies. The drugs involved in nephrotoxicity were similar as the reported in international bibliography. Colystin and amphotericin were the most nephrotoxic drugs because almost half of the treated patients suffered nephrotoxicity. The elevated number of cases induced by colystin is because the high consumption of this antibiotic due to the prevalence of multiresistant gram negative bacilli, mainly in the critical care units.

6. Pharmacovigilance in a Tertiary Care Hospital in Argentina (Developing Country)

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Introduction: Pharmacovigilance is actually growing up in developing countries because the impact in morbimortality that Adverse Drug Reactions have. Hospitalary pharmacovigilance is not developed as needed. The aim of this study is to describe the pharmacovigilance results in a tertiary care hospital in Buenos Aires, Argentina.
Material and Methods: The study took place in Hospital Argerich (a tertiary care hospital), Buenos Aires, Argentina. We have a Pharmacovigilance Department since June 2008 and for this study we describe a period of eleven months (since June 2008 until April 2009). All the departments except for the emergency room were included. All the ADRs were reported to the national regulatory agency ANMAT (Agencia Nacional de Medicamentos, Alimentos y Tecnología Médica).
Results: In this period there were 9053 hospital admissions. 960 ADRs were found, 567 in men and 393 in females. The average age was 58.67 years (CI 95% ±1.14 years). Of the 960 ADRs, 113 were serious; there were 61 drug-related admission (0.67% of the total admissions) and 4 drug related deaths. Considering organs and systems, the most frequent were endocrinemetabolics 399, drug induced hepatotoxicity 155, nephrotoxicity 114, skin 83 and gastrointestinal 48. Considering the groups of drugs, the most frequently involved were cardiovascular 302, antibiotics 221, neuropsychiatrics drugs 110 and glucocorticoids 60. The groups of drugs most frequently involved in drug related admission were antiepileptic and cardiovascular drugs 9 cases, oncological and hematological drugs 7. The organ/system mainly involved in serious ADRs were gastrointestinal (C. difficile diarrhoea and gastrointestinal bleeding) and neurological.
The departments with greatest reports of ADRs were Internal Medicine, Intensive Care Unit and Cardiology.
Conclusions: The drug related admissions were slightly higher than reported in some international studies[1] but lesser than others.[2,3] Hepatotoxicity and nephrotoxicity were relatively higher than reported in international bibliography. We found a relative lesser incidence of RAMs induced by NSAIDs and antineoplasic drugs and a higher relative incidence by antiepileptics than reported in international bibliography.

References

1. Patel H, Bell D, Molokhia M, et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005. BMC Clin Pharmacol 2007; 7: 9

2. Brvar M, Fokter N, Bunc M, et al. The frequency of adverse drug reaction related admissions according to method of detection, admission urgency and medical department specialty. BMC Clinical Pharmacology 2009; 9: 8

3. Pouyanne P, Haramburu F, Imbs JL, et al. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. BMJ 2000; 320: 1036

7. Cardiovascular Drugs Consumption in Ambulatory Care

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Background: The pharmacoepidemiological studies were first realized in Nordic countries (DURG) and then estimated and promoted by the World Health Organitation (WHO) to the rest of Europe, with the purpose to detect a probable misuse of drugs, to evaluate the prevalence of different patologies in a determinate population and to determine and estimate the actual and future costs of medicaments in a health system.
Objective: The purpose of this work was to evaluate the consumption of cardiovascular drugs from Buenos Aires population under the Federal Program of Health No. 13236.
Material and Methods: We evaluated the consumption of cardiovascular drugs from the Buenos Aires population for a hole year (from January 1st to December 31st 2008).The drug consumption was expressed in DHD (Daily Definite Dose per 1000 inhabitants per day) according to the parameter suggested by WHO. The Definite Daily Dose for each drug was taken from de WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcddd/).
Results: The consumption of antihypertensive drugs were 104.09 DHD. The most consumed group of drugs were ACE antagonists 43.47 DHD, Calcium channel blockers 20.69 DHD, Beta adrenergic receptors blockers 14.05 DHD, Angiotensin II Receptors antagonists 12.20 and Diuretics 9.03 DHD. Considering individual drugs, the most consumed drugs were enalapril 42.99, amlodipine 17.64, atenolol 10.43, furosemide 4.38 and hydrochlorothiazide 4.17 DHD.
Hypolipemiants consumption was 22.20 DHD (statins 18.31, fibrates 2.82 and ezetimibe 1.24 DHD). The most consumed were atorvastatin 13.14 DHD, simvastatin 4.59, fenofibrate 1.6, ezetimibe 1.24 and gemfibrozil 1.13 DHD.
Other cardiovascular drug consumption were amiodarone 5.08, isosorbide mononitrate 3.60 and digoxin 2.89 DHD.
Conclusions: The total consumption of antihypertensive drugs was sharply lesser (approximately half) than the reported in international bibliography.[1,2] The ACE inhibitors and calcium channel blockers were the antihypertensive drugs groups most consumed. Like the recommendation of international guidelines, hydrochlorothiazide consumption was very low. The consumption of hypolipemiants drugs was lesser than those reported in international bibliography, being the statins the pharmacological group most consumed. The consumption of amiodarone was higher than all other studies we reviewed.

References

1. Nordic Medico Statistical Committee 2004. Medicines Consumption in the Nordic Countries 1999-2003. At nomesco-eng.nom-nos.dk

2. García del Pozo J, Ramos Sevillano E, de Abajo y Ramona Mateos Campos FJ. Utilización de antihipertensivos en España (1995-2001). Rev Esp Cardiol 2004; 57 (3): 241-9

8. Antibiotic Consumption in Ambulatory Care

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Background: The pharmacoepidemiological studies were first realized in Nordic countries (DURG) and then estimulated and promoted by the World Health Organization (WHO) to the rest of Europe, with the purpose to detect a probable misuse of drugs, to evaluate the prevalence of different pathologies in a determinate population and to determine and estimate the actual and future costs of medicaments in a health system.
Objetive: The purpose of this work was to evaluate the antibiotic consumption in the ambulatory care patients from Buenos Aires Argentina under the Federal Program of Health No. 13236.
Material and Methods: We evaluated the antibiotics consumption from Buenos Aires population for a whole year (from January 1st to December 31st 2008). The consumption was then expressed in DHD (Daily Definite Dose per 1000 inhabitants per day) according to the parameter suggested by the WHO. The Definite Daily Dose for each drug was taken from de WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atcddd/).

Results: Total antibiotic consumption was 5.96 DHD and the most consumed groups were beta lactamics 3.17, quinolones 1.27, sulphamides 1.16, macrolides 0.37, azole antifungal agents 0.29 and tetracyclines 0.23 DHD. Penicillin (2.73) were two fold more consumed than cephalosporins (0.44 DHD). The individual drugs consumption was amoxicillin + beta lactamase inhibitor 1.43 DHD, amoxicillin 1.23, trimethoprim and sulfamethoxazole 0.91, ciprofloxacin 0.83, cephalexin 0.39 and levofloxacin, clarythromycin norfloxacin 0.22 DHD.

Conclusion: The total consumption of antibiotic was lesser than reported in international bibliography.[1,2] Like other studies reviewed, Beta lactamics antibiotics (mainly penicillins) were the most consumed. The relative consumption of sulphonamides was higher and macrolides was lesser then reported in international bibliography.

References

1. Nordic Medico Statistical Committee 2004. Medicines Consumption in the Nordic Countries 1999-2003. At nomesco-eng.nom-nos.dk

2. Agencia Española de Medicamentos y Productos Santiarios (AEMPS) y Dirección General de Farmacia y Productos Santiarios (DGFPS). Uso de antibióticos en España. En http://www.agemed.es/profHumana/observatorio/docs/Evo_uso_antibioticos96-06.pdf

9. Interferon Alfa-2b and Ribavirin-Induced Lichenoid Eruption

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Introduction: Chronic hepatitis C infection is a worldwide public health problem. Until recently, the most effective therapy available for this disease was the co-administration of pegylated interferon-α-2b and ribavirin.[1] However, this association may increase the incidence of adverse effects.[2]

Aim: To report a rare case of a lichenoid eruption induced by a combined therapy of interferon alfa-2b and ribavirin.

Case report: A 64-year-old woman with a history of chronic hepatitis C treated with the association of interferon alfa-2b and ribavirin once-weekly. She presented a widespread eruption occurring three weeks after starting antiviral treatment. The lesions affected the face, the arms and the trunk. Laboratory investigations were normal. The skin biopsy revealed an epidermal spongiosis and hyperkeratosis and a perivascular inflammatory infiltrate composed mainly of lymphocytes. The results of direct immunofluorescence were negative. After the initiation of treatment by topical dexamethasone, there was a partial improvement in the lesions.

Discussion: Combined therapy with interferon alfa-2b plus ribavirin is currently considered the treatment of choice of chronic hepatitis C. However, there is a significant increase in adverse skin reactions which are more frequent compared to a monotherapy by interferon or ribavirin.[3]

Cutaneous side-effects of the association consisted on Meyerson's naevi, lichen planus, hyperpigmentation, photoallergic eczema, alopecia, itching, xerosis, erythema, induration at the injection site and a transient generalized rash. However, none of these cutaneous adverse reactions were severe sufficiently to deserve the discontinuation of the therapy.[4]

Conclusion: Clinicians should be aware of the increasing possibility of cutaneous adverse reactions in patients undergoing PEG-interferon α and ribavirin treatment for hepatitis C. They should advise and support the patients receiving these treatments.

References

1. Koshy A, Marcellin P, Martinot M, et al. Improved response to ribavirin interferon combination compared with interferon alone in patients with type 4 chronic hepatitis C without cirrhosis. Liver 2000; 20: 335-9

2. Takai I, Katsuura J, Sadahira C, et al. A case of the generalized eruption occurred during combination therapy with peginterferon α-2b and ribavirin. Rinsho Hifuka 2006; 60: 789-92

3. McHutchinson JG, Gordon SC, Schiff ER, et al., for the Hepatitis Inteventional Therapy Group. Inteferon alfa- 2b alone or incombination with rebavirin as initial as treatment for chronic hepatitis C. N Engl J Med 1998; 339: 1485-92

4. Hashimoto Y, Kanto H, Itoh M. Adverse skin reactions due to pegylated interferon alpha 2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus. Journal of Dermatology 2007; 34: 577-82

10. Infliximab-Induced Bone Marrow Aplasia and Vasculitis

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Introduction: Infliximab, a TNFα antagonist, is licensed for the treatment of ankylosing spondylitis, in patients with severe axial symptoms.[1] TNFα antagonists are generally well tolerated, the most commonly adverse effects reported are cutaneous adverse reactions.[2] Hematological toxicity, especially leuconeutropenia, is a rare but a serious side effect associated with infliximab therapy.[3]

Aim: To report a case of infliximab-induced bone marrow aplasia and vasculitis.

Case: A 32-year-old patient suffering from ankylosing spondylitis treated with infliximab. The patient developed pancytopenia four days after the injection of the drug and vasculitis two days later. Laboratory investigations showed a severe pancytopenia. Microbiological and immunological results were negative. Skin biopsy was in favour of a drug-induced vasculitis. Bone marrow examination revealed desertic aspect without viral inclusion or tumoral infiltration suggesting toxic aplasia. Infliximab was withdrawn, skin abnormalities started to heal progressively and the blood formula fully normalized 16 days later.

Discussion: The time of onset, duration, and rapid spontaneous recovery of these adverse effects are probably related to infliximab toxicity especially in the absence of administration of any other toxic drug. TNFα antagonists exert its functions, through its ability to regulate some proinflammatory cytokines. It is theoretically conceivable that TNFα blockade could induce bone marrow failure by blocking stem-cell differentiation.[4]

It is reported that the use of infliximab in the treatment of rheumatoid in patients with renal failure is relatively safe. However, the decrease in renal clearance of creatinine may lead to an accumulation of this drug in patient's serum and may precipitate aplasia.[5]

Conclusion: The use of infliximab in the treatment of severe inflammatory diseases is not entirely safe. It should be reevaluated especially with the increased cases of severe hematological accidents.

References

1. Valesini G, Iannuccelli C, Marocchi E, et al. Biological and clinical effects of anti-TNFα treatment. Autoimmunity Rev 2007; 7: 35-41

2. Day R. Adverse reactions of TNF-α inhibitors in rheumatoid arthritis. Lancet 2002; 359: 540-1

3. Montané E, Sallés M, Barriocanal A, et al. Antitumor necrosis factor-induced neutropenia: a case report with double positive rechallenges. Clin Rheumatol 2007; 26: 1527-9

4. Keystone EC. Tumor necrosis factor-alpha blockade in the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 2001; 27: 427-43

5. Hammoudeh M. Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis. Rheumatology 2006; 45: 357-9

11. Assymptomatic Drug-Induced QTc Prolongation in Hospitalized Patients

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Introduction: Drug induced QTc prolongation is an Adverse Drug Reaction (ADR) that can lead to Torsade de Pointes (TdP) and occasionally to death. Actually the importance of recognizing this ADR is increasing because a growing number of drugs are associated with QTc prolongation and because this ADR is almost ever assymptomatic and the clinical manifestation is usually severe.
The aim of this study was to determine the assymptomatic QTc prolongation in patients exposed to drugs undoubtly associated with this ADR.
Material and Methods: We realized this study in the Internal Medicine Department of the Argerich Hospital, Buenos Aires, Argentina. We performed a prospective controlled study. One group (n = 71) was exposed to drugs that can prolong the QTc, and the control group (n = 71) included patients not exposed to drugs that can prolong the QTc. Basal and 72 hours standard 12 Lead ECG were performed in all the patients included in the study. Significantly, prolongation was considered when the QTc augmented 50 mseg or more or augmented to more than 500 mseg.
Results: 26 cases (36.61%) of QTc prolongation appeared in the exposed group and none in the control one, Relative Risk 12.77, Odds Ratio 95.2. The drugs most frequently associated with QTc prolongation were quinolones, halopidol, diphenhydramine and amitriptyline. The average modification of QTc was +33 mseg (IC 95%, ±16.56 mseg) in exposed group and −12.91 mseg (CI 95%, ±10.35 mseg) in control group ($p < 0.0001$). When analyzing each group of drugs and compared with the control group the results were the following: psychiatric drugs+70 mseg (CI ±37.58) (p 0.001), RR 12.77, OR 95.2, antimicotics +17 mseg (IC ±25 mseg) ($p = 0.068$) and antibacterials +7.57 (CI 95%, ±24) ($p = 0.131$). All cases of prolongation of QTc were asymptomatic.
Conclusion: In more than two-thirds of the patients exposed to drugs than can prolong QTc we detected a significately QTc prolongation. Despite all these cases were asymptomatic, we consider these results to be very important because when another factor associated with QTc prolongation happen, the chances of TdP increase significantly. We consider of good practice to perform a control ECG in all patients that are exposed cronically to this kind of drugs or in those who are exposed to this drugs and have another factor than can prolong QTc (hypokalemia, hypomagnesemia, cardiac congestive failure, etc).

12. Inappropriate Drug Use (IDU) in the Hospitalized Elderly Population

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Introduction: The inappropriate use of medications in elderly population can lead to a sharply increase in morbimortality and in the last decades several criteria have been described to decrease and to detect the inappropriate use.
The aim of this study is to describe the IDU in hospitalized patients in a tertiary care hospital.
Material and Methods: The study was performed between June 2008 and April 2009 in Argerich Hospital, Buenos Aires, Argentina within the Department of Pharmacovigilance. All persons 65 aged or older admitted in Argerich Hospital (except the emergency room) in this period were included for this study. We checked the medication they received during the hospital stay and determine the IDU according to the Beers Criteria.
Results: 400 persons 65 aged or older were admitted during this period. The average age was 75.35 (CI 95%: ±0.74) years, 57% were males and 43% were females. IDU was detected in 86 differents patients (21.5%). Propoxiphene, diphenhydramine, other ancticholinergic drugs and amiodarone were the most relevant drugs causing IDU. Other harmful drugs associations were detected too, mainly NSAIDs-ACE and NSAIDs-SSRIs. There was no significant difference between sex and age in IDU. IDU was clearly associated with the number of drugs the patients received, being detected in 15.87%, 26.84% and 45.45% in this respective groups: less than 4 drugs, 5–9 drugs and 10 or more drugs (p 0.0056). The departments where we detected most frequently IDU were nephrology, cardiovascular surgery, neurosurgery and traumatology.
Conclusions: The IDU was slighlthy higher than reported in international bibliography[1–3] but not all this studies were realized according to Beers Criteria and most were realized in ambulatory care and not in hospitalized patients. The drugs most frequently involved in IDU were similar than reported in other studies.

References

1. van der Hooft C, Jong G, Dieleman J, et al. Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria – a population-based cohort study. Br J Clin Pharmacol 2005; 60 (2): 137-44

2. Brekke M, Rognstad S, Straand J, et al. Pharmacologically inappropriate prescriptions for elderly patients in general practice: how common? Scandinavian Journal of Primary Health Care 2008; 26: 80-5

3. Pugh M, Hanlon J, Zeber J, et al. Assesing potentially Inappropriate Prescribing in the Elderly Veterans Affairs Population Using the HEDIS 2006 Quality Measure. Journal of Managed Care Pharmacy 2006; 12 (7): 537-45

13. Using the Capture–Recapture Method to Assess the Incidence of Drug-Induced Liver Injury in a French University Hospital

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Background: Liver damage remains the most frequent type of adverse drug reactions (ADR) that can lead to the withdrawal of a drug from the market. There is evidence that different methods used to estimate incidence of ADR in hospitals are not exhaustive (spontaneous reporting or computerized medical databases). The combination of different sources of data could improve knowledge about ADR frequency in hospitals. The more the number of analyzed sources is, the more reliable the estimated incidence is.

Aim: The aim of this study was to estimate the incidence of DILI in medical wards of Toulouse University Hospital (France) from 4 sources: the ''Programme de Médicalisation des Systems d'Information'' (PMSI), spontaneous reports recorded in the ''French Pharmacovigilance Database'' (FPVD), Biochemistry Laboratory Analysis Data (BLAD) and Anatomo-pathology Laboratory Analysis Data (ALAD).
Methods: The study took place in 2006. From PMSI, all hospitalization summaries including an ICD-10 code related to hepatitis were selected. From FPVD, all DILI which occurred during the study period and were reported by physicians working in the University Hospital were collected. From BLAD, all patients with an alanine aminotransferase or aspartate aminotransferase (over 5-fold normal) and/or alkaline phosphatase (over 2-fold normal) were selected. From ALAD, all the patients for whom a hepatic biopsy was performed in study period, were selected. After identification of common cases, the capture-recapture method was applied in order to estimate the real number of DILI occurring in 2006.
Results: From PMSI, we identified 27 patients hospitalized because of a DILI or presenting a DILI during their hospitalization. From the FPVD, we retained 34 DILI for analysis. From BLAD, 127 patients, and from ALAD, 9 patients were identified. The real number of DILI identified by the 4 sources was 138 corresponding to an incidence of 156.5 for 100 000 patient-years [IC 95%: 121.7, 198.0]. Two DILI were common in the 4 databases, 12 in 3 databases and 29 in 2 databases, giving an estimated number of 158 cases and an estimated incidence of 179.1 for 100 000 patient-years [IC 95%: 159.9, 198.4] by capture-recapture method.
Conclusions: This study shows that underreporting remains important for potentially serious ADR such as DILI, even in a university hospital. The exhaustiveness of ADR reporting is limited whatever the source of data and underlines the interest of merging data from different databases to identify fully the real impact of ADR in hospitals.

14. Is There Any Relationship Between Drug Therapeutic Advance, Efficacy and Pharmacovigilance Alerts?

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Background: For evaluating drugs, French National Authority for Health (HAS) assigns two scores to all new marketed drugs: a score for drug therapeutic advance (ASMR, 5 levels: I–V) and another for drug therapeutic efficacy (SMR, 5 levels: ''insufficient'', ''weak'', ''moderate'', ''important'', ''major''). The lower the ASMR score is, the more innovating the drugs are.
Aim: We investigated putative associations between drug therapeutic advance (ASMR), efficacy (SMR) scores and pharmacovigilance (PV) alerts.
Methods: PV alerts concerning serious adverse drug reactions, warnings and inefficacy studies, diffused by French Drug Agency (AFSSaPS), were analyzed from 1st January 2006 until 24th November 2008. ASMR and SMR scores of drugs involved in these alerts were found using HAS documents. Firstly, we compared frequency of PV alerts in each score group with other score groups. Then, we compared frequency of PV alerts between the drugs with low ASMR scores (I–III) and those with high scores (IV–V). Finally, drugs with ''insufficient'', ''weak'' or ''moderate'' SMR scores were compared to those with ''important'' or ''major'' SMR scores.
Results: Comparison of ASMR score groups showed that PV alerts are significantly more frequent in ASMR II (OR: 2.17; CI 95%: 1.52, 3.09; $p<0.001$) and ASMR III (OR: 1.96; CI 95%: 1.40, 2.73; $p<0.001$) groups and significantly less frequent in ASMR V group (OR: 0.42; CI 95%: 0.33, 0.54; $p<0.001$). Comparison of SMR score groups showed significantly more frequent PV alerts in ''moderate'' group (OR: 1.41; CI 95%: 1.07, 1.85; $p=0.011$) and less frequent PV alerts in ''insufficient'' group (OR: 0.41; CI 95%: 0.27, 0.62; $p<0.001$). Comparison between low (I–III) and high ASMR (IV–V) score groups showed that PV alerts are significantly more frequent in drugs belonging to I to III ASMR groups (OR: 2.13; CI 95%: 1.64, 2.77; $p<0.001$). No difference was found between drugs with ''insufficient'', ''weak'' or ''moderate'' SMR scores and those with ''important'' or ''major'' SMR scores.
Conclusion: Our data show that PV alerts are more frequent with innovating drugs. Several factors could explain this association: higher consumption, mediatization and prescription in serious diseases and/or in at risk patients.

15. Adverse Neurological Events of Antiretroviral Therapy in Mali

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Introduction: Adverse neurological events during antiretroviral treatment are frequent and various.[1-3] Their diagnosis occur some difficulties in different orders according to the geographical context.
Aim: To identify the frequency with neurological side effects.
Methods: We performed prospective taking care of any patient und antiretroviral treatment and developing neurological manifestations in a period of 12 month in the service of infectious diseases teaching hospital ''point G'' of Mali. Neurological diagnostic have been done with the guidance of a neurolog and the results are in stored in an investigation file. We have used done WHO classification of side effects.[4] Analysis of data have been done in the logiciel SPSS version 12.0.
Results: 420 seropositive patients under antiretroviral treatment have been followed. Between them 37 cases have been discovered with adverse neurological events during that treatment what is 8.08%. The sex ratio was 1.06. The age average was 41.2 years. Polyneuritis alone represented 83.8%, and then Polyneuritis associated to vertigo, headache and depression. We didn't notified any symptoms of neuropathies at the beginning and almost the totality of the patients are HIV-1 infected (91.9%) and under treatment of Triomune® at 89.2%. In etiological way, Stavudine (d4T) was the most neurotoxic between the antiretroviral. 5 cases were at third stage of WHO classification (13.5%) what justified consequently the stop of d4T.
Conclusions: Nevertheless, adverse neurological events may arise from the use of Triomune®. In future, antiretroviral therapy must take into account neurological consequences and the instauration of pharmacovigilance to detect eventual drugs with neurological side effect.

References

1. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. J Peripher Nerv Syst 2001; 6: 14-20

2. Lichtenstein KA, Armon C, Baron A, et al. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease

factors in the HIV outpatient study cohort. Clin Infect Dis 2005; 40 (1): 148-57

3. Moulignier A, Girard PM. Principaux traitements anti-VIH, Toxicité neurologique et interactions à éviter. Neurologie 2003; 4: 140-4

4. WHO. ARV drugs adverse events, case definition, grading, laboratory diagnosis and treatment monitoring. Geneva: WHO, 2008

17. Herbal Beverages: Perceptions and Knowledge Among General Public Towards its Safety and Efficacy

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Introduction: The use of herbal beverages in order to maintain general well being is on the rise in many Asian countries.[1,2] In Malaysia, the availability of various herbal beverages such as herbal coffees and teas in the market is matter of concern due to the unknown long-term effects of these drinks on population health.

Aim: To ascertain general public's knowledge towards the safety and efficacy of herbal beverages.

Methods: A cross sectional survey was carried among general public in the State of Penang using a pre-tested questionaire. The sample size consisted of 400 individuals randomly selected from three major area of public interest in the State of Penang, Malaysia.

Results: A total of 400 questionnaires were completed and were considered for further analysis. From the response received, a total of 228 (57.0%) respondents had used herbal beverages before. Majority of the respondents, 249 (62.25%) believed that by taking herbal beverages it's improved their health status. Moreover 193 respondents (48.25%) believed that herbal beverages boost the energy level of user. A total of 120 respondents (30.0%) stated that they use it in order to prevent any ill health from occurring. In a response to question about the safety and efficacy of herbal beverages about 300 respondents (75%) agreed that herbal beverages are safe to use and they have less side effects compared to the allopathic medicines available in market. Majority of the respondents, 193 (48.2%) mentioned that the main reason for them to use herbal beverages is to boost their energy level and 74 (18.5%) of them use it for curative purpose of their illnesses.

Conclusions: This cursory knowledge and non-evidence based proof for the use herbal beverages will hinder the ability of respondents to seek appropriate and evidence base medical help for the various medical illness. In addition the ignorance toward the side effect of herbal beverages will put the users at a risk of additional complications associated with their use.

References

1. Aziz Z, Tey NP. Herbal medicines: prevalence and predictors of use among Malaysian adults. Complement Ther Med 2009; 17 (1): 44-50

2. Riewpaiboon A. Increasing herbal product consumption in Thailand. Pharmacoepidemiol Drug Saf 2006; 15 (9): 683-6

18. Comparative Utilization of the French Consensus List vs Beers List of Criteria for Identifying Potentially Inappropriate Medications in Elderly Inpatients

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Background: Inappropriate drug prescribing is a well-acknowledged cause of preventable adverse drug events and is frequently reported in elderly patients. Existing criteria for detection of inappropriate drug prescribing in the elderly are still controversial.

Aim: To compare the recently published French consensus list of criteria for identifying potentially inappropriate medications (PIM) with Beers criteria in the geriatric (>65 y) inpatient population of a 600-bed teaching psychiatric hospital.

Methods: The study consisted of a cross-sectional review of all the ongoing drug regimens in the geriatric psychiatry inpatients, performed on 3 separate days 1 year apart. Data were pooled for analysis. PIM were classified into 3 categories: drugs with unfavourable benefit/risk ratio (category I), drug orders exceeding a maximum recommended dose (category II), drug-drug or drug-disease combinations to be avoided (category III).

Results: In total, 227 elderly inpatients were included. Median age was 72 y (range 65–93). Taking all criteria together within each list, 73% ($n = 166$) vs. 35% (n=79, $p < 0.001$) of the patients received at least one PIM according to the French list vs. Beers list, respectively. Frequency of PIM was, respectively, 42, 37, and 36 per 100 patients in categories I, II, and III with the French list, vs. 21, 13, and 8 per 100 patients with Beers list. In category I, anticholinergic drugs accounted for 63% (60/95) of PIM with the French list, while anticholinergic drugs and propoxyphen-containing products accounted for, respectively, 31% and 23% of PIM with Beers list. In category II, supratherapeutic doses of zopiclone accounted for 60% of PIM with the French list, while supratherapeutic doses of short/intermediate-half-life benzodiazepines accounted for 55% of PIM with Beers list. In category III, combinations of anticholinergic drugs or combinations of psychotropics of the same therapeutic class accounted for 73% of PIM with the French list, while anticholinergic drugs in dementia or prostatic hypertrophy accounted for 73% of PIM with Beers list.

Discussion-conclusion: The French list identified more PIM than did Beers list in this study, and patterns of PIM were different. These findings stem from differences in some criteria between the two lists: (i) inclusion of more psychotropic agents with anticholinergic properties in category I of the French list, (ii) inclusion of zopiclone (extensively used in the study patients) in category II of the French list, iii) inclusion of more drug-drug combinations in category III of the French list. Controlled studies are needed to demonstrate that utilization of these instruments could improve patient outcome.

19. Human Factors Affecting PSUR Preparation

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Together with other documents, the PSUR is a tool for optimizing patient safety by maintaining awareness of a product's evolving safety profile and by anticipating situations that place the patient at risk. It is one of basis for establishing if and which actions need to be taken for minimizing the risks associated with a drug so to maintain a favourable benefit-risk balance.A PSUR that misses its scope can have huge consequences on patient's health and can expose Companies to great risks. Human factors impacting on PSUR preparation mainly regard two areas: (1) how the Companies and the Authorities perceive drug safety (2) the specific processes underpinning PSUR preparation and the understanding of its scope.

The company's top management should encourage a safety culture within the Company[1]: drug safety should not be perceived as a costly bureaucracy exercise,[2] as a commercial selling point or as defence against legal trials. Governments should not reduce the price of drugs on one hand and increase the burden of regulatory requirements on the other, otherwise the few resources available for drug safety will be

drained by regulatory compliance not by the science underpinning drug safety evaluation. For drug safety in general and for PSUR preparation, there should be a correct balance between the formal and the scientific contents. For the correct analysis of safety issues, these should not only be driven by pathology, but the correct mixture of sciences should be used (e.g. pharmacology, statistics, pharmacokinetics, genetics, etc.).

The PSUR processes[3] and the procedures should be flexible enough to fit for both simple and complex PSURs and to ensure the adequate skills and resources[4] are used for products yielding a different risks. Procedures should be as simple as possible[5] and they should be prepared by the people in charge of preparing PSURs. Key people in charge of preparing/contributing to PSUR preparation belong to different departments: they should exchange information on the product evolving safety profile on an ongoing basis, so to know on which risks they have to focus before the PSUR data lock point. Every PSUR contributor should know what information he has to provide and in what format. Everyone must be free to speak-up and propose improvements, so to feel the PSUR is also his and he can be proud of it. Mistakes should be a learning opportunity within a blame-free environment.

References

1. Canadian Patient Safety Institute. The Safety Competencies. Ottawa Ontario, 2008

2. Provnost PJ, et al. Reducing Health Care Hazards: Lessons From the Commercial Aviation Safety Team. Health Affairs 2009; 28 (3): 479-89

3. Seal C, Edwards B, Morrisroe J. Aviation Crew Resource Management (CRM) – A pharmacovigilance perspective. Pipeline 2008; (20): 7-9

4. Edwards B. Using the Human Factor to improve PSUR quality and compliance. Jun 09, Annual DIA, San Diego

5. Institute of Medicine. To Err is Human. National Academy Press, 2000

20. A Cross-Sectional Analysis of Potentially Inappropriate Use of Psychotropic Medications in a French Cohort of Hospitalized Elderly Patients

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Background: Although it is known that use of psychotropic medications increases the risk of adverse outcome (falls, fractures, delirium…), there is evidence to suggest that 50% of elderly individuals are prescribed theses agents.

Objective: To study the consumption of ''Potentially Inappropriate Medication'' (PIM) among elderly patients, paying particular attention to potentially inappropriate psychotropics (PIPs).

Methods: This was a cross-sectional analysis of the prospective multicentre SAFEs cohort of hospitalized French patients aged 75 years. This analysis involved the 1176 patients for whom there was information on the usual treatments in the 2 weeks before hospitalization. The drugs were coded according to the Anatomical Therapeutic Chemical classification; the Beers's list as updated in 2003 defined PIPs. Logistic regression analysis was performed to identify factors linked to use of psychotropics and PIPs.

Results: Patients took on average 5.7 ± 2.9 drugs. Twenty-eight percent of patients took at least one PIM. The number of patients who had taken at least one psychotropic drug in the two weeks before hospitalization (mean 1.6 ± 0.9 psychotropics per patient) was 589 (50.1%). More than half of both the 510 patients with a depressive syndrome and the 543 patients affected by dementia were treated with psychotropics. Prescription of psychotropics was independently linked to the presence of a dementia syndrome (OR = 1.4; 95% CI = 1.1, 1.9; p = 0.03), the presence of a depressive syndrome (OR = 1.7; 95% CI = 1.3, 2.1; p < 0.001), living in an institution (OR = 2.2; 95% CI = 1.5, 3.4; p < 0.001), use of more than five drugs (OR = 3.2; 95% CI = 2.5, 4.2; p < 0.001) and Charlson's co-morbidity score (OR = 0.6; 95% CI = 0.5, 0.8; p = 0.001). Nineteen percent of all psychotropics prescribed were PIPs. Of these PIPs, 66.5% were anxiolytics, 28.4% were antidepressants and 5.1% were antipsychotics. Use of PIPs in the multivariate analysis was associated only with consumption of more than five drugs (OR = 1.7; 95% CI = 1.1, 2.5; p = 0.01).

Conclusion: The elderly, who have multiple co-morbidities, complex chronic conditions and are usually receiving polypharmacy, are at increased risk for adverse drug events. These adverse events are often linked to problems that could be preventable such as delirium, depression and falls.

21. Medication Errors in Intrathecal Application: A Rare but Severe Occurrence

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Medication errors are a possible cause of poisoning with drugs. In the last ten years (1999–2008) the Poisons Information Centre Erfurt was consulted in 1153 cases of iatrogenic medication errors, representing 1.5% of all enquiries regarding drug poisoning. Only seven of them (0.6%) are related to intrathecal application. All patients affected by intrathecal medication errors were adults. Two patients were assessed as to be at moderate risk, whereas in 5 cases the risk of toxicity was severe. The drugs involved were morphine (3 cases), baclofen (3 cases), and methylene blue (1 case). In five cases drugs were overdosed inadvertently. In one case morphine was applicated intrathecally instead of epidurally. Methylene blue was used in false indication. Two representative cases are presented in detail.

Case 1: A 51-year-old male patient accidentally received an overdose of baclofen (0.06 mg/kg). First symptoms developed after one hour including clouding of consciousness, hallucinations, dyspnoea, hypotension, sinusbradycardia, and flush. To reduce baclofen concentration in cerebrospinal fluid, a portion of liquor was withdrawn. The patient was intubated and ventilated over 48 hours. Cardiovascular symptoms were responsive to the administration of atropine, dopamine, and dobutamine, whereas, physostigmine was ineffective. After

four days the patient was discharged from intensive care unit. He recovered without sequelae.

Case 2: Methylene blue was injected intrathecally to a 60-year-old woman to detect a spinal dura defect. The patient developed paraplegia, progressing to tetraplegia a few hours after the injection. She had to be intubated because of respiratory failure. Investigation of nuclear magnetic resonance showed an extended intramedullary signal enhancement in the whole spinal cord up to the medulla oblongata. The liquor was blue-coloured and its protein concentration was extremely elevated. The patient was given highly-dosed methylprednisolone and finally the lumbar liquor was drained. In the further course, all brainstem reflexes extinguished and the patient died six days later. In this case the contraindication for intrathecal administration of methylene blue, because of its neurotoxicity, was disregarded.

In comparison with other routes, intrathecal application plays a minor role in the administration of drugs. Accordingly, medication errors in intrathecal application rarely occur. However, they may result in severe poisoning and even fatal outcome as demonstrated by case reports from other authors[1-4] and the cases reported to the Poisons Information Centre Erfurt.

References

1. Dalton C, Keenan E, Stevenson V. A novel cause of intrathecal baclofen overdosage: lessons to be learnt. Clin Rehabil 2008; 22 (2): 188-90

2. Qweider M, Gilsbach JM, Rohde V. Inadvertent intrathecal vincristine administration: a neurosurgical emergency. Case report. J Neurosurg Spine 2007; 6 (3): 280-3

3. Tournel G, Bécart-Robert A, Courtin P, et al. Fatal accidental intrathecal injection of vindesine. J Forensic Sci 2006; 51 (5): 1166-8

4. Barrett NA, Sundaraj SR. Inadvertent intrathecal injection of tramadol. Br J Anaesth 2003; 91 (6): 918-20

22. First Results from an Intensified Monitoring System to Estimate and Characterize Adverse Drug Reactions in a Department of Internal Medicine

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Introduction: Adverse drug reactions (ADRs) are a major cause of hospital admission and in-hospital morbidity.[1-4] Our objective was to describe the frequency and characteristics of ADRs identified by intensive pharmacovigilance in hospitalized patients.

Methods: The prospective observational study included all patients admitted to an internal medicine department over a one month period. Patients were evaluated by a pharmacist trained in pharmacovigilance in order to detect and asses ADRs. Age, gender, admission diagnosis, medicines taken in the previous month, adverse reactions, suspected drug, severity and preventability were analyzed. The imputability was established using Karch-Lasagna algorithm.

Results: 61 patients were hospitalized during this period. The majority of patients received an average number of 6 drugs (range 1–13) and presented comorbidity. 15 patients presented 18 ADRs; 17 ADRs were present at admission; from these, 7 ADRs were the cause of admission. One ADR appeared during hospitalization. The mean patient age was 58 years (range 31–74); from the total of 15 patients with ADRs, 11 were women. The affected systems were gastrointestinal (8), renal (3), dermatologic (2), neurological, hematologic, metabolic and musculoskeletal. The drugs implicated were NSAIDs (6), cardiovascular medication (4), antibiotics (3), corticosteroids (2), diuretics, anticoagulants and a cholinergic agent. Nine of the ADRs could be considered preventable. In 3 cases drug interactions were the causes of the ADRs. Two ADRs were definite, 13 were probable and 3 were possible.

Conclusion: ADRs represent an important health problem. In order to face it, ADRs identification and prevention systems have to be implemented in the Romanian clinical practice.

References

1. Lazarou J, Pomeranz B, Corey P. Incidence of Adverse Drug Reactions in Hospitalized Patients. A Meta-analysis of Prospective Studies. JAMA 1998; 279 (15): 1200-5

2. Pirmohamed M, James S, Meakin S, et al. Adverse drug reaction as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329: 15-9

3. Lagnaoui R, Moore N, Fach J, et al. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. Eur J Clin Pharmacol 2000; 55: 181-6

4. Moore N, Lecointre D, Noblet C, et al. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998; 45: 301-8

23. Doxycycline-Induced Severe Thrombocytopenia: A Case Report

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Drug-induced thrombocytopenia, although relatively rare, is a serious side-effect of a large number of drugs. Doxycycline is generally a well tolerated antibiotic, with known side-effects such as gastrointestinal symptoms, tooth discoloration, candidasis, photosensitivity reactions, pigmentation changes and CNS effects.[1] Doxycycline induced thrombocytopenia is uncommon. We have found only one previous adverse event of thrombocytopenia reported, during a randomized, multicenter clinical trial, in a doxycycline-treated patient, shortly after completing therapy.[2]

We want to describe a case of a 31-year-old woman who was admitted to hospital for gastrointestinal bleeding, repeated gingival bleeding, fatigability, over the preceding week. She had no significant medical history. About 4 weeks before hospital admission she was prescribed doxycycline by the dentist. She followed a 7 days treatment of doxycycline, then a 7 days break, followed by another 10 days doxycycline. She stopped taking doxycycline 3 days prior to admission. The patient was taking no other drugs. Laboratory investigations showed on admission day a platelet count of 22 000, leukocyte count 5000/mm^3, hemoglobin 6.6 g%. A diagnosis of drug-induced thrombocytopenia was considered. The patient was treated with dexamethasone for two weeks. The platelets on hospital day 6 were 75 000 and on day 14 they were 195 000. The diagnosis of drug-induced thrombocytopenia is supported by the resolution of thrombocytopenia after discontinuation of doxycycline and by exclusion of other causes. Use of Naranjo probability scale indicated a probable relationship between thrombocytopenia and doxycycline therapy.

References

1. Smith K, Leyden JJ. Safety of Doxycycline and Minocycline: A Systematic Review. Clin Ther 2005; 27: 1329-43

2. Nadelman RB, Luger SW, Frank E, et al. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. Ann Intern Med 1992; 117: 273-80

24. Compliance Survey for Thalidomide use in Japan

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Introduction: In Japan, thalidomide was approved in October 2008 and was launched in February 2009 under a risk management program named TERMS (Thalidomide Education and Risk Management System).

Aim: To construct a system to evaluate patients', physicians', and pharmacists' compliance to TERMS.

Methods: The survey consists of three parts as follows;

1. Patients: All the patients are registered into the TERMS and classified into three groups-(i) Male, (ii) Female of non-childbearing potential, and (iii) Female of childbearing potential. When thalidomide treatment is initiated, each patient will receive a request letter to participate in the survey by calling an interviewer. The interviewer will ask the patient's understanding, compliance and free comments. The interviews are planned to conduct every six months.
2. Physicians: All the physicians will be asked to fill out a questionnaire once a year.
3. Pharmacists: All the pharmacists will be asked to fill out a questionnaire once a year

Results: Patient interview scripts were prepared. The data management system was constructed in which the interview results will be stored and can be retrieved for further analysis. Patient interview has been conducted since March 30, 2009. The most recent statistics will be presented in the poster session.

Conclusion: Systems to evaluate compliance to TERMS are constructed which is expected to contribute for the improvement of TERMS.

25. The Importance of Regional Pharmacovigilance Centres

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Adverse reactions, interactions and other drug related problems are commonly encountered in medical practice. Manifold as they are, however, it often comes as a surprise to the individual prescriber. Because of the complexity of modern pharmacotherapy, the vast and often inconclusive literature and the continuous extension of the available knowledge, in the management of such problems often expert advice is welcome. At the same time, real-life experiences with drug problems often constitute valuable information, for other patients and for regulators.

'Spontaneous reporting' was originally introduced as a collaborative effort of prescribers and regulators, as a shared concern and responsibility, aiming at safer medicines and safer use. Over the years, national pharmacovigilance centres have primarily become a source of information for post-approval drug regulation: the regulator values the data in the context of regulatory requirements and needs, while information to prescribers is issued often ad hoc in the case of serious findings or acute problems. Although related, the interests, needs and priorities of regulators differ in many respects from those of prescribers and patients.

In an increasing number of countries in all parts of the world regional pharmacovigilance centres have evolved, linked to academic or large regional hospitals. In addition to supplying national pharmacovigilance with high-quality case reports, such regional centres maintain intensive and interactive communication with physicians and pharmacists and provide a wide range of information regarding pharmacotherapy to practitioners and also to drug information officers, bulletins and local formularies, which is often complementary to that from regulators. Regional pharmacovigilance centres have become valuable players, fostering rational prescribing and safer use of medicines.

26. Potential Adverse Drug Reactions from Herbal Products in Patients with Kidney Disease

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Introduction: Adverse drug reactions (ADRs) are a common cause of hospital admission and make a significant contribution to healthcare costs.[1,2] Herbal medicines (HMs) are popular in many communities and patients are reluctant to link herbs with risk of adverse effects. Little information is available about HM use in the kidney disease population.[3]

Objective: To provide qualitative and quantitative data on the safety of HM use in patients with renal disease, visiting a hospital nephrology clinic in Sheikh Khalifa Medical City (SKMC), Abu Dhabi.

Methods: A prospective, 3-month, cohort study followed all presenting patients. Patients were interviewed by one of us (FA) using a structured, piloted questionnaire to determine previous and current use of HMs and prescribed medicines (PMs) and descriptions of any ADRs. Clinical records and the attending doctor's opinion were consulted for corroborative evidence. Potential links between HM use and ADRs were assessed by consensus of a panel of investigators using the Naranjo algorithm.[4]

Results: 468 (68%) of 688 patients were currently taking HMs. 365 (78%) patients currently taking HMs were also taking PMs and 439 (93.8%) said they started taking HMs before the onset of their current illness. Over two-thirds of patients currently taking HMs (69.9%) said they had not informed their doctors. Presenting conditions included: renal transplantation (25.9%), kidney dialysis (21.8%), proteinuria (17.3%), chronic kidney disease (17.3%) and nephropathy (7.9%).

Over 100 different HMs were being taken with 65.6% taking three or more together. The most common were ginger (50.9%), thyme (38.2%), peppermint (37.7%), unspecified herbal mixtures (30.5%: over a third of respondents could not name the active ingredients); fenugreek (30.6%), black seed (25.2%), senna (19.2%), cardamom (14.3%), anise (11.1%), sage (10.5%) and chamomile (10.0%). HMs were probably (12) or possibly (16) involved in 28 ADRs in 26 patients.[4] Seven (25%) were attributed to HMs and 21 (75%) to HM/PM interactions. ADRs ranged in importance from minor to life-threatening.

Conclusions: HM taking was higher in this secondary care setting than in a primary care setting studied previously (38%).[5] Renal patients were at risk of ADRs from both HMs and PMs.
HMs are not without risk and could contribute to morbidity in renal patients. Thorough drug histories should be taken on admission to ensure that the attending clinician is aware of all potentially harmful preparations taken by the patient.

References

1. Primohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ 2004; 329: 15-9

2. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacol 2008; 42: 1017-25

3. Burrowes JD, Van Houten G. Use of alternative medicine by patients with stage 5 chronic kidney disease. Adv Chronic Kidney Dis 2005; 12 (3): 312-25

4. Naranjo CA, Buasto U, Sellers P, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30 (2): 239-45

5. AlBraik FA, Rutter PM, Brown D. A cross-sectional survey of herbal remedy taking by United Arab Emirate (UAE) citizens in Abu Dhabi. Pharmacoepidemiol Drug Safety 2008; 17: 725-32

27. Prevalence of Fixed-Dose Combinations in Nepal: A Preliminary Study

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Introduction: Fixed dose combinations (FDCs), though offer certain advantage in terms of patients compliance, their use is highly debatable. Studies from Nepal have documented a high prevalence of prescribing FDCs.[1-3] However, there are no extensive studies on FDCs.
Aim: To study the registration status, availability and utilization pattern of FDCs in Western region of Nepal.
Methods: Initially the registration status of 50 FDCs in the national drug regulatory authority was studied. The availability of these 50 FDCs in ten retail pharmacies was studied. Following which, a total of 25, 50 and 75 prescriptions were collected from primary, secondary and tertiary health care (PHC, SHC, and THC) centers, respectively, from October 18th to December 15th 2008 and were studied.
Results: Among the 50 FDCs studied, 4 (8%) were present in Nepalese National Formulary (NNF) and 2 (4%) in the later version of the Essential Drug list of Nepal, and 4 (8%) were present in WHO model list of Essential medicines (15th Edition). Four FDCs that were not registered in the national drug regulatory authority were found in the market. We found 77% of FDCs prescribed in PHC to be 'antimicrobials' and 29% and 35% of FDCs prescribed in SHC and THC respectively were for respiratory diseases. We found 68% and 73% of the total FDCs prescribed in secondary and tertiary health care center were in the range of 'up to NRs 100 (US$1.33)'.
Conclusion: Although, some FDCs are not registered in the national drug regulatory authority of Nepal they are still available in the market. Large proportions of FDCs are widely utilized in different health care settings zof Nepal. Availability, utilization pattern and rationality of FDCs in different cities and health care centers of Nepal are urgently needed.

References

1. Poudel A, Palaian S, Shankar PR, et al. Irrational fixed dose combinations in Nepal: Need for intervention Kathmandu Univ Med J 2008; 6: 53-9

2. Mishra P, Alurkar VM, Subish P. Functions of a drug and therapeutics committee in Nepal. J Pharm Pract Res 2006; 31: 81

3. Das B. Prescribing trend of fixed-dose drug combinations in a tertiary hospital in Nepal. J Inst Med 2000; 22: 212-8

28. Adverse Drug Reactions to Dopaminergic Agonists in the French Pharmacovigilance Database

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Introduction: In France, dopaminergic agonists (DA) are primarily used for the treatment of Parkinson's disease (apomorphine, bromocriptine, lisuride, pergolide, piribedil, pramipexole, ropinirole) or hyperprolactinemia (bromocriptine, cabergoline, lisuride, quinagolide). Differences in the pharmacodynamic properties of these drugs suggest possible divergences in the kind of adverse drug reactions (ADRs).
Objective: We compared the frequency of different kind of ADR between the aforementioned DA.
Methods: We used the French Pharmacovigilance Database to select ADR reports from 1st January 1984 to 31st December 2008, in which at least one DA was suspected. The numbers of ADRs by organ class were compared between the DA, and odds ratios (OR) with their 95% confidence interval were calculated for each kind of ADR using ropinirole as reference.
Results: 2189 suspected reports were analyzed (bromocriptine: 39%, piribedil: 28%, ropinirole: 13%, others: 20%). Hospitalization was significantly more frequent with cabergoline, quinagolide or bromocriptine than with ropinirole (OR 1.8–3.3). No major differences were found in the frequency of gastrointestinal or general ADRs. Cardiac ADRs were more frequently reported with pergolide (OR 16.9 [8.7–33.5]), 50% of the cases corresponding to cardiac valvulopathies. Disorders of the nervous system were significantly less frequently reported with pramipexole, apomorphine, pergolide, bromocriptine, lisuride, or piribedil, as compared to ropinirole (OR 0.1–0.6). Diurnal somnolence was significantly less frequently reported with all DA as compared to ropinirole (OR 0.01–0.3). Psychiatric ADRs were more frequent with pramipexole (OR 3.6 [1.8–7.1]) and less frequently reported with cabergoline, apomorphine or pergolide (OR 0.2–0.5). Whereas no differences were found in hallucination frequency, confusion was significantly more frequently reported with piribedil, lisuride or bromocriptine (OR 2.6–6.7). Significant differences were also identified in the frequency of skin, ocular, respiratory, vascular or metabolic disorders.
Conclusion: Our data show significant differences in the kind of ADRs reported for each DA. Pergolide appeared as the leading cause of cardiac ADRs, while ropinirole was associated with the highest frequency of diurnal somnolence reports and pramipexole with more frequent psychiatric ADR reports.

29. A Pilot Safety Climate Questionnaire

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This original research project was carried out to extrapolate from evidence from other safety conscious sectors to the pharmaceutical

sector so as to better implement and manage pharmacovigilance processes within a drug safety system.

Following several drug safety crises and a drop in confidence in the way the safety of medicines is handled, it is logical to look at the ways other safety-conscious organisations maintain compliance and so retain society's confidence in safety. Examining what can be extrapolated from these sectors with a view to implementation in the pharmaceutical sector might well form the basis for restoring trust and improving confidence in the safety of pharmaceutical systems. I believe such research will help contribute to improved business safety practice and so help complement the regulatory reform of pharmaceuticals announced by the European Commission in February 2007 and adopted in December 2008.

To begin to implement and improve safety culture within an organisation, the first step is to assess its safety climate and then discuss the results with management. Such safety climate surveys have been developed and well tested in other sectors such as healthcare and I have adapted one of these surveys to use as part of my original research project. This particular survey is adapted from the 'Safety Attitudes Questionnaire (Pharmacy Version)' developed by the University of Texas. I conducted the survey in 40 companies as a pilot study to identify and examine what the challenges are with such a survey. The anonymised data together with respondent's comments are discussed.

The project also examines the importance of human interaction in complex safety systems, in particular the concept of Human Factors (HFs) which underpins safety climate in all organisations. In addition, I shall discuss how safety and human factors has been actively implemented using the technique of 'Crew Resource Management' in the aviation industry and the was this has been adapted into the 'TeamSTEPPS™' programme for delivering safety culture within the US healthcare system and the US Department of Defence.

30. Some Practical Processes for Streamlining Post-Marketing Product Surveillance: A Synergistic Approach

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Introduction: Epidemiological studies and non-interventional Post-Authorisation Safety Studies (PASS) are an increasingly requested part of Risk Management Plans (RMPs) in the European Union. Our experience suggests the pragmatic challenges resulting from this situation to Marketing Authorisation Holders (MAHs) as: (1) which type of epidemiological study corresponds best to what type of risk/agency request (e.g. quantification of rare ADRs, characterisation of product utilisation, etc) and (2) what is the most efficient way to embed epidemiological studies and risk management systems which have to be maintained over long time periods into the routine activities of Pharmacovigilance departments in the industry.

Aim: To provide answers to the above mentioned questions based on practical examples from a broader perspective involving various therapeutic areas and different types of requirements.

Discussion: We will (1) demonstrate relevant components of Risk Management Systems on signal detection (including an innovative approach that is based on observational longitudinal data), Risk/Benefit Analysis and Risk Minimisation strategies, (2) describe methods for efficient management of the components and (3) highlight the contribution of epidemiological studies.

31. Availability of Harmful Medicines in Nepal: Findings from a Multicentric Study

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Introduction: Medicines that are proven to be more harmful than beneficial can be categorized as 'harmful' or restricted' medicines.[1] In order to protect the consumers from the negative consequences of drug therapy, many countries have banned the harmful medicines. The United Nations (UN) has prepared the consolidated list of total of 51 medicines whose consumption andor sale have been banned, withdrawn, severely restricted or not approved by in more than five countries.[2] The availability of these medicines in Nepal is not studied.

Aim: To evaluate the registration status and availability of the 51 medicines from the UN consolidated list in Nepal.

Methods: Registration status of the 51 medicines from UN consolidated list was checked in through online search in the Department of Administration (DDA) website and personnel communication with the DDA. Similarly, a market survey involving six major cities of Nepal (Kathmandu, Pokhara, Birgunj, Biratnagar, Bhairhawa and Nepalgunj) was carried out to find the availability of harmful 51 medicines from UN consolidated list. Among these six, the last four are located in Indo-Nepal border.

Results: Out of the 51 medicines from the UN consolidated list, chloroform (in combination with camphor oil, menthol and phenol), phenylbutazone (2 mg injection), somatotropin (pitutory derivative), terfenadine (60 mg tablet and 30 mg/60 mL suspension), cisapride (10 mg tablets), erythromycin estolate (250, 500 mg tablet and 125 mg/60 mL liquid) and thalidomide (registered for restricted use) were registered in Nepal. During the market survey, we found cisapride (tablet) and erythromycin estolate (both tablet and suspension) were found in all the six cities. Thalidomide and diphenoxylate + atropine combination were found in three cities and quinidochlor and furazolidone were found in two cities. Sulphaguanidine, metamizole and furazolidone + metronidazole combination was found in one city.

Conclusions: The availability of harmful medicines can provoke their use and may lead to serious consequences. Thus, it is a public health concern and the issue needs to be sensitized among key players of the healthcare system.

References

1. Kafle KK. Karkee SB. Re-evaluation of registered drugs with the purpose of deregistering irrational medicines. Department of Drug Administration (DDA) a report submitted by Pharmaceutical Horizon of Nepal (PHON), Kathmandu (2007)

2. UN Consolidated List of Products Whose Consumption and/or Sale Have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments (Eighth Issue, Pharmaceuticals, 2003)

32. Observed Frequency of Adverse Events Associated with Aripiprazole Use in Child and Adolescent Age Group

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Background: Aripiprazole is considered by many as a third generation antipsychotic drug. This is owing to the proposed mechanism of action of this drug as a partial dopamine and serotonin agonist.[1] The effects as well as the adverse events associated with anti-psychotics are attributed to dopamine receptor antagonism. Aripiprazole being a partial agonist can be thought of, on theoretical grounds, to not cause such adverse events (eg. extra pyramidal side effects) to the same degree as compared to other conventional antipsychotic drugs . Also, there are a few studies on aripiprazole use conducted in the child and the adolescent age group.[2]

Aim: The study tries to quantify the observable adverse events associated with use of aripiprazole in children and adolescents.

Method: This was an open-label study design. Aripiprazole was prescribed for behavioral disturbances, associated with various psychiatric disorders to 35 children. The diagnoses were brief psychotic disorder; schizophrenia, bipolar disorders with psychotic features. The frequency of adverse events was observed. Average doses were 2.5–15 mg per day.

Results: The observed frequency of major adverse events were extra pyramidal side effects (dystonias): 22.86%, sedation: 22.86%; fatigue: 20%; akathisia: 14.29%; nausea: 8.57%; increased salivation: 8.57%; dizziness 5.71%; blurred vision: 5.71%. Frequency of less common adverse events will be listed in the presentation.

Conclusion: Although credited with negligible EPSE in adults, use of aripiprazole was associated with acute dystonias and other EPSEs in children. Other major adverse events were sedation, akathisia and fatigue etc. Hence caution is advised with use of Aripiprazole in this population. Also, further studies about prophylactic use of preventive drugs for the EPSEs are required.

References

1. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with serotonin and dopamine receptor subtypes. Neuropsychopharmacology 1999; 20 (6): 612-27

2. Findling RL, Kauffman RE, Sallee FR, et al. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. J Clin Psychopharmacology 2008 Aug; 28 (4): 441-6

33. Significant Challenges Remain for the Optimum Implementation of EU Risk Management Plans (EU-RMPs)

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Introduction: Since 2005 the EU-RMP has been mandatory for approval of new medicines. EU-RMPs include a safety specification, pharmacovigilance plan and, if required, a risk minimisation plan. Although a large number of RMPs have now been submitted, there is only limited information available on how they are viewed by companies and regulatory authorities and what impact they have had on companies.[1,2]

Aim: To: (1) investigate how industry and regulatory authorities currently view the EU-RMP, (2) determine what impact the EU-RMP has on their organisations and (3) provide recommendations to improve risk management.

Methods: Seventeen respondents with experience of EU-RMPs were interviewed (5 from ''Top 10'' pharma, 8 from other pharmaceutical and biotechnology companies, and 4 from the EMEA or national regulators) using a discussion guide questionnaire.

Results: Generally, all respondents believed that the EU-RMP is a good instrument to structure and think earlier about drug risks, and protect public health. Perceived remaining challenges included:

1. Risk assessment and prioritisation;
2. Quality control of EU-RMPs;
3. EU-RMP template duplication and length;
4. Concerns over public disclosure and confidentiality;
5. Amount of work and resources required, even for well established products;
6. Choice and evaluation of effective risk minimisation activities;
7. Difficulty in implementation of pharmacovigilance and risk minimisation commitments;
8. Obtaining precise and consistent feedback from national regulatory agencies;
9. Effective global-to-local roll-out of plans and cross-functional working;
10. Uncertainty about EU-RMPs for emerging technologies.

Conclusions: The establishment of EU-RMPs is viewed positively, but there are still a number of areas for improvement. Proposed recommendations include:

1. Companies and regulatory authorities should share best practice on choosing risk minimisation activities and measuring their effectiveness;
2. Regulatory authorities, in collaboration with companies, should update the EU-RMP template to reduce duplication, increase flexibility and focus more on risk/benefit. They should exchange feedback on improving EU-RMP quality;
3. Publicly available EU-RMP executive summaries would assist transparency;
4. Pharmacovigilance departments should receive more top management support and commercial/marketing should be appropriately involved earlier in EU-RMP planning;
5. Management should be more aware that the Developmental RMP can be a tool to aid earlier ''go–no go'' decisions;
6. Regulatory authorities should share best practice and provide better advice on how to judge risks as ''important'';
7. National agencies should cooperate further to improve consistency and be more pragmatic about the feasibility and cost of pharmacovigilance activities.

References

1. Ingate S, Tranter D, Banerjee A, et al. An Industry perspective on the Erice Declaration and Risk Management Plans. Drug safety 2006; 29 (8): 733-4

2. MHRA. Risk management plans (RMPs). Mail: The MHRA updating service for medicines 2006; 155: 3-4

34. Hospital Admissions to a Cardiology Department due to Adverse Drug Reactions

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Background: The multicentric study EMIR[1] conducted in 2007 in French medical departments evaluated at 3.6% the incidence of

adverse drug reactions related hospitalisations (ADR-RHs). Drug related admissions to a cardiology department were last assessed in Denmark by Hallas[2] at 4.1% in 1988.

Aim: To estimate the incidence of ADR-RHs to a french cardiology department, to evaluate the most frequently drugs involved and the proportion of preventable ADRs.

Methods: A 6-months prospective observational study including all patients admitted from emergency units to the cardiology department of Caen University Regional Hospital from March to August 2008. Cases with suspicion of ADR-RHs were evaluated for age, sex, underlying cardiac diseases, renal function, natremia, kaliemia and number of drugs exposures at the time of hospitalisation, suspected drugs, type and evolution of ADRs. Drug causality was assessed using the french algorithm,[3] and avoidability with the four scale score developed by APNET.[4]

Results: Incidence rate was 3.71% (1105 admissions, 41 suspected ADR-RHs). Mean duration of ADR-RHs was 11.2 days. Patients with ADR-RHs were significantly older than those without (73.5 vs 65.1 years, $p < 0.002$), sex ratio was smaller in cases than in patients without ADR-RHs (0.58 vs 1.72, $p < 0.001$). Pre-existent cardiac pathologies in ADR-RHs patients were: arrhythmias 61%, conductive disorders 39%, ischaemic heart disease 31.7%, valvular heart diseases 24.4% and congestive heart failure 14.6%. At the admission of ADR-RHs patients, Cockcroft's creatinine clearance was <60 mL/min in 72.5% and <40 mL/mn in 40%. The number of drug exposures was significantly higher in ADR-RHs group than in the other patients (8.2 vs 5.2, $p < 10^{-5}$). ADR-RHs were more frequent in patients receiving ≥5 drugs than in those treated with <5 ($p < 0.02$). ADR-RHs patients were mostly admitted for malaise 62.8% (23.3% with consciousness loss), cardiovascular disorders 25.6% or haemorragic syndrome 7%. A drug-induced conductive or rythmic disorder was suspected in 51%, an oral anticoagulant overdosage in 6.1%. The most involved ATC classes in ADR-RHs were cardiovascular system 68.2% (antiarrhythmics 36.5%, diuretics 17.7%) nervous system 9.4%, antithrombotics or anti-agregants 5.6%. One patient died. Hyponatremia (3 cases) and/or kaliemia disorders (7 cases) may have contributed to the ADRs. 26.8% of ADRs were evaluated as likely or probably avoidable.

Conclusion: Antiarrhythmics and diuretics are the most frequently involved drugs in ADR-RHs to a cardiology department. It seems necessary to reinforce therapeutic education and close monitoring of patients receiving these medicines, especially the oldest with polypathology.

References

1. Etude EMIR sur les hospitalisations liées à un effet indésirable médicamenteux. Commission nationale de pharmacovigilance du 25 mars 2008. http://www.afssaps.fr/var/afssaps_site/storage/original/application/bd7be64de27e31df5c8182983443353f.pdf

2. Hallas J, Haghfelt T, Gram LF, et al. Drug related admissions to a cardiology department; frequency and avoidability. J Intern Med 1990; 228: 379-84

3. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

4. Queneau P, Trombert B, Carpentier F, et al. Adverse drug effects : a prospective study by Apnet performed in seven emergency care units in France : propositions for preventive measures. Ann Pharm Fr 2005; 63: 131-42

35. Contemporary Approach for Risk Management Plan Involving Human Factor

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Developing an effective Risk Management Plan is an important part of any project. The inherent limitations of premarketing testing and ongoing focus on the risks associated with medical product use have fostered new thinking and methods for monitoring the evolving safety profiles of marketed products throughout their life cycle.[1]

Risk Management is a fluid process because risks are always changing. One of the hardest things to do and one of the most critical is to make sure that you have all the information. Even on the ongoing basis, the sources of information are not completely accurate. A recent report from the Consumer Union in the US shows that one in six Americans who have ever taken a prescription drug experienced a side effect serious enough to send them to the doctor or hospital, but the majority of consumers don't know they can report these side effects to the FDA, which is responsible for tracking drug safety problems.[2] Further, a national poll by the Consumer Reports National Research Center found that among consumers, one in six had experienced a serious drug side effect at some time in their life– described by the FDA as a reaction that led them to visit a doctor or hospital, was life-threatening or caused a significant disability or incapacity. But only 35 percent of consumers polled were aware that serious side effects can be reported to the FDA. Unfortunately, the IOM statistics show most physicians aren't reporting side effects to MedWatch.[3]

Consumers and patient organizations have been identified by European Regulatory Stakeholders as an important component of the European Pharmacovigilance System not only in their capacity to provide drug related information but also as an important lever to evaluate and communicate safety information.[4,5]

Independent of local regulations, protecting the health of the patient/consumer is the purpose of any safety surveillance system. If we consider the exposure of a drug in a market is never close to the knowledge we acquired during clinical evaluation and furthermore, the consumer reports conducts its own testing. Throughout the field of health care, consumers have become empowered to take greater responsibility for their own wellbeing.[6,7]

In conclusion, the value of a report lies not in who made it, but in the care and thoroughness with which it is prepared, documented, received, recorded, followed up, clarified, and analyzed in evaluation of possible drug-associated problems. Nearly every major disaster involved multiple failures.[8,9]

References

1. Current Challenges in Pharmacovigilance: Pragmatic Approach – Report of CIOMS Working Group V – Geneva 2001

2. Fernandopulle RBM, Weerasuriya K. What Can Consumer Adverse Drug Reaction Reporting Add to Existing Health Professional-Based Systems? Focus on the Developing World. Drug Safety 2003; 26 (4): 219-25

3. Code of Federal Regulations, Title 21, Volume 5, Chapter I, Subchapter D, Part 314, Sec. 314.80 "postmarketing reporting of adverse drug experiences" Revised as of April 1, 2007

4. MedWatch: Managing Risks at the FDA-Norman Marks, M.D., director of the FDA's MedWatch program-A Special Report from FDA Consumer Magazine

5. Problems with FDA Oversight–Consumer Report-Consumer Reports: Drug Approval, Follow-Up 'Flawed'-Daniel DeNoon, Brunilda Nazario, MD-December 05, 2005

6. New Consumer Reports Poll Finds Most Americans Don't Know They Can Report Bad Reactions to FDA Safety Program – ConsumerUnion.org

7. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf (accessed June 14, 2008)

8. http://www.emea.europa.eu/pdfs/human/pcwp/pcwpworkprogramme.pdf (accessed June 14, 2008)

9. Bringing the Consumer Revolution to the FDA-April 25, 2005-Alexander Tabarrok

36. Portuguese Physicians' Attitudes Towards the use of Herbal Complementary and Alternative Medicines in Oncology

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Background: The use of herbal complementary and alternative medicines (CAM), is growing among Portuguese cancer patients, contributing to a higher risk for unwanted interactions with conventional cancer therapies.[1,2]

Although physicians are becoming aware that patients use some forms of CAM, in particular phytotherapy, few discuss these therapies with them. Therefore, interactions may not be recognised as such, or may only be reported if considered serious, leading to the under-reporting of herb-drug interactions.[1]

Objective: To assess physicianś perceptions and attitudes towards the use of herbal CAM by cancer patients.

Methods: A survey using an *ad hoc* questionnaire was conducted among physicians attending a 2-day oncology scientific event.

Results: A total of 122 physicians, of which 57 oncologists, completed the questionnaire. Data indicates that Acupunture, Massage, Yoga and Homeopathy are the most commonly known CAM therapies and the mostly used by patients. Massage, Acupunture and Yoga are also the therapies mostly suggested by physicians. Regarding herbal CAM, 78% of physicians don't inquire patients about their use, 72% don't know which herbals are consumed and 59% is not aware of the risk for herb-drug interactions. 95% of physicians never suggested the use of herbal CAM.

Conclusion: Results indicate that efforts need to be made to increase the communication between pysicians and their patients about complementary therapies, and that information concerning herb-drug interactions should be more available to physicians.

References

1. Fønnebø V, Verhoef M, Paterson C. Cancer and complementary medice: an international perspective. Support Care Cancer 2007; 15: 999-1002

2. Cassileth B. Complementary and alternative cancer medicine. Journal of Clnical Oncology 1999;17 (11): 44-52

37. Portuguese Physician and Pharmacist Attitudes Towards the Use of Herbal Complementary and Alternative Medicines in Oncology

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Background: Complementary and alternative medicines (CAM) are becoming extremely popular among health products consumers and patients in Portugal.

Although many forms of CAM pose no risk or a minimal risk to consumers and patients, others make use of some herbal substances and preparations containing ingredients known to be toxic, genotoxic and carcinogenic, which may become reasons of concern at specific levels of exposure.

The use of herbal complementary and alternative medicines is growing among Portuguese cancer patients, contributing to a higher risk for unwanted interactions, especially due to the narrow therapeutic index of most oncolytic drugs.

Although physicians and pharmacists are becoming more conscientious about the use of some forms of CAM by patients, in particular phytotheraphy, they doṅt routinely ask about their use nor associate it with eventually observed adverse effects or interactions. Therefore, it is crucial to assess both physicianś and pharmacists' familiarity with most commonly used forms of CAM and to evaluate their attitude towards its use by cancer patients. Unfortunately, in Portugal, no questionnaires have been developed to measure this topic.

Objective: Evaluate the reproducibility of *ad hoc* designed questionnaires.

Methods: Questionnaires were separately constructed for physicians and pharmacists. Both included 3 questions related with 15 most common CAM therapies and 1 set of questions related with phytotherapy.

To assess reproducibility, each questionnaire was used in the pilot tests. One pilot test test was performed at the Hospital Infante D. Pedro (Aveiro) on a sample of 15 doctors and the other was performed at 8 pharmacies in the surrounding area of the Hospital, on a sample of 15 pharmacists. The questionnaires were administered twice, with 3 weeks interval. The questionnaires reproducibility was assessed using Cohen's kappa coefficient.

Results: Kappa values obtained in the pilot studies were above 0.6 for the majority of the questions, revealing a substantial degree of agreement.

Conclusion: The level of reliability estimated suggests that physicianś and pharmacistś familiarity with CAM, and attitude towards its use by cancer patients, can be adequately measured by the developed questionnaires.

38. Topiramate-Induced Diarrhoea in a 2-Month-Old Breastfed Child

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Introduction: A woman was treated with topiramate 50 mg × 2 during pregnancy and breast feeding. On the 40th living day, the baby's stool increased in frequency up to 10 times daily and became watery and slimy. The child was referred to hospital. No infection or somatic cause was found. Two weeks later, it was questioned whether topiramate in the mother's milk could cause the persistent diarrhea. Breastfeeding was suspended. Within 24 hours, the stool became more solid and the colour and smell returned to the previous pattern. Stool frequency declined to 2–3 times daily.

Methods: The mother's milk was analyzed for topiramate by fluorescence polarization immunoassay. A literature search was conducted using EMBASE, Medline, Ovid, and handbooks and databases on drugs and lactation.

Results: Topiramate was found in the mother's milk. The topiramate concentration was 15.7 micromol/L, corresponding to 5.33 mg/L.

The Summaries of Product Characteristics (SPCs) states that topiramate should not be used during nursing since there is no documentation on safety in nursing children. In the literature, we found only eight cases describing topiramate and breastfeeding.[1-4] Topiramate has been shown to be present in breast milk and has been found in the plasma of nursing children, without apparent clinical effects.

Conclusion: Topiramate may cause diarrhea as an adverse drug reaction and the prolonged diarrhea may have been caused by topiramate in the mother's milk. A continuing situation with untreated diarrhea may put children at risk for dehydration and electrolyte disturbances. Withdrawal of breast milk was associated with rapid clinical improvement of the child's diarrhea. The safety profile and pharmacokinetics of topiramate in children have not been not assessed.

References

1. Öhman I, Vitols S, Luef G, et al. Topiramate kinetics during delivery, lactation, and in the neonate: Preliminary observations. Epilepsia 2002; 43 (10): 1157-60

2. Öhman I, Leuf G, Tomson T. Topiramate kinetics during lactation. Epilepsia 2007; 48 Suppl. 7: 156-7

3. Fröscher W, Jürges U. Topiramateinnahme während des Stillens. Aktuelle Neurologie 2006; 33: 215-7

4. Gentile S. Topiramate in pregnancy and breastfeeding. Clin Drug Invest 2009; 29 (2): 139-41

39. Pancreatitis Associated with the Use of Itraconazole

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Introduction: Acute pancreatitis is a relatively rare, but serious clinical disorder with high mortality. The acute inflammation of the pancreas is believed to be caused by inappropriate intra-pancreatic activation of digestive enzymes, which leads to subsequent auto-digestion. Clinical symptoms are acute and constant pain in the epigastric area or the right upper quadrant. The most frequent causes of acute pancreatitis are alcohol abuse and cholelithiasis, comprising 70–80% of all cases.[1] Drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of 0.1–2%.[2] In literature reviews various different drugs have been associated with pancreatitis. Literature on itraconazole-induced pancreatitis is as far as we know limited to only one Dutch case report.[3]

Aim: To call attention to the assumed association between itraconazole and pancreatitis by presentation of four cases.

Methods and Results: The Netherlands Pharmacovigilance Centre Lareb, maintaining the voluntary adverse drug reaction reporting system in the Netherlands received four case reports of pancreatitis associated with use of itraconazole. Indication for use was onychomycosis for two female patients, 50/67 years old, and tinea pedis for two male patients, 55/15 years old. Time to onset varied from 3 days to 7 weeks after start of the medication. The diagnosis pancreatitis was confirmed by lab tests. In two of these cases, recurrent use of itraconazole resulted in recurrent symptoms. All four patients had been using relatively high doses of itraconazole. The database of the WHO Collaborating Centre contains 34 additional reports of pancreatitis on itraconazole.

Mechanism of itraconazole-induced pancreatitis: Given the low incidence and poor predictability of this adverse drug reaction, an idiosyncratic cause seems plausible. The relatively short time period to onset and the rapid de- and rechallenge that were reported are in line with an immune response.[4] However, relatively high doses of itraconazole were used in all four cases, which would be in favor of an accumulation of a toxic metabolite.[5]

Conclusions: The presented cases suggest a causal relation between itraconazole and pancreatitis. More data on this association are needed. We intend to stimulate awareness of this association among physicians, so they can inquire about the possible use of itraconazole while diagnosing patients with unexplained abdominal complaints. Given the mild indication for the use of itraconazole and the seriousness of this possible adverse drug reaction, physicians may wish to reconsider the prescription of itraconazole to patients with risk factors for drug-induced pancreatitis.

References

1. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008; 371:143-52

2. Balani AR, Grendell JH. Drug-induced pancreatitis : incidence, management and prevention. Drug Saf 2008; 31: 823-37

3. Langers AM, Jonkers GJ. Pancreatitis ascribed to the use of itraconazole. Ned Tijdschr Geneeskd 2001; 145: 1127-8

4. Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007; 5: 648-61

5. Dhir R, Brown DK, Olden KW. Drug-induced pancreatitis: a practical review. Drugs Today (Barc.) 2007; 43: 499-507

40. The Development Safety Update Report: A New Challenge for Academic Sponsors?

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Introduction: Periodic reporting to Competent Authorities concerning the safety of marketed drugs is mandatory in the ICH regions and the reports are standardized in the form of the Periodic Safety Update Report (PSUR) defined by ICH E2C.[1] Concerning periodic reports for clinical trials there is no standard throughout the ICH regions and differences in content, periodicity and format between countries exist, bringing to light the need for a standardized report. The Development Safety Update Report (DSUR) was initiated by the CIOMS VI working group[2] in 2005. The purpose of DSUR would be to inform appropriate stakeholders of new safety data and the evolving safety profiles of drugs, vaccines, and therapeutic biological products before they are marketed, and also when new indications or formulations are being studied for already marketed products.[3] Periodic safety reports on clinical trials already exist in the US (Investigational New Drug Annual Report), in the EU (Annual Safety Report). In Japan, there is no standard concerning clinical trial safety reporting. As the DSUR fits mainly for clinical trials conducted by the pharmaceutical industries it would concern only one investigational medicinal product (IMP) whereas for non commercial sponsors it would concern one or more IMPs in only one trial, therefore it appears that there is a need for developing a DSUR that suits for one single trial with several IMPs.

Methods: In respect of ICH E2F recommendations, we have worked on different DSUR templates for clinical trials with several IMPs that are mainly conducted by non commercial sponsors.

Results: We established 2 templates both in French and English for academic sponsors that incorporate at least some items from the Clinical Trial Application, aggregated tables for both serious adverse events and reactions and templates for Suspected Unexpected Serious Adverse Reaction narratives. The adapted DSUR was already sent to Competent Authorities and Ethics Committees for 3 clinical trials with several IMPs.

Conclusion: The adapted DSUR appears to increase the visibility in terms of safety and to facilitate the analysis and detection of safety

issues and safety signals in clinical trials. The ICH E2F guidelines are currently in step 3 of the ICH process and are therefore still subject to change, step 4 is planned for June 2009.

References

1. ICH E2C. Note for guidance on clinical safety data management: Periodic Safety Update Reports for Marketed Drugs, CPMP/ICH/288/95; 1997

2. CIOMS Working Group VI. Management of Safety Information from Clinical Trials; 2005

3. ICH E2F. Note for guidance on Development Safety Update Report, EMEA/CHMP/ICH/309348/2008

41. REVISE: The French Academic Clinical Trials Safety Working Group

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Introduction: The EU Clinical Trials Directive (2001/20/EC) sets out the regulatory environment for clinical trials on medicinal products for human use. The directive was transposed into French law in 2004 not only for medicines but also for other interventional studies resulting in difficulties to comply with this new law. In others words, the sponsor's responsibilities in terms of safety are not easily applicable for clinical trials involving several investigational medicinal products or for medical device and physiopathology studies. On behalf of the French Hospital Federation, a working group on clinical trials safety was created to face this challenge.

Methods: This group gathers together more than 80% of the University Hospitals' (CHU) safety clinical trials departments and the majority of non-commercial sponsors. This French academic working group includes over 40 stakeholders at the present time. This academic safety working group has at least three face-to-face meetings a year. Furthermore, a secure internet forum exchange was implemented with possible download of documents and posted alert sending. All relevant information issued from the Eudravigilance website is also put on line. An action points table was also established to clearly define each member's tasks and deadlines.

Results: The working group actions are the following:

- to establish minimal common safety standard operating procedures
- to set up material for training investigators and clinical research associates
- to provide templates for annual safety reports, to offer support for detecting safety alerts
- to search available relevant literature
- to think of a common definition of imputability for clinical trials
- to elaborate guidelines regarding the expectedness of events when several investigational medicinal products are involved
- to draw contract templates for commercial partners
- to organise free MedDRA training sessions
- to address common comments to the competent authorities.

Conclusion: Almost two years after being implemented, this young working group has achieved several goals, it provides practical support for academic sponsors. The sharing of information between all stakeholders aims to improve the safety of clinical trials. Next steps would be to harmonise the vigilance practices within the non-commercial sponsors for multinational clinical trials.

42. Gemcitabine-Induced Arrhythmia: An Underestimated Side-Effect?

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Introduction: Gemcitabine is a cell cycle-specific antineoplastic agent for solid tumor namely lung, breast, pancreatic, genitourinary cancers. Major side effects with gemcitabine are hepatic dysfunction, myelosuppression, renal and pulmonary toxicities. Development of cardiac arrhythmia during gemcitabine treatment is rarely reported in the literature. We report five cases of gemcitabine-related cardiac arrhythmia which occurred in patients with nonsmall cell lung cancer.

Methods: These five case reports are issued from the same clinical trial involving patients with non-small cell lung cancer. They received the following chemotherapy scheme: I.V. Cisplatine (80 mg/m^2) on day 1 and I.V. Gemcitabine (1250 mg/m^2) on day 1 and day 8 every 3 weeks.

Results: A 68-year-old man presented a tachyarrhythmia: gemcitabine latency 1st dose: 67 days/last dose: 4 days (7 doses in total). He was treated with amiodarone.

A 69-year-old man developed a supraventricular arrhythmia: gemcitabine latency 1st dose: 38 days/last dose: 10 days (4 doses in total). He was treated with amiodarone.

A 70-year-old man did an atrial flutter: gemcitabine latency 1st dose: 80 days/last dose: 10 days (8 doses in total). He was treated with amiodarone but as he presented a therapy failure, the patient went under a cardiac-endocavity stimulation.

A 57-year-old man presented a paroxysmal atrial tachycardia: gemcitabine latency 1st dose: <24 hours (1 in total). He was treated with amiodarone then with diltiazem.

A 47-year-old man presented atrial flutter: gemcitabine latency 1st dose: 7 days/last dose: <24 hours (2 in total). The corrective therapy remained unknown.

None of the patients had a cardiac past medical history and gemcitabine was definitively stopped in all cases. All the 5 patients recovered.

Conclusion: All arrhythmias were assessed as related to gemcitabine and occurred within a timeframe of 0–10 days. All the cases lead to hospitalisation and patients required appropriate corrective therapy. Regarding the mechanism of gemcitabine-related cardiac toxicity, the causative role of the primary gemcitabine metabolite is supported by its kinetics with an average half life of 65 hours. None of the patients had predisposing factors such as electrolytic imbalance, impaired neurologic and endocrine functions. Gemcitabine and its metabolites can interfere with sinoatrial conduction but the exact pathogenetic mechanism has yet to be determined. Therefore, gemcitabine-induced arrhythmia should be suspected whenever the patients complain of dyspnoea and palpitations.

43. Gemcitabine-Induced Posterior Reversible Encephalopathy Syndrome: A Case Report

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Introduction: Gemcitabine is an anti-metabolic drug frequently utilised in the treatment of many solid tumors. The most common toxicities of gemcitabine are blood and lymphatic system disorders as well as hepatobiliary, respiratory, thoracic and mediastinal disorders. Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological syndrome of incompletely understood pathogenesis. We report a case describing a posterior reversible encephalopathy syndrome in a patient treated with gemcitabine for non small cell bronchial carcinoma.

Methods: Case report.
Results: This case is issued from a clinical trial including patients with non small cell lung cancer.The chemotherapy scheme was the following: I.V. Cisplatine (80 mg/m^2) on day 1 and I.V. Gemcitabine (1250 mg/m^2) on day 1 and day 8 every 3 weeks. A 41-year-old male patient who had completed his induction chemotherapy phase (4 injections of cisplatine and 8 injections of gemcitabine) was hospitalised for sudden blindness, aphasia, confusional state and epileptic seizures less than 4 days after his last injection of gemcitabine. An MRI was performed which showed a definite inflammation of the occipital lobe leading to a posterior reversible encephalopathy syndrome diagnosis. The patient had no previous history of central nervous system disorders, no predisposing factors and lab data showed no abnormalities. Later the patient developed a chemo-induced aplasia followed by candida sepsis and gastrointestinal haemorrhage that led to death. At the time of death, the patient was still suffering from PRES.
Conclusion: Only very few reports of gemcitabine-associated PRES have been reported in the current literature. Some cases have previously been described with cisplatine, cytarabine or cyclosporine. The exact mechanism of toxic induced PRES is still not fully comprehended although impairment in cerebrovascular autoregulatory control due to toxic damage to the vascular endothelium or bloodbrain barrier is a major hypothesis. Even though cisplatine cannot be ruled out, the chronology of this event strongly suggests the implication of gemcitabine. This rare but potentially lethal side effect should be closely monitored as fatal cases have been reported within as few as 3 days from symptoms onset. MRI and/or CT scan should be performed as soon as central nervous system disorders are reported.

44. Progressive Multifocal Leukoencephalopathy: A Survey on HIV-Negative Patients with Non-Hodgkin's Lymphoma Receiving Rituximab

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare and often lethal opportunistic infection of the central nervous system caused by the human polyomavirus JC (JCV). The productive infection is probably triggered by all conditions, including drug exposure, leading to severe deficiencies of the immune system. In recent times concerns about cases of PML in patients receiving rituximab have been rised.[1]
Aim: To estimate the incidence rate (IR) of PML in patients receiving rituximab for non-Hodgkin's lymphoma (NHL), and to compare such value with IRs reported for different patients in the medical literature.
Methods: Medical records of patients accessing our Haematology Unit were reviewed retrospectively. Data on HIV-negative patients, receiving the first dose of rituximab for NHL between January 1st 2000 and June 30th 2008, were analyzed. The follow-up comprised a period ranging from the first rituximab dose to the last recorded visit, at the date of September 30th 2008. PML cases were included if the diagnosis was supported by both magnetic resonance imaging and detection of JCV DNA in stereotactic brain biopsies and/or cerebrospinal fluid. In addition, we reviewed the medical literature in order to check for studies allowing the calculation of IR for PML in different populations.
Results: Data from 821 consecutive patients (mean age: 59.5 ± 15.1; male: 54%), who met the inclusion criteria, were collected. The median time of follow-up was 20 months (range 1–106) for a total of 1725.2 patient-years at risk. Five cases of PML were identified with an IR of 2.89 cases per 1000 patient-years. Six studies were selected in which the IR of PML can be retrieved for the following populations (IR per 1000 patient/person-years): general population (USA, 1984; IR: 0.0002; USA, 1994: IR: 0.0033); patients with B chronic lymphocytic leukaemia (USA, 1987–1991: 1.08); patients with Hodgkin's disease (Holland, 1970–1984: IR: 0.46), HIV-positive patients (Denmark 1995–1996, IR: 3.3; Denmark, 1997–1999: IR: 1.8; Denmark 2000–2006, IR: 1.3); renal transplanted recipients treated with mycophenolate mofetil (USA, 2000–2004, IR: 0.144); patients treated with natalizumab for multiple sclerosis, Crohn disease or rheumatoid arthritis (clinical trials involving several countries, 2001–2005: IR: < 0.64).
Conclusions: The IR of PML in the present population is higher than or close to values recorded in populations traditionally regarded as carrying the higher risk (HIV+ and B-chronic lymphocytic leukaemia patients). Among the possible explanations for such a high incidence, the contribution of rituximab exposure warrants investigations.

Reference

1. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009 14; 113: 4834-40

45. Drug-Induced Taste and Smell Alterations: A Case/Non-Case Study on an Italian Database of Adverse Drug Reactions

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Introduction: Pharmacological treatments are among the most frequent cause of impairments in taste and smell. These alterations have the potential of significantly affecting the quality of life and of resulting in discontinuation of treatments.[1]
Aim: To identify drug classes associated with high report rates of taste and smell impairments, with particular focus on unlabelled associations.
Methods: The present analysis was performed on an Italian database of spontaneous reports of adverse drug reactions (ADR) managed by the Interregional Group of Pharmacovigilance (1988–2006), integrated with data retrieved from the database of the Italian drug agency (2007–2008). Only reports ranking at least as ''possible'', according to WHO causality assessment criteria, were considered. Associations between drugs and taste and/or smell alterations were assessed by the case/non case methodology, calculating the ADR reporting odds ratio (ROR) as a measure of disproportionality. Cases were defined as

patients with at least one ADR reported under the following WHOART preferred terms: ''parosmia'', ''taste loss'', ''taste alterations''. The non-cases comprised all remaining patients. Index reports included ADR associated with drug classes (third level ATC) with at least 5 reports of taste and/or smell alterations, while all ADR reports not involving index drugs were used as controls.

Results: According to selection criteria, 54 546 reports were included in the analysis. A total of 197 cases were identified (mean age: 56.17 ± 14.83; females: 66.50%). Taste alterations were reported in 176 patients (89.3%) and smell disturbances in 47 patients (23.9%). Drug classes most frequently reported with taste and/or smell alterations were macrolides (30 patients, 16.5%; ROR: 7.6; 95% CI: 5.1, 11.2), antifungals for dermatologic use (all terbinafine; 17 patients; 9.3%; ROR: 64.8; 95% CI: 41.2, 101.7), fluoroquinolones (15 patients, 8.2%; ROR: 1.7; 95% CI: 1.1, 3.0) and protein-kinase inhibitors (10 patients; 5.5%; ROR: 4.1; 95% CI: 2.1, 7.7). The outcomes for these ADR were ''resolved'' (76 reports; 38.6%), ''not yet resolved'' (44 reports; 22.3%), ''resolving'' (20 reports; 10.1%) and ''resolved with sequelae'' (12 reports; 6.1%), while 45 reports (22.8%) were recorded as ''not available outcome''.

Conclusions: Significant ROR for taste and/or smell alterations was found for macrolides, antifungals for dermatologic use (terbinafine), fluoroquinolones and protein-kinase inhibitors. Taste impairments were generally expected, while smell disturbances were unexpected or expected only for some drugs within each class. High rates of unresolved outcomes may suggest that some of these ADR may be permanent or associated with long-term recovery. Further investigations are warranted to validate these signals and their impact on patient quality of life.

Reference

1. Doty RL, Bromley SM. Effects of drugs on olfaction and taste. Otolaryngol Clin North Am 2004; 37: 1229-54

46. Physician's Awareness of Safety Information on the Risk of Cardiovalvulopathy Related to Pergolide Use in Japan

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Background: Several studies have suggested a high frequency of cardiovalvulopathy in Parkinson's disease (PD) patients treated with ergot derived dopamine agonists, including pergolide. In order to mitigate the risk of valvulopathy in patients treated with pergolide and to optimize the safe use of pergolide in patients with PD, a revised package insert was developed in 2007, warning prescribing physicians of the risk of new-onset valvulopathy with pergolide. The Contraindications and Important Precautions Section of the package insert in Japan were modified.

Aim: To assess physician's awareness of the changes made to the package insert of pergolide as well as their understanding of the wording and their adherence to the package insert changes which include: mandatory echocardiograms for all patients upon initiation of pergolide treatment and regularly throughout the treatment. This survey will determine the effectiveness of the risk minimization activities as implemented by neurologists in their daily clinical practice, and also act as a reminder to neurologists that a change in practice may be needed.

Methods: We surveyed neurologists to determine their awareness on safety information on the risk of cardiovalulopathy related to pergolide use in Mar, 2009. Self-administered questionnaires were mailed to a neurologist population (n = 2374) pooled in a commercial database for physician survey (EPOCA, Osaka, Japan), and collected from them during the survey period of two weeks.

Results: Response rate was 14.3% (n = 339). Overall awareness of the package insert change for pergolide was 98%. Most neurologists performed echocardiogram at baseline for patients who started treatment with pergolide/cabergoline (77%) and during treatment with pergolide/cabergoline (70%) according to the package insert.

Conclusions: Most neurologists who responded to this survey were aware of the package insert change of pergolide and indicated that they would perform echocardiograms prior to starting treatment, as well as during treatment. Although the response rate was low, this survey showed that neurologists were aware of the changes made to the package insert in relation to the valvulopathy risk of pergolide.

47. Bias in Signal Detection

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The tendency or preference towards a particular perspective especially when it adversely affects the results is known as bias. Like any other activity, the process of signal detection may be biased and can result in a systematic, non-random deviation of results from truth. Sources of bias in signal detection include the limitations of spontaneous reporting, like incomplete reporting, duplicate reports; incorrect causality assessment and the methodological errors. In addition, several external factors like media attention, privacy and data protection issues, law suits, marketing and financial pressures on the marketing authorization holders can also influence signal detection. Further, methodological errors like inappropriate selection of the comparator drug, incorrect stratification and inadequate use of MedDRA for database search while developing case series can adversely influence the process of signal detection and the life cycle management of a medicinal product. Detailed descriptions of various types of biases, viz. Notoriety bias, Protopathic bias, Channeling, 2-peak distribution, Weber effect etc are available in literature[1] and there are case studies describing regulatory actions (and amendments thereafter) resulting from such biases.[2,3]

Therefore, the possible sources of bias in signal detection, their potential impact on signal detection and the feasible solutions should be considered and appropriately addressed while developing the Risk Management Plan. The presentation will discuss various sources of bias, their effect on life cycle management and handling bias.

References

1. Stang P. Epidemiological Context of Signalling. Drug Saf 2007; 30 (7): 611-3

2. Moore N, Hall G, Sturkenboom M, et al. Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf 2003; 12: 271-81

3. Pariente A, Gregoire F, Fourrier-Reglat A, et al. Impact of Safety Alerts on Measures of Disproportionality in Spontaneous Reporting Databases. The Notoriety Bias. Drug Saf 2007; 30 (10): 891-8

48. Quality Management System as a Tool for Improvement of the Dutch Pharmacovigilance System

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Introduction: The Netherlands Pharmacovigilance centre Lareb started as a regional organization in 1985. In 1995 it was appointed by the

Health Authorities as the national centre for collection and analysis for reports of adverse drug reactions. Since then, Lareb has become a solid, professional organization with an efficient way of handling reports of adverse drug reactions and signal detection. Procedures covering these primary processes of pharmacoviglilance in Lareb have been developed during the past years. In 2008 a start was made with the introduction of a quality management system according to the ISO (International Organization for Standardization) standards.[1,2] In March 2009 Lareb achieved the ISO 9001-2000 certificate.

Aim: The aim is to describe the experience with the implementation of a quality management system and the influence hereupon the pharmacovigilance system in Lareb.

Methods: Description of the process of achieving the ISO 9001–2000 certificate. An analysis of the main aspects influencing the pharmacovigilance processes is performed.

Results: The organisation responsible for certification according to ISO standards in 'knowledge-driven' associations, investigated Lareb for the status of main topics in the ISO 9001–2000 requirements, including policy, organization, processes, results, employees and cooperation/automation. Within all these aspects, the basic principle of Plan-Do-Check-Act should be visible. Following this, several actions had to be undertaken to prepare for the final certification inspection. One of the main issues was to formalize all processes in a quality management manual covering all requested topics. Beside this, a process for internal auditing had to be commenced. The audits of the primary processes resulted in a welcome improvement in the performance of the pharmacovigilance processes. Finally a (bi)annual management review had to be undertaken, which ended up in a better view of the necessary steps for efficient planning of activities and resources.

Conclusions: The implementation of a quality management system shows to be a valuable and supplementary system to the already existing procedures and instructions regarding the collection and analysis of reports of possible adverse drug reactions. The continuous process of improvement warrants an efficient method for pharmacovigilance activities.

References

1. http://iso.ch

2. Quality management systems. Requirements ISO 9001:2000. Comité Européen de Normalisation, 2000

49. Report Processing and Signal Management at the Netherlands Pharmacovigilance Centre

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Introduction: The fast developments in pharmacovigilance in the past decades have had far-reaching consequences for the way of working in national pharmacovigilance centers. Firstly, processing and distribution of adverse drug reaction reports on both national and international levels became more complicated and required an adequate working flow of the reports and quality control to meet all regulatory requirements and technical standards. Secondly, the application of quantitative approaches in signal detection enabled the detection of large numbers of possible signals, still needed to be evaluated from a clinical perspective. This requires an adequate prioritisation and efficient diffusion of the signals involved. Both developments ask for a more efficient way of report processing and signal management. In the past decades the Netherlands Pharmacovigilance Centre Lareb developed a way of working to improve report processing and signal detection to meet the current needs.

Aim: The aim of this presentation is to describe the various work flows concerning report processing and signal detection. In addition, steps taken to increase the efficiency, reliability and transparency of the system will be discussed.

Description: The infrastructure of the Netherlands Pharmacovigilance centre consists of four main elements. In the first place a computerised working flow for the coding, assessment, filing and distributing the ADR reports in the database is available. Quality checks and systems are in place to ensure an effective processing of the reports. Secondly, information from other sources like literature, other databases and analysis which are previously carried out, are made automatically available for the assessors to reduce the workload. In addition, an automated signal management system ensures a transparent signal detection and handling of the publication process. Finally, a dedicated website presents the output in a transparent and automated way, both in respect to the individual case reports as for signals issued. Handling of the reports and signal detection are closely interrelated. Actions needed for processing reports are also the basis in the first steps of signal detection and diffusion of the signals, thus increasing the efficiency of the system.

Conclusion: The growing number of reports and signals are a challenge for many pharmacovigilance centers and asks for tuning of these various processes in which information technology plays a pivotal role. In order to ensure a high quality of both reports and signals regulatory requirements should be realistic and easy implementable in the current routines. Transparent processes will enhance the acceptability of our work by the general public.

50. Hepatic Adverse Events Associated with the Use of Herbal Drugs in Norway (''the Fortodol Case'')

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Introduction: In Norway the majority of herbal products are legally sold without applying for a marketing authorisation, and thus without the products being evaluated for quality, safety and efficacy. The reporting of adverse effects from health care personnel is spontaneous and not mandatory for herbals. Only about 30 adverse events associated with herbal drugs are reported annually in Norway. In spite of the limitations of the reporting system for herbals, we illustrate how it has worked in ''the Fortodol case''. The company (Bringwell) declared that Fortodol sold in Norway as a ''natural'' analgesic contained a turmeric extract (*Curcuma longa*).

Case reports: RELIS received the first report on Fortodol in 2007. A 47-year old female was diagnosed with hepatitis after use of 1–2 capsules per day for approx. 2–3 weeks. Several weeks after withdrawal her liver enzymes turned to normal. In 2008 RELIS received 4 more reports on Fortodol associated with hepatic adverse events. Symptoms developed from 2 weeks to 6 months after start. In three of four cases the patients also used other drugs associated with increase in liver enzymes. In 2 cases liver tests normalised after withdrawal of Fortodol, one patient was recovering at the time of reporting and the last patient died. In the same period the Swedish Medical Products Agency received 4 reports of liver toxicity, including one fatal case. An analysis of the Fortodol capsules used by the patient who died in Norway showed an undeclared content of 42 mg nimesulid per capsule.

Discussion and conclusion: Seven million capsules of Fortodol has been sold in Norway from 2007 to withdrawal of the product from the Norwegian market on 25 February 2009, and 7 of 9 lots have contained nimesulide.[1] Nimesulide is not authorised in Norway and is

associated with a risk of liver damage.[2] It is a common misunderstanding that herbs are natural and thus safe. However, analysis has shown increasing numbers of dietary supplements adulterated with drug substances.[3] Adulterated dietary supplements pose a high health risk. Practitioners should be encourage to discuss the use of herbal products with the patients, and use of herbals should be stated in the patients notes. Stronger regulation of these products is essential.

References

1. Norwegian Medicines Agency. Legemiddelverket advarer mot kosttilskuddet Fortodol: Ny rapport viser at 7 av 9 varepartier inneholder ulovlig tilsatt legemiddel (nimesulid) [document on the Internet]. Oslo: 2009 [2009 May 12; cited 2009 Jun 11]. Available from: http://www.legemiddelverket.no

2. EMEA (European Medicines Agency). Press Release: European Medicines Agency recommends restricted use of nimesulid-containing medicinal products [document on the Internet]. London: 2007 [2007 Sept 21; cited 2009 Jun 11]. Available from: http://www.emea.europa.eu

3. Venhuis BJ, Zwaagstra ME, van den Berg JDJ, Wagenaar HWG, van Riel AJHP, Barends DM et al. Trends in drug substances detected in illegal weight-loss medicines and dietarty supplements. A 2002-2007 survey and health risk analysis. National Institute for Public Health and the Environment, The Netherlands, 2009

51. Risperidone-Induced Photosensitivity

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Introduction: Risperidone is an atypical antipsychotic drug indicated for the treatment of schizophrenia. Many adverse drug reactions have been described with risperidone, including skin disorders as acne, discoloration of skin, dry skin, hypesthesia, peeling of skin, rash... One non expected case of risperidone-induced photosensitivity was reported to our Pharmacovigilance centre. Photosensitivity is not mentioned as a risperidone-induced adverse drug reaction in French Summary of Product Characteristics (SPC).

Methods: This study includes all spontaneous reports of suspected photosensitivity reactions with risperidone recorded in the French Pharmacovigilance database until the 15th of May, 2009. We also reviewed the international literature.

Results: Ten cases were reported for photosensitivity risperidone-induced in the French Pharmacovigilance database. In 5 cases risperidone was the only suspected drug (involving 3 women and 2 men, mean age was 41 years). For all patients, symptoms appeared from 3 to 42 days after starting the treatment with risperidone. All patients recovered, using corticoids or/and antihistaminic drugs for at least 3 patients. Only one case was considered as serious, leading to a 60 year old woman hospitalization. In regard to the severity of the effect for that patient, she was the only one who had her treatment with risperidone discontinued.

An international literature review allowed to find only one publication reporting one severe case of photosensitivity with risperidone and mentioning only one previous case.[1]

Discussion: During the pre-marketing evaluation of risperidone, this adverse reaction was observed in more than 1% of the patients and classified as frequent (Physician's Desk Reference). Very few cases have been reported, possibly because of the low severity of photosensitivity reactions with risperidone or because skin reactions to sun are usually not considered as adverse drug reactions by health practitioners or by patients themselves. Those case reports confirm the potential photosensitizing effect with risperidone.

Conclusions: Physicians should be aware of this potential adverse reaction when prescribing risperidone to their patients. Photosensitivity must be mentioned as a risperidone-induced adverse reaction in every SPC. National agencies should inform their physicians.

Reference

1. Almond DS, Rhodes LE, Pirmohamed M. Risperidone-induced photosensitivity. Postgrad Med J 1998; 74: 252-3

52. Difficulties and Consequences of Pharmacovigilance Assessment in Cancerology: Example with a Mylotarg's Study

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Introduction: Through our experience, we discuss the importance of quality of recorded safety data in results analysis. The aim of this presentation is to study the pejorative impact of the misinterpretation of some rules on recording mandatory data in clinical trials (CT) and the difficulties of respecting the guidelines in hospital real life.

Methods: The Goelams randomized multicenter open phase III clinical trial, sponsored by CHU Nantes, was leaded to test the efficacy of gemtuzumab-ozogamycin (Mylotarg®) associated with intensive conventional chemotherapy for patient presenting acute myeloid leukemia with intermediate risk. 400 patients should be included. Patients data were registered by clinicians in computerized clinical reporting form (CRF) and safety informations, transmitted with a safety form, were included by pharmacovigilance teams in the sponsor's pharmacovigilance dedicated data base. On the 100-first patients planned evaluation, based on both pharmacovigilance and CRF data base extractions, an unexpected excess of serious drug adverse reactions (SAR) and deaths was identified in experimental group, without increased complete remission rate, leading to rapid study suspension. As a consequence, a detailed analysis of each patient data was performed.

Results: This examination revealed abnormalities in screening of some patients with consecutive probable over expression of some toxicities. Information concerning past medical history, biological results and evolution failed to be mentioned correctly and at time in CRF or in safety form. The expectedness and relatedness were often misinterpreted with regard to the disease and not to the drug. Considering these points and their links with the causality's assessment, no difference persisted in safety or benefit/ risk analysis. A readjustment of the protocol was proposed.

Because safety constitutes a major concern in CT, investigators and sponsors have to apply many mandatory rules. For clinicians, patient's outcome is the main preoccupation, before drug evaluation. So, the interest of the requested informations seems often overdeveloped compared with the immediate medical situation and benefit, specially for life threatening diseases. The expectedness of an event is misinterpreted too. The frequency of SAR during chemotherapy, often expected, although protocol's instructions limiting the reporting, enhances difficulties. Delayed and incomplete transmission to sponsor modify imputability and consecutively the benefit/risk result.

Conclusion: From our experience, we suggested the establishment of specific and adapted reporting guidelines, necessary to unify the

evaluation of drug safety in cancerology. Authorities, pharmacovigilance teams and investigator have to work together to develop these guidelines and to promote training course for CT.

53. Spontaneous Reporting of Hepatotoxicity: Data from the Serbian Pharmacovigilance Database

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Introduction: Many drugs may cause hepatotoxicity ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. This safety issue is the major reason for regulatory measures, including drug withdrawal.[1,2] Since hepatotoxicity is a rare and usually unpredictable adverse drug reaction (ADR), postmarketing surveillance and spontaneous reporting are essential tools for its identification.

Aim: To determine drugs that were frequently reported with a suspicion of hepatotoxicity to the Serbian pharmacovigilance database (SPD).

Methods: We performed a retrospective observational study of the suspected ADRs reported to SPD from January 1995 to December 2008. The Medical Dictionary for Regulatory Activities (MedDRA) code was used to identify cases of hepatotoxicity (HC). All drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification code system. Due to a small number of reports instead of statistical analysis data were observed for patients' characteristics such as: age, sex, alcohol consumption, systemic diseases, and concomitant therapy.

Results: SPD contains the total number of 1804 reports submitted in the period 1995–2008. Trend for ADRś reporting over time was significantly increasing (102, 266, 337, 423 cases per each year respectively during 2005–2008). Retrieval of this database revealed 70 individual HC. In majority of selected cases (45.71%) an increase in the level of hepatic enzymes was reported, followed by hepatitis (20%), and unspecified hepatic reactions (hepatotoxicity, liver injury) (18.57%). In total, 81 drugs were reported on suspicion of hepatotoxicity. Drugs most frequently associated with hepatotoxicity were: antiinfectives for systemic use (AI), nervous system drugs (NSD) and herbal medicines (HM) (27.16%, 24.69% and 12.35% cases, respectively). The highest number of reports on hepatotoxicity in regards to drug class was recorded for AI among females older than 51 years (7), for NSD among males aged between 18 and 50 years (8), and for HM among females aged between 18 and 50 years (6). In 31 HC (44.29%) concomitant therapy was reported. Majority of patients (75.71%) recovered. However, four (5.71%) cases were fatal-suspected drugs were valproic acid (1), concomitantly used sevoflurane and heparine (2), and rituximab (1), whereas 11 (15.71%) cases required hospitalization. Hepatotoxicity accounted for 10.26% of the fatal cases of ADRs reported to SPD.

Conclusions: Our analysis suggested that varieties of drug classes were associated with hepatotoxicity. Antiinfectives for systemic use, nervous system drugs, and herbal medicines were three most common therapeutic agents reported for hepatotoxicity.

References

1. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003; 349: 474-85
2. Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Safety 2007; 30: 277-94

54. Evaluation of Medication Safety in Medical Inpatients With Three Different Prescription Support Solutions

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Background: Electronic prescribing and prescription support software (PSS) provide new opportunities for the evaluation and prevention of medication errors (ME).

Objectives: (1) To identify and quantify ME in medical inpatients. (2) To evaluate and compare the performance of different PSS in detecting ME.

Methods: Prospective cross-sectional analysis of current prescriptions in medical inpatients of a tertiary care hospital. We identified drug interactions using the PSS TheraOpt, Micromedex Drug-Reax and Pharmavista. Pharmavista only checks interactions for up to 8 concomitantly used drugs. TheraOpt also generates dose adjustment alerts based on individual age and renal function. The generated alerts were evaluated by expert discussion followed by recommendations when considered appropriate.

Results: We studied 100 patients with a median of 8 concomitant drugs. The total number of interactions in all patients and number for each severity grade (severe/moderate/mild) according to each PSS were as follows: TheraOpt 326 (9/104/213), Drug-Reax 362 (91/248/23), Pharmavista 53 (0/17/36). TheraOpt further recommended 31 dose adjustments and generated 221 additional warnings. Among all automatically generated alerts 34 interactions, 2 dose alerts and 8 additional warnings were considered as justified and sufficiently relevant to recommend prescription changes. We found 2 additional ME not detected by any PSS. Altogether 46 recommendations for medication changes were actually followed in 23 instances.

Conclusions: PSS can sensitively detect ME, but there are major differences in their functions and severity grading. Only a small proportion of all alerts were evaluated as clinically relevant. Lack of scientific evidence in complex individual patient care and common off-label use remain major challenges for PSS. The studied systems have great potential to reduce ME in clinical practice, but irrelevant alerts are frequent and should be reduced.

55. Risk of Incident Autoimmune Diseases After Hepatitis B Vaccination: A Large Cohort Study in the U.K. General Practice Research Database

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Background: A close temporal relationship between hepatitis B vaccination (HBVac) and several incident autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyalgia, glomerulonephritis, multiple sclerosis, polyradiculoneuropathy and type I diabetes mellitus has been documented in a number of case reports and case series. Several epidemiological studies have evaluated a possible link between HBVac and multiple sclerosis. However, studies on other autoimmune disorders following HBVac are sparse.

Objective: The purpose of the current study was therefore to further investigate such a possible association between HBVac and autoimmune diseases.

Methods: We conducted a historical cohort study in the population-based UK General Practice Research Database. We identified an exposed cohort of 38 277 patients between the age of 6 and 60 years and no prior history of rheumatoid diseases with a first-time recording of

HBVac. The date of the first HBVac was defined as the index date. We then identified an unexposed comparison cohort of 112 185 patients without HBVac, matched on age, gender, index date and practice to the exposed cohort. Within those cohorts we searched for incident cases of autoimmune diseases (rheumatoid arthritis, HLAB27 associated rheumatoid diseases, rheumatoid collagenoses, glomerulonephritis and polyradiculoneuritis) within 12 months after the index date.
Results: We found 23 patients with a first-time diagnosis of the studied autoimmune diseases within 12 months after the index date in the HBVac exposed cohort (absolute 12-month risk = 0.06%), vs. 55 such patients in the unexposed cohort (absolute 12-month risk = 0.05%). The relative risk associated with HBVac was 1.23 (95% confidence interval 0.75, 1.99). Additional analyses stratified on number of HBVac and different autoimmune disease groups also showed no significant association between HBVac and autoimmune diseases.
Conclusions: This study found no significant association between HBVac and the studied autoimmune diseases. Our results provide reassurance regarding ongoing safety concerns, particularly in light of the fact that several countries still have not implemented the World Health Organization's recommendation of universal HBVac because of such concerns.

56. Phynx: An Open-Source Software Solution Supporting Web-Based Patient-Level Data Review for Drug Safety Database Studies

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Background: Validation of patient-level information from automated medical databases in its clinical context is a key process for drug safety studies. This concerns initial signal evaluation in pharmacovigilance as well as formal pharmacoepidemiological studies.
Objective: To develop a software solution that supports management and clinical review of patient data from electronic medical records databases or claims databases for drug safety studies.
Methods: We used the open source software Talend Open Studio, MySQL Server, MySQL Connector, Java SE, Eclipse, Apache Tomcat and Adobe Flex 3 to build a system named Phynx that supports data management, and Web-based display and review of patient-level information in the individual clinical context. This system was applied to and tested with a dataset containing the complete information of 46 501 patients from the UK General Practice Research Database (GPRD).
Results: Our solution can be setup and customized with limited programming resources, and there is no extra cost for software. The initial load of the master patient index took approximately 1.5 seconds in a standard environment with a regular 100 mbit/s network. After initial master patient index load three separate fields are displayed simultaneously in one browser window:
1. Patient index from where individual patients can be selected for display of their detailed profile;
2. Detailed patient profiles showing all information for a selected patient in chronological order and with color markings according to the nature of the information,
3. Interactive reviewer field allowing external experts to save evaluations and comments via a common Web browser. Additional features include color-coding of patients in the index according to their review status and blinding of selected information such as drug exposure if necessary. Because we pre-generated patient profiles as XML objects and stored them on a server, the time to display a complete patient profile for the user in a standard environment was less than one second after selection from the patient index. Time to review the complete medical information of one patient with a longitudinal follow-up time of 5–10 years is approximately 5 min.
Conclusions: Phynx provides a flexible solution for patient-level review of electronic medical information from databases considering the individual clinical context. Access times are short, and the displayed information is structured in chronological order and visually attractive. Phynx can therefore make an important contribution to an efficient use of electronic medical information for signal evaluation in pharmacovigilance as well as for formal pharmacoepidemiological studies.

57. Eltroxin Formulation Change: the New Zealand Experience

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Background: In June 2007 a new approved formulation of Eltroxin, already available elsewhere, was distributed in New Zealand. Eltroxin was the only brand of levothyroxine approved, due to the market size and the funding mechanism for medicines. Of the total population (around 4 million), 70 000 patients require thyroxine replacement therapy. The NZPhvC which operates the national ADR monitoring system regularly receives reports associated with patients changing brands of medicines.
Results: The first spontaneous report of an adverse reaction to the new formulation was received in October 2007. By 31 August 2008, 663 reports were received (more than 15% of the reports expected in one year). Of these, 622 of the reports were received following media coverage in June 2008.
There were several clusters of suspected ADRs: rapid onset, nonspecific; rapid onset allergy type symptoms; slower onset thyroid disease type symptoms and a small group of unusual eye symptoms including eye pain and conjunctivitis.
Following introduction in November 2008 of an alternative brand of levothyroxine the number of reports declined dramatically (177 in October 2008 to 21 in November 2008).
Discussion: It became evident that various networks were influencing the level of spontaneous reporting. These networks included healthcare professional blogs, community internet support groups and media activities. There was no evidence of a quality issue or problem in other countries.
Outcome: The introduction of choice by approval of an alternative brand of levothyroxine reduced the number of suspected adverse reactions and allayed concerns within the affected population. Initially the market share of the alternative brand reached 80%, however by March 2009 the market share had dropped. Currently 60% of patients requiring levothyroxine are taking Eltroxin. Although no convincing explanation for the root cause for the events reported has been identified, factors that may have had influence on the scenario include: lack of choice; previous sensitivity to brand switch problems; direct to consumer advertising of medicines and the potential for propagation of misinformation.

58. Angioedema Associated with Angiotensin-II Receptor Blockers: A DoTS Classification and Analysis

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Background: Angioedema is a rare serious adverse reaction to angiotensin-converting enzyme inhibitors (ACE-I), with an incidence

of 0.1–1.0%.[1] Debate exists over the safety of switching to an angiotensin-II receptor blocker (ARB), due to case reports of angioedema.[2]

Aim: To systematically examine published case reports of ARB-associated angioedema using the DoTS classification system.[3]

Methods: Published case reports of ARB-induced angioedema from January 1966 to January 2009 were identified using MEDLINE. Bibliographies of all retrieved case reports were used to identify any additional cases.

Information on age, gender, ethnicity, ARB regimen, duration of ARB therapy, severity of angioedema, prior use of ACE-I, rechallenge, history of angioedema, known allergies, co-morbidities, and concomitant medication was abstracted from individual case reports. Dose data for different ARBs were normalised and expressed using multiples of the Defined Daily Dose (DDD) for each drug.[4]

Results: Thirty-six case reports were retrieved: candesartan (2), irbesartan (2), losartan (25), olmesartan (1), telmisartan (1), valsartan (5). ARB dose information was available for 31 case reports. Sixty-eight percent of cases occurred at the DDD. Five cases of angioedema occurred below the DDD; one case occurred at 4 times the DDD (table I). ARB-induced angioedema occurred within hours of administration or up to a year (median onset 19 days).

Female patients accounted for 78% of the reports of angioedema. Age ranged from 27 to 81 years (median 59 years). In 81% of cases the ethnicity of the patient was unspecified. Prior use of an ACE-I was present in 12 cases, with eight cases having previous ACE-I-induced angioedema.

Conclusions: ARB-induced angioedema is a collateral time independent reaction. Gender and prior ACE-I-induced angioedema appear to be susceptibility factors for the development of ARB-induced angioedema. The DoTS classification system served as a useful template for the analysis of published case reports.

Table I. A dose-time susceptibility analysis of 36 case reports of ARB-induced angioedema

Multiple of Defined Daily Dose (N)	Time (N)	Susceptibility	
		Age (N)	Gender (N)
0.5 (5)	<24 h (7)	<30 (1)	Female (28)
1 (21)	<7 days (6)	30–44 (3)	Male (8)
2 (4)	7 days–1 month (8)	45–59 (14)	
3 (0)	1–6 month (7)	60–74 (17)	
4 (1)	6 month–1 y (5)	75–89 (1)	
	>1 y (3)	>90 (0)	

References

1. Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med 2004; 164: 910-3

2. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? Drug Safety 2002; 25 (2): 73-6

3. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327:1222-5

4. WHO. (2008) About the ATC/DDD system. WHO Collaborating Centre for Drug Statistics Methodology [online]. Available from: http://www.whocc.no/atcddd/ [Accessed 14 Jan 2009]

59. Spontaneous Ejaculation with the Use of ADHD Drugs

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Background: Methylphenidate and atomoxetine are indicated for treatment of attention deficit-hyperactivity disorder (ADHD). The Netherlands Pharmacovigilance Centre Lareb received two reports of spontaneous ejaculation associated with the use of these drugs.

Objective: To describe two case reports of spontaneous ejaculation associated with the use of methylphenidate and atomoxetine. In addition, a suggestion for a possible mechanism is provided.

Methods: A search of spontaneous reports received by the Netherlands Pharmacovigilance Centre Lareb between January 1996 and May 2009. Medline search of the published literature.

Results: Lareb received two reports of spontaneous ejaculation associated with the use of these drugs. The first report from a psychiatrist concerns a 40-year-old male who receives atomoxetine for ADHD. Three weeks after start, he develops spontaneous ejaculations following micturition urgency up to eight times a day. There were no sexual feelings. In the past, the patient used dexamphetamine, which gave also spontaneous ejaculations. The patient recovered after dexamphetamine and atomoxetine withdrawal. Concomitant medication is not reported. The second report from a consumer concerns a 25-year-old male who experiences spontaneous ejaculation following testicular cramps after micturition with the use of methylphenidate. Sexual feelings are not present. The spontaneous ejaculations are mainly present in times of stress and fatigue. Concomitant medication is not reported. Past drug therapy included atomoxetine which gave also spontaneous ejaculations following micturition. At the time of reporting, the patient is still using methylphenidate and is still having testicular cramps and spontaneous ejaculations.

Discussion: Atomoxetine is a norepinephrine reuptake inhibitor. Methylphenidate and dexamphetamine are amphetamines, who act as reuptake inhibitors of norepinephrine, serotonin and dopamine. The exact mechanism of these drugs on ADHD is not clear.[1] Ejaculation is a complex mechanism with a central and peripheral pathway. The peripheral pathway is adrenergic and mainly facilitated by norepinephrine. Also, adrenergic activity may decrease ejaculatory latency and induce spontaneous ejaculation.[2] Through the inhibition of the reuptake of noradrenalin spontaneous ejaculation can occur. In literature, a few cases are described concerning spontaneous ejaculation with the use of milnacipran,[3] reboxetine[2] and zotepine[4] due to a norepinephrine-reuptake effect.

Conclusion: The two case reports illustrate a new possible adverse drug reaction of spontaneous ejaculations with the use of methylphenidate and atomoxetine which may be mediated by to the re-uptake inhibition of norepinephrine. Physicians should be aware of the possibility of these drugs to cause spontaneous ejaculations.

References

1. Dutch SmPCs Strattera® and Ritalin®. www cbg-meb nl 2009 April 29

2. Sivrioglu EY, Topaloglu VC, Sarandol A, et al. Reboxetine induced erectile dysfunction and spontaneous ejaculation during defecation and micturition. Prog Neuropsychopharmacol Biol Psychiatry 2007 Mar 30; 31 (2): 548-50

3. Yoshida K, Higuchi H, Takahashi H, et al. Ejaculation after defecation without orgasm induced by milnacipran. J Neuropsychiatry Clin Neurosci 2004; 16 (4): 544

4. Wang PW, Wang SY, Huang CJ. Zotepine-induced spontaneous ejaculation. Int J Clin Pharmacol Ther 2008 Nov; 46 (11): 571-3

60. Surveillance of Adverse Events Following HPV Vaccination

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Background: A national immunisation program for human papillomavirus (HPV) started in Italy in 2008. The HPV vaccine offer is free and active for female adolescents in the twelfth year of life. Some Regions has extended the HPV vaccine offer to other cohorts, free or in co-payment. The vaccine is however available at pharmacies with a doctor's prescription. Around 400 000 doses of Gardasil and 310 000 of Cervarix were administered in Italy during 2008. Spontaneous reporting rate in Italy was 2,4 reports/million doses.
Objectives: To carry out a surveillance of common and rare adverse events on 9-26 years old women receiving HPV vaccine.
Methods: The study population is represented by all the women who will go to the local health units for HPV vaccine (Gardasil or Cervarix) administration (either free active offer and co-payment) and will give their consent to participation. Common adverse events are collected for each woman receiving the HPV-vaccine by questionnaires filled in at enrolment, at each dose administration and, by phone, after the last dose. A specific web platform will be created to enter data at regional level. Rare adverse events are evaluated by hospitalization and mortality archives following HPV vaccination. Pharmaceutical prescription archives are used to estimate the prevalence of drugs' use in the period following HPV vaccination.
Results: Fourteen Italian Regions accepted to participate to the study. The inclusion criteria for the regional participation are the capability of recording vaccination and follow up data in an electronic standard format and transmitting them via web. A first analysis of the data gathered through the surveillance is planned at the beginning of September.
Conclusions: As all vaccines, in particular for new vaccines, the adverse events surveillance represents an essential step of the evaluation of a vaccination programme.

61. Risk of Oxatomide Overdose in Children in Italy

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Background: Oxatomide is a second generation antihistamine largely used in Italy for the symptomatic treatment and prevention of allergic reactions. The drug is indicated for children of any age at the recommended dosage of 0.5 mg/kg twice a day. In 2008 around 750 000 packages of oxatomide containing products were sold in Italy. Two different oral liquid formulations, containing 0.25% and 2.5% of active principle, are marketed in Italy. Serious adverse reactions due to overdose were reported in children.
Objective: To evaluate the risk of adverse reaction associated with oxatomide overdose and to investigate the possible role of dosage error and accidental ingestion.
Methods: Two different surveys were conducted in Italy. All spontaneous reports reported to the National Pharmacovigilance System during the period January 2001 trough May 2009 were reviewed. Furthermore, a special surveillance is being carried out since May 2009 on children visiting the Emergency Department of four hospitals participating in a Multicenter Study on Adverse Drug Reactions in Children. Admission for any cause related to oxatomide exposure are considered of interest. An ad hoc questionnaire was set up and special attention is placed on the modalities of assumption (indication, dose, duration of use).
Results: Eleven serious cases of suspected adverse reactions associated with oxatomide, many of which of overdose, were reported in children ≤5 years to the Pharmacovigilance System. Among the reported ADRs were dyskinetic neurological reactions, such as muscular weakness, and incoordination; cases of somnolence, aphasia and QT prolongation were also reported. Thirty four cases of neurological disorders associated with oxatomide use were enrolled in the Multicenter Study on Adverse Drug Reactions in Children. The diagnosis, that required hospital admission, were apyretic convulsions, syncope and dizziness, somnolence, peripheral neuropathy, extrapyramidal symptoms. In some cases mistaken doses (overdoses) were attributed to great similarity of the two marketed oral liquid formulations. An interim analysis of the data gathered through the special surveillance is planned at the end of August.
Conclusions: Overdose is confirmed as a cause of adverse reactions related to oxatomide use in children, for incorrect dose administered and accidental ingestion.

62. A "Decalogue" to Inform Consumers on Risks Associated with Natural Health Products

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Background: Natural health products are promoted to the public as safe, because "natural", and are often used as self medication even if used to treat health conditions, that would require a diagnosis and a treatment prescribed by a physician.
Objective: To inform consumers on risks associated with use of natural health products, and to underline the opportunity in consulting medical professionals to treat health conditions.
Methods: A leaflet to inform consumers on complementary and alternative medicine and the possible risks associated with its use was issued by the Italian National Institute of Health, in collaboration with the Natural Centre for Natural Medicine, S. Giuseppe Hospital in Empoli and the Italian Society of Pharmacology. The content was signed by more than 30 associations of complementary alternative medicine.
Results: The main messages of the leaflet are: to search always advise from expert medical doctors when using complementary alternative medicine; to inform always the doctor or the pharmacist about use of natural health products; not to leave effective treatments in favour of not proved non conventional therapies.
Conclusions: The leaflet will be used to promote an information campaign addressed to consumers, conducted in pharmacies, physicians offices, etc.

63. Simulation of the Possible Effect of Nimesulide Withdrawal in Italy

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Background: In 2007, the Irish Medicines Board (IMB) was made aware of a retrospective review, performed by the Irish National Liver Transplant Unit, of three new cases of fulminant hepatic failure among

users of nimesulide. The IMB suspended the marketing authorisation of nimesulide in Ireland and opened a referral procedure at the EMEA. The possible withdrawal of nimesulide from the EU market, as a consequence of a greater risk of hepatopathies among users of nimesulide in comparison with other NSAIDs, was discussed. In assuming regulatory decisions, a comprehensive evaluation of the risk-benefit profile should always be conducted. In particular, the hepatotoxic risk of nimesulide should be analysed in the context of other potential risks, and specifically of the gastroduodenal damages, which represent the most frequent ADR related to NSAIDs use.

Objective: The aim of the presentation is to illustrate the results of a simulation we carried out in Italy, assuming the hypothesis of a possible nimesulide withdrawal from the market.

Methods: Data on NSAIDs use in Italy refer to 2006 and were derived from the Italian National Observatory for Pharmaceutical Use. Total DDDs and person-years of utilisation were calculated for each NSAID. We estimated person-years of specific NSAIDs use, in case of nimesulide withdrawal, assuming that nimesulide sales would be proportionally distributed among all the remaining NSAIDs in the Italian market. The expected figures of hospitalisation for hepatopathies and upper gastrointestinal bleedings, with and without the inclusion of nimesulide, were calculated according to two epidemiological studies.

Results: Around 2 300 000 person-years of NSAIDs, of which 1 066 000 of nimesulide, were used in Italy in 2006. With regard to liver injuries, a total number of 802 events could be estimated in 2006 (including nimesulide); the corresponding estimates in case of nimesulide withdrawal would be 564. The same procedures were adopted for estimating the expected number of gastrointestinal bleeding: the total number of events would be 13 540 with nimesulide and 17 491 without.

Conclusion: The results of the simulation suggest that the withdrawal of nimesulide might cause the prevention of 238 events of liver injuries and an increase of 3951 events of gastrointestinal bleeding (4.1 and 67.2 per million inhabitants, respectively). Our simulation helped to clarify the potential effects of nimesulide withdrawal in the Italian market. Similar exercises should always be conducted when the protection of citizens' health is at stake.

64. Standardised MedDRA® Queries (SMQs): Practical Approaches

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Standardised MedDRA Queries (SMQs) have been developed to facilitate retrieval of MedDRA coded cases by presenting a list of MedDRA terms related to a condition of interest (e.g., anaphylactic reaction). This presentation will describe the background of how SMQs have been developed and maintained to date and also provide practical advice on how SMQs might be applied in pharmacovigilance (e.g., safety signals) from a regulator and company perspective.

Standardised MedDRA Queries (SMQs) are the result of a joint effort between CIOMS (the Council for International Organizations of Medical Sciences) and the MedDRA Maintenance and Support Services Organization (representing ICH). They have been developed to facilitate retrieval of MedDRA coded cases in a consistent and standardized fashion by presenting a list of MedDRA terms related to a condition of interest (e.g., anaphylactic reaction). They are especially useful in instances where relevant terms for the condition of interest are widely scattered throughout the MedDRA terminology. Besides being a standard approach, SMQs offer a number of options – such as ''narrow'' (high specificity) and ''broad'' (high sensitivity) search options. Another benefit is that SMQs are maintained and synchronized with MedDRA versions, thereby relieving the end user of the burden of upkeep. As the MedDRA user community becomes more familiar with SMQs, one question that often arises is – how do I use them? This presentation will provide practical advice on how SMQs might be applied in pharmacovigilance (e.g., safety signals) from a regulator and company perspective and what advantages they might offer to the user.

Reference

1. Pearson RK, Hauben M, Goldsmith DI, et al. Influence of the MedDRA((R)) hierarchy on pharmacovigilance data mining results. Int J Med Inform, 2009 Feb 18

65. Varenicline: Evaluation of the Utility of Spontaneous Consumer Reports of Suspected Adverse Effects Filed on Internet Sites

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Background: Concerns exist about a possible association between neuropsychiatric events and the smoking cessation drug varenicline (Champix®).[1] Reports of deaths in the media, and a Public Health Advisory notice from the FDA, prompted a number of varenicline users to leave reports of suspected adverse drug reactions (ADRs) on website forums and blogs.

Objectives: To examine the utility of spontaneous consumer reports of suspected ADRs left on internet websites relating to the use of varenicline.

Methods: Websites were identified by searching for varenicline using the Technorati search engine. We harvested user comments from six websites on 28th February 2008. Comments were imported into Microsoft Access for further analysis. We analysed those comments that provided personal experiences of ADRs.

Reports were compared with the ICH's minimum criteria for a valid ADR case: an identifiable reporter, an identifiable patient, a reaction or event, and a suspected medicinal product. We used the DoTS system of classification to assess the nature of reports,[2] and examined challenge and dechallenge, and susceptibility factors, such as previous history of psychiatric events. We coded ADRs using MeDRA (*version 11.1*). Reports were also qualitatively analysed, using NVIVO software, to examine the patient experience.

Results: We found 370 patient reports of ADRs contained in 601 comments from the internet. Fourteen percent (n = 52) contained dechallenge information; only seven cases included rechallenge information. Thirty-four cases included the age of the patient (average 41.6, range 19–64). One hundred and thirty-seven cases reported they had stopped smoking. Onset time was recorded in 135 case reports, with an average onset time of 16.5 days (range 0–90 days). A psychiatric history was noted in 15% (n = 55) of patients.

Reported ADRs included depression, suicidal ideation, suicide attempts which have been noted post marketing, as well as other unlabelled reactions such as epistaxis, pathological gambling, joint pain, compulsive sexual behaviour, and withdrawal syndrome. Although two criteria for a valid ADR (a reaction/event and a suspected medicinal product) were met by cases, few reports provided sufficient information to provide an identifiable reporter or patient as defined by CIOMS.[3]

Conclusions: Internet users provide a rich source of material about suspected reactions, although they fail to provide identifiable reporters

or patients. However, monitoring of websites, particularly after major news stories about drugs may provide additional information for regulators and market authorisation holders.

References

1. Varenicline: safety update. Drug Safety Update 2008;1:3-4

2. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327:1222-5

3. Report of CIOMS Working Group V. Current Challenges in Pharmacovigilance: Pragmatic Approaches. Geneva: CIOMS, 2001

66. Pharmacovigilance and Drug Consultation for Health Professionals: Long-Term Experience at the Division of Clinical Pharmacology and Toxicology in Zurich, Switzerland

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Background: The Division of Clinical Pharmacology and Toxicology at the University Hospital Zurich is one of six regional pharmacovigilance centers in Switzerland. In this function we assess the causality of adverse drug reaction (ADR) reports according to CIOMS criteria and forward our evaluations to the national drug authority Swissmedic (Swiss Agency for Therapeutic Products), from where reports are further forwarded to the WHO's Monitoring Center in Uppsala, Sweden. Our division also receives and evaluates ADRs collected through the Swiss section of the AMSP project (drug safety in psychiatry). Furthermore, we are actively involved in patient care and drug therapy consultations for health care professionals supporting external physicians as well as those within the hospital.

Objective: To present an overview of the different services provided by our division.

Methods: Descriptive evaluation of our division's drug safety and therapy consultation activities between January 2003 and July 2008.

Results: During the study period we received and evaluated a total of 3010 ADR reports. Of those, 59.6% came from hospitals, 35.4% from office-based physicians, 2.5% from pharmacies, and 2.5% from other sources. These reports involved a total number of 3772 drugs. Given our continuous collaboration with the AMSP project antipsychotic agents were the drug class most frequently associated with ADR reports: olanzapine accounted for 3.9% of all reports, followed by quetiapine (2.7%), risperidone and clozapine (each 2.3%). We also made 133 follow-up evaluations of previous reports when new information about the case was available. As part of our pharmacotherapy consultation activities we performed 2438 consultations. 40.9% of those answered questions from external health professionals. Consultations between May 2007 and July 2008 were analyzed in more detail: of 694 inquiries, 55.5% originated from in-house physicians, and we performed 107 bedside consultations and 121 outpatient consultations. These were mainly related to the treatment of liver diseases and inflammatory bowel diseases, as well as to ADRs.

Conclusions: Today the Division of Clinical Pharmacology and Toxicology at the University Hospital Zurich is the regional pharmacovigilance center that produces the highest number of ADR reports in a national comparison. Our division also provides a range of other services relating to all issues of drug safety and pharmacotherapy, which are frequently used by internal and external physicians, and it appears that particularly the combination of both, pharmacovigilance as well as general pharmacotherapy services, is the foundation for a high number of referrals to our center.

67. Drug Prescription Before and During Pregnancy in South West of France: A Study of Drugs Inducing Abnormalities

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Introduction: Several studies have shown that women of childbearing age use drugs which could induce birth defects if they are consumed during pregnancy (for instance: antiepileptic drugs, non-steroidal anti-inflammatory drugs -NSAIDS).

Aim: To compare prescription of some teratogenic or fcetotoxic drugs which are contraindicated or must be avoided in pregnant women before and during pregnancy.

Methods: The present study analyzed pharmacy records of women who gave birth between January 1st, 2007 and December 31st, 2007 in Midi-Pyrenees and who were registered in the French Health Insurance Service. Pharmacy data were analyzed from nine months before pregnancy until delivery. Drugs were classified according to the Anatomical Therapeutic Chemical code.

Results: The study included 23 898 women who gave birth in 2007. About 77% of the women received at least one prescription before pregnancy and 92% during pregnancy. The number of women who were prescribed contraindicated drugs dramatically decreased before pregnancy (retinoid 63 vs 374, angiotensin converting enzymes 36 vs 73, NSAIDS 3219 vs 10641 and valproic acid 51 vs 85, $p < 0.0001$). Most of the drugs were stopped during the three months before pregnancy without alternative treatment even for chronic diseases. However, for some women, potentially dangerous prescriptions were maintained during pregnancy and for others women, these drugs were dispensed for the first time during critical periods of pregnancy.

Conclusion: Prescriptions of drugs which are contraindicated or avoided during pregnancy decrease when women become pregnant but, despite recommendations, some teratogenic and/or fcetotoxic drugs are always dispensed to pregnant women. As many pregnancies are unplanned, the choice of drugs for childbearing women must be evaluated with more caution.

68. Effectiveness of Proactive-Approach in a Pharmacovigilance Unit: Review and Analysis of 1729 Notifications Received

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Introduction: In Argentina, National Network of Pharmacovigilance was created in 1993 centered in the the national regulatory agency with peripheral nodes. Our node, created in 1998, changed its structure in 2004. Proactive approach was established since 2006, in addition to the registration of spontaneous reports. Notifications are incorporated into a database, and then sent to ANMAT.

Methods: The notifications are incorporated into a database (SQL), in addition to being sent to ANMAT. We describe the notifications received (demographics and types of events reported; side effects, ineffectiveness or failure of quality) and the result of the intervention of analytical INAME, when it was required.

Results: From November 2004 to May 2009 1729 notifications corresponding to 1743 drugs were received. There was no differents between sex, with a low proportion of pediatric patients (1.11%) and high proportion of ederly (>65 years) patients (36.09%). Most corresponded to adverse effects (93%), followed by cases of lack of efficacy (7%). The degree of severity was mild in the majority (76.7%), followed by severe (12.8%) and moderate (10.5). The largest categories of drugs involved in adverse effects were antimicrobials (31%), drugs for cardiovascular disorders (20%),drugs for CNS disorders (15%), and antineoplastics (8%). Among cases of lack of efficacy the most frequently involved were drugs used in anesthesia and CNS disorders (23%) followed by antimicrobials (19%), drugs for cardiovascular disorders (18%), and NSAIDs (12%). All samples of products involved in notifications of failure of efficacy or quality were sent to the National Institute of Medicines (INAME). Strikingly all but one case (early in 2008) were subjected to quantitative analysis and reported as ''meets the specifications.'' The presence of old people and groups involved in drug side effects is consistent with data from other pharmacovigilance studies. In the cases of lack of efficacy reports the marked difference between the perception of prescribers/notifiers and current analytical assessment probably requires additional studies to verify or exclude the reported event.

Discussion: The unit obtained a gradual and sustained increase in the number of notifications received by adopting a proactive approach. Possible causes of lack of notification by the health professionals seem to include ignorance, fear, lack of time, lack of incorporation of the drug, and lack of necessary data, among others. The proactive approach allows the systematic inculcation of side effects and effectiveness evaluation as part of the activity.

69. Economic Impact of Switchback from Generic to Brand-Name Drugs: Example of Allopurinol

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Background: For economic reasons, generic substitution has been authorized in France since 1990. Sometimes, generic substitution is not maintained in chronic treatments. This non-continuation of substitution is a possible economic loss for the Health Insurance system.

Objective: To estimate the economic impact of the switchback from generic to brand-name drug, using the chronic treatment of gout with allopurinol as an example.

Methods: In a cohort of 3404 patients identified from the database of the Health Insurance system, reimbursement of brand-name (BN) and generic (G) allopurinol was followed-up for one year. From the data gathered in this survey using the different reimbursement schemes by the National Health Insurance system, a follow-up of patients treated for one year by allopurinol 100 mg/day was conducted. In 2008, the cost of BN allopurinol was 1.91€ and 1.66€ for G per box of 28 tablets.

Results: During the survey, 38,446 allopurinol boxes were reimbursed (83% G). 11.6% (394/3404) of the patients used only BN allopurinol throughout the year and 7% (238/3404) did not maintain G substitution and returned to BN drug. The following treatment patterns and costs could be hypothesized in the cohort:

First hypothesis: all patients took BN allopurinol for one year; overall cost: 78 019.68€/year.

Second hypothesis: all patients took G allopurinol for one year; cost: 67 807.68€/year (−15% compared with 1st hypothesis).

Third hypothesis: 394 patients took BN allopurinol and 3,010 G for one year; cost: 68 989.68€/year (−13% compared with 1st hypothesis).

Fourth hypothesis (non-continuation of substitution): 394 patients took BN allopurinol, 238 patients were 6 months on G and 6 months on BN and 2772 took a G for one year; cost: 69 346.68€ (−12.5% compared with 1st hypothesis).

Conclusion: Under these simulations, the non-continuation of generic substitution has a weak economic impact on reimbursement cost for French Health Insurance. However the choice of drugs influences largely the results; for example, when drugs with a narrow therapeutic index such as anti-epileptic drugs are chosen, the use of generics is significantly associated with increased overall medical costs compared to BN anti-epileptic use.[1] Therefore, pharmaco-economic models should be devised and applied so as to define the threshold value where substitution is no longer cost-efficient.

Reference

1. LeLorier J, Duh MS, Paradis PE, et al. Econonomic impact of generic substitution of lamotrigine: projected costs in the US using findings in a Canadian setting. Curr Med Res Opin 2008; 24: 1069-81

70. Reasons for Switchback from Generic to Brand-Name Drugs in a Cohort of Patients Treated by Allopurinol

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Background: The substitution of generic drugs (GD) for brand-name drugs (BND) is a source of errors (confusion, duplication, poor compliance…) and adverse effects, especially in the elderly. Sometimes, during a chronic treatment with GD, patients do not remain on generic and switchback to the BND. The Health Insurance system obviously tends to avoid this situation in order to minimize drug spending.

Objective: To evaluate reasons for switchback from generic to BND, using the chronic treatment of gout with allopurinol as an example.

Method: Patients from the Health Insurance database of the Limousin Region (Centre of France), with an initial prescription of allopurinol, were enrolled in a cohort study (2005–2007). The allopurinol prescription for each patient was followed up for one year. When substitution from GD to BND was detected, the patient, the physician and the pharmacist were questioned on the reasons for this change (response rate: 50%). A qualitative and quantitative analysis of the responses was conducted.

Results: The cohort was composed of 3404 patients (70.3% men), aged 68.7 ± 13.5 years; 3010 (88.4%) patients used at least one GD. The substitution GD to BND was encountered in 238 cases (7% of patients). Only 192 switches were completely analysed, encompassing 426 reasons (2.2 reasons/switch) but 1 reason/switch was evoked by each protagonist. Reasons for not remaining on a GD were various and opposed between the three protagonists. For example, the opposition of a patient to substitution was the first reason mentioned by pharmacists (72%), but this reason was evoked by only 7.5% of patients and by 5.5% of physicians. The ignorance of the drug actually delivered by pharmacists was the main reason evoked by physicians (39.1%). The first reason evoked by all three protagonists was the free choice of the drug by pharmacists. Adverse drug effects was the fifth reason evoked by all protagonists and mentioned essentially by physicians and patients, but twice less by pharmacists. Adverse drug effects reported with GD were nausea, diarrhoea, digestive pain, headache, allergic disorders. Patients mentioned most often poor compliance, confusion and suspicion of poor efficacy of the generic.

Conclusion: This study is the first one which compares opinions from patients, physicians and pharmacists within a substitution setting. Reasons for switching drugs were various and at times opposed, between the three protagonists. Therefore, information, inter-relations between health providers and with patients, and traceability, are the mainstay of a safe and protracted use of generic drugs.

71. Cost-Effectiveness of Two Approaches Pharmacovigilancia: Pro-Active Versus Passive

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Introduction: In Argentina, the national pharmacovigilance system has had a slow but steady increase in the number of reports. There is a need of a ceaseless dissemination and motivation to health professionals because there were fewer reports than expected, which is not an isolated phenomenon of Argentina. In the meantime the problems associated with the use of drugs like adverse events cause a high cost to the health system. The analysis of the reasons for this underreporting is a difficult research topic. However it can be corrected with the work of dissemination and education to health professionals through a ''Pro-Active'' approach. These actions involve '' be closer to the health professionals'' unlike the traditional approach of ''passive'' pharmacovigilance waiting for spontaneous reporting. It is not known the true cost-effectiveness of this approach.

Methods: The unit quantifies the economic costs of different approaches to pharmacovigilance and the results in terms of quantity and quality of service received at the end of one year.

Results: The results show a notable increase in the quantity and quality of submissions received as a result of a proactive approach. Some additional benefits have not been quantified. These are the effect of direct contact with doctors.

Discussion: While the analysis and comparison of costs and profits obtained by a passive and pro-active approachs can be difficult to quantify, it is clear the benefits derived from pro-active approach. This approach should be promoted as a way to improve pharmacovigilance systems.

72. Analysis of NAT2 Acetylation Genotype and Phenotype in Children Under Isoniazid Treatment in Argentine

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Introduction: Isoniazid is metabolized by the genetically polymorphic (NAT2). Diverse alleles are related to increased or decreased acetylation capacity and in some reports to low efficacy and toxicity of isoniazid. Polymorphic NAT2 is also involved in the metabolism of several compounds relevant in pharmacology or toxicology, with diverse clinical consequences.

Methods: Arylamine N-acetyltranferase 2 (NAT2) genotype and phenotype was studied in 50 children with tuberculosis treatment or chemoprevention after administration of isoniazid. The genetic profile of the NAT2 gene, the most frequent NAT2 alleles, and genotype classiffication as slow or fast acetylator in children will be described. Isoniazid acetylation metabolic ratio (MR) will be calculated as the molar acetylisoniazid to isoniazid concentration ratio and will be used as a probe for N-acetyltransferase activity and to determine the acetylation phenotype. MR distribution with be described as percentage of slow ($MR < 0.48$), intermediate ($0.48 < MR > 0.77$) or fast ($MR > 0.77$) acetylators at different age. The cumulative frequency of fast acetylators will be described in function of age to calculate maturation of isoniazid acetylation period of age. The concordance between genotype a phenotype of NAT2 acetylation will be described.

Results: We found a significant percentage of the population with low rate of acetylattion genotype. Children presents acetylation phenotype changes depending on age, showing a maturation process. In individuals younger than 4 years regardless of their acetylation genotype, the immaturity of NAT2 system generates high concentrations of isoniazid.

Discussion: An impaired isoniazid elimination could be present in children, specially in children less than four years old, which may be in favour of an individual dose adjustment in this population. This finding will have implications in the determination of nationwide policies for use of appropriate anti-tuberculosis drugs.

73. Intussusception in an Infant Vaccined by Rotarix*

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Introduction: A rotavirus infection can lead to serious vomiting and diarrhoea in very young population up to lethal dehydration. In developed countries, main consequences are economic, while in developing countries, according to the study of Coluchi N. of Paraguay Public Health Laboratory,[1] more than 125 million cases of rotavirus diarrhoea have been estimated to occur annually in children under the age of 5 years and as many as 873 000 cases lead to death. In both contexts a safety and effective vaccine provide a real benefit to industries. The first oral rotavirus vaccine, Rotashield® (an oral live attenuated tetravalent (G1, G2, G3, G4) vaccine which derived from monkey) was available for USA in 1998 and withdraw after an increase of intussusceptions in infants. Until now no mechanism has explained the relationship between Rotashield® and intussusceptions. Thereafter two other oral vaccines have been commercialised: Rotarix® (monovalent live attenuated human vaccine) and Rotateq® (pentavalent live attenuated bovine and human vaccine). They presented fewer adverse effects during the second phase of clinical trials than Rotashield®.

Case study: A male infant born on the 15/05/2008 was hospitalised the 07/07/2008 because of vomiting beginning 06/07/2008 and bloody stools from 06/07/2008 until 07/07/2008. The scan presented a right ileo-caeco colic intussusception. He underwent surgery on the 07/07/2008 leading to a fast and complete regression of the pathology. This infant, without any medical history and any regular treatment, received a first oral dose of Rotarix on the 30/06/2008, so just one week before the symptoms began.

Discussion: During clinical trials, new rotavirus vaccine (Rotarix® and Rotateq®) didn't showed more intussusceptions than placebo, however their administration is contra-indicated in case of intussusceptions predisposition or previous intussusceptions. The intussusceptions physiopathology isn't defined yet, but scientific community tend to blame inflammation factors and pre-existent infections. In the present case, the infant was one and a half months old, while usually most acute intussusception is expected around 6 months old and he didn't present any risk factors to develop such a digestive suffer. The Lille's pharmacovigilance center imputed this case C2S3B3 (so I3B3). That's why it's important to warn carers about this effect and to encourage them to declare the acute intussusceptions that they could diagnose.

Conclusion: Since nothing can put in evidence to one or more elements contributing intussusceptions, nor distinguish spontaneous intussusceptions, chronology study of symptoms occurring in infants, drive us to consider Rotarix® vaccination as the responsible factor of the intussusception.

Reference

1. Coluchi N, Munford V, Manzur J, et al. Detection, subgroup specificity, and genotype diversity of rotavirus strains in children with acute diarrhea in paraguay. J Clin Microbiol 2002; 40: 1709-14

74. Acute Pancreatitis Induced By VELCADE (Bortezomib) with Positive Rechallenge

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Introduction: VELCADE (bortezomib) was indicated as monotherapy for treatment of multiple myeloma. Until now, no case of pancreatitis related to bortezomib has been published in the international literature.

Aim: We describe a case of pancreatitis related to bortezomib with positive rechallenge declared to Regional Pharmacovigilance Center of Saint-Antoine hospital (Paris, France).

Case summary: A 58-year-old female with a medical history of myeloma treated with VAD protocol (vincristine, adriamycine and dexamethasone). She underwent a cholecystectomy in 2005. She had no dyslipedimia or alcohol abuse. She received two doses of Velcade® (1.8 mg) by intravenous route on 09-Aug-2007 and on 13-Aug-2007. Concomitant treatment included: dexamethasone, levothyroxin, zolpidem, bromazepam, propoxyphene, and paracetamol. On 15-Aug-2008, she experienced abdominal pain. Examination was normal except periumbilical sensibility. Biologic work-up showed hyperlipasemia at 493 UI/L (normal value <200 IU/L) but all the other biologic parameters assessed were within normal range. The diagnosis of acute pancreatitis was suspected. A MRI-Cholangiopancreatography showed normal pancreatic and biliary tracts. Serum lipases levels decreased progressively to 419 IU/L on 17-Aug-2007 and to 256 IU/L on 21-Aug-2007. Dexamethasone and concomitant treatments were further administered without recurrence. On 21-Aug-2007, the patient received again Velcade® and she developed a second episode of acute pancreatitis with high serum lipases levels (477 IU/L). She improved quickly after Velcade® withdrawal. The combination of the following arguments: a positive re-challenge with Velcade® therapy with the absence of history of dyslipidemia, alcohol abuse and pancreatic malformation allow the responsibility of Velcade® to be considered as likely.

Conclusion: The patient was discharged with the diagnosis of acute pancreatitis induced by VELCADE (Bortezomib). No other cause was found. In this case, the authors estimated the causal relationship as 'likely'.

75. Erythroblastopenia Induced By Di-hydan® (Phenytoine): Case Report

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Introduction: Phenytoin, one of the most common antiepileptic drugs, erythroblastopenia is a rare side effect of phenytoin treatment.

Aim: We report a case of erythroblastopenia confirmed by myelogram associated with Di-hydan® (phenytoine) treatment declared to Regional Pharmacovigilance Center of Saint-Antoine hospital (Paris, France).

Case report: A 59-yera-old female patient with history of hiatus hernia, allergic rhinitis, repeating bronchititis, penicillin allergy and cirrhosis C (with episode of edemato-ascitic decompensation) but without alcohol or tobacco abuse. She was hospitalized on 12-Jul-2007 for convulsive status epilepticus in intensive care unit. She was treated with levetiracetam, clobazam, phenobarbital, lamotrigine, pantoprazole, spironolactone, furosemide, hydroxyzine and paracetamol. Due to persistent status epilepticus, levetiracetam and Phenobarbital were stopped and Di-hydan® (phenytoine) was initiated in combination with lamotrigine. Seizure disappeared but she experienced fever and amoxicilline was initiated. On 09-Aug-2007, she was transferred to internal medicine department. Examination showed no particularity except impairment of health status and dyspnea related to pleurisy. Moderate abnormal liver function tests were present and related to cirrhosis. Blood culture and pleural puncture were negative. Serologic tests for viral B hepatitis, HIV, EBV and HHV-8 were negative. A complete blood count performed on 09-Aug-2007 showed pancytopenia (hemoglobin: 10.4 g/dL, WBC count: 2900/mm^3 and platelets: 52 000/mm^3). Another complete blood count performed on 13-Aug-2007 confirmed the pancytopenia (hemoglobin: 8.2 g/dL, WBC count: 3100/mm^3 and platelets: 39 000/mm^3). The myelogram disclosed erythroblastopenia with no erythroblast (0%), many megakaryocytes and a partial blockade of granulocytic maturity (eosinophilia and basophilia with hypergranular aspect of granulocytes) compatible with drug toxicity. Phenytoin was suspected and was stopped immediately. She was switched to lamotrigine and gabapentine. She received two packed of red blood cells, seven platelet units, and immune globulins by intravenous route, hematopoietic growth factor, folic acid and vitamin B12 supplementation. On 30-Aug-2007, the complete blood count improved dramatically and normalized on 04-Sep-2007 (hemoglobin: 12.6 g/dL, WBC count: 17 100/mm^3 and platelets: 236 000/mm^3. She was discharged from hospital on 04-Sep-2007 with the following treatment including: lamotrigine, gabapentine, lactulose, metronidazole, terbutaline, heparine and albumine.

Conclusion: The patient was discharged with the diagnosis of of erythroblastopenia induced by Di-hydan® (phenytoine) treatment. No other cause was found. In this case, the authors estimated the causal relationship as 'probable'.

76. Hemolytic Uremic Syndrome During Gemcitabine Treatment

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Introduction: Hemolytic Uremic Syndrome (HUS) may be associated with a variety of etiologies, and chemotherapeutic agents have also been reported to be associated with HUS, and most recently Gemcitabine.

Aim: We report a case of HUS related to Gemcitabine treatment declared to Regional Pharmacovigilance Center of Saint-Antoine hospital (Paris, France).

Case report: A 47-year-old male patient with history of pancreatic adenocarcinoma diagnosed in April 2004 which was surgically treated (cephalo-duodenopancreatectomy). He received several cycles of chimiotherapy including Gemcitabine and oxaliplatine from 12-Jul-2004 to 27-Sept-2004. The cumulative dose of Gemcitabine was 10.6 g before starting radiotherapy from 25-Oct-2004 to 22-Nov-2004. In March 2006, the patient developed a loco-regional recurrence with hepatic metastasis and he received new cycles of chimiotherapy with Gemcitabine from 26-Apr-2006 to 17-Oct-2006. The cumulative dose of Gemcitabine was 43.6 g (from July 2004 to October 2006). In October 2006, a biologic work-up showed anemia and thrombocytopenia. On 24-Oct-

2006, the patient was hospitalized due to suspicion of HUS. Examination showed no particularity except hypertension (181/105 mmHg). Biologic analysis showed: Hb (6.9 g/dL), platelets (104000), creatininemia (133 μmol/L), haptoglobine level (< 0.08 g/L), LDH (685), bilirubine level was normal, schizocytes (1.6%) and reticulocytes (30 000).
The diagnosis of HUS was hardly suspected but etiologic research was negative. The patient was treated with plasma infusion, antihypertensive drugs. The renal puncture-biopsy performed on 27-Oct-2006 showed chronic thrombotic micro-angiopathy lesion that evoked the toxic origin. The diagnosis of HUS related to Gemcitabine treatment was retained. On 03-Nov-2006, the biologic examination control showed: Hb (8.1 g/dL), platelets (210 000), creatininemia (193 μmol/L), haptoglobine level (0.17 g/L), LDH (350), bilirubine level was normal, and reticulocytes at 102 000. No schizocytes.
He was discharged from hospital the same day with antihypertensive treatment. On 21-Nov-2006, the patient was hospitalized again for a new episode with hypertension at 180/100 mmHg, anemia with Hb at 6.7 g/dL, thrombopenia at 60 000, creatininemia at 193 μmol/L, haptoglobine level at <0.08 g/L, LDH at 605, bilirubine level was normal, reticulocytes at 167 000 and no schizocytes. The patient was treated with plasma infusion, antihypertensive drugs. He improved progressively with normalized blood pressure (138/86 mmHg), and Hb at 8.3 g/dL, platelet at 179 000, creatininemia at 176 μmol/L, and the patient was discharged with antihypertensive drugs.
Conclusion: The patient was discharged with the diagnosis of HUS related to Gemcitabine treatment. No other cause was found. In this case, the authors estimated the causal relationship as 'possible'.

77. Reversible Acute Mixed-Type Liver Injury Related to TRACLEER® (Bosentan) Therapy

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Introduction: Tracleer® (bosentan) is a competitive antagonist of endotheline-1; it is indicated in the treatment of pulmonary hypertension associated to sclerodermia without significative interstitial pathology.
Aim: We report the case of a patient who developed a reversible acute mixed-type of liver injury after starting Tracleer® (bosentan) therapy for pulmonary hypertension declared to Regional Pharmacovigilance Center of Saint-Antoine hospital (Paris, France).
Case report: A 56-year-old female patient with a medical history of type CREST sclerodermia since 2000, complicated with pulpal necrosis of the fourth left finger in Mars 2007, Gougerot Sjogren syndrome and severe Raynaud syndrome, no alcohol and tobacco abuse, received Tracleer® (bosentan) 125 mg two tablets daily and Cortancyl (prednisone) 5 mg, one tablet daily, initiated on unspecified date. She was hospitalized from 22-Aug-2007 to 24-Aug-2007 for hepatic cytolysis, which had been ongoing for one month when the patient developed jaundice with right hypochondrium pain. The biologic work up performed on 21-Aug-2007 showed cholestasis and hepatic cytolysis with ALAT (4.9 × ULN), ASAT (5.8 × ULN), AlP (1.2 × ULN), G-GT (8 × ULN) and total serum bilirubine (2 × ULN). Acute viral hepatitis were excluded (normal serologies). No inflammatory or infectious syndrome was detected. No cardiac dysfunction was noted. Abdominal ultrasonography showed normal liver and biliary tract. Mixed liver injury induced by Tracleer® (bosentan) was suspected, and it was stopped on 21-Aug-2007 but Cortancyl was continued. The patient improved quickly, the hepatic abnormality rapidly decreased on 24-Aug-2007 with ALAT (2.5 × ULN), ASAT (2.7 × ULN), PAL (1 × ULN), G-GT 150 (5 × ULN) and total serum bilirubine 26 (1.2 × ULN) and became normal on 29-Oct-2007 (ALAT 14, ASAT 20, PAL 65, G-GT 20 and total serum bilirubine 15).
Conclusion: Tracleer® (bosentan) was not restarted. The patient was discharged with the diagnosis of Tracleer® (bosentan)-induced acute mixed liver injury. No other cause was found. In this case, the authors estimated the causal relationship as 'probable'.

78. Agranulocytosis Associated With Ceftriaxone Treatment

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Introduction: Ceftriaxone, a third-generation cephalosporin, is a frequent choice for the treatment of infections because it has some advantages: a long half-life, a wide spectrum, a high tissue penetration rate, and a good safety profile. It was well known to induce biliary lithiasis but rarely hematological disorders.
Aim: We report a case of agranulocytosis associated with Ceftriaxone treatment declared to Regional Pharmacovigilance Center of Saint-Antoine hospital (Paris, France).
Case report: A 52-year-old male patient with a medical history of alcoholic cirrhosis, tabacco use and without chronic treatment. In October 2007, the patient was hospitalized for bilateral pyelonephritis and prostatitis followed by septicemia related to Echerichia-Coli infection. His examination was without particularity. No signs of liver failure nor signs of septic shock were present. On 30-Oct-2007, the patient was treated with Ceftriaxone. The biologic work-up especially the white blood cell (WBC) count showed a normal level of leucocytes at 6100/mm^3 including 55% of neutrophils (3380/mm^3). His infection state improved rapidly and he was discharged from hospital on 12-Nov-2007. On 15-Nov-2007, the patient was hospitalized again for malaise, nausea and vomiting. His examination was unchanged. However, his WBC count disclosed agranulocytosis (no neutrophil) and leucopenia (1600/mm^3). The patient was isolated. A myelogram performed the following day showed a promyelocytic blockage of the myeloid series. The diagnosis of agranulocytosis induced by Ceftriaxone was suspected. Ceftriaxone was discontinued and he received intravenous filgrastrim therapy. On 19-Nov-2007, the WBC count showed leucocytosis (22 100/mm^3) with 11 271/mm^3 neutrophils. He was followed in up to 6 months without recurrence.
Conclusion: The patient was discharged with the diagnosis of Ceftriaxone-induced agranulocytosis. No other cause was found. In this case, the authors estimated the causal relationship as 'probable'. Other similar cases have been reported. In view of these data, WBC count should be monitored in patients receiving prolonged courses of Ceftriaxone.

79. New Biomarkers for Predicting Anti-Tuberculosis Drug-Induced Hepatotoxicity in Tunisian Patients with Tuberculosis

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Introduction: Antituberculosis drug-induced hepatitis is the most serious problem in tuberculosis treatment. The enzyme N-acetyl-

transferase-2 (NAT2) metabolizes isoniazid in the liver so it is considered to cause hepatotoxicity. The association of polymorphic NAT2 acetylator status and antituberculosis drug-induced hepatitis is discussed.
Aim: To investigate an association between NAT2-haplotypes and adverse effects in Tunisian tuberculosis patients.
Methods: We studied 66 patients with tuberculosis (TB) treated with anti-TB drugs including INH. The frequencies and distributions of single nucleotide polymorphisms, haplotypes, and diplotypes of NAT2 were determined by the PCR-restriction fragment length polymorphism method,[1] and the results were compared between TB patients with and without adverse effect.
Results: 52 patients who did not develop hepatotoxicity were classified as the control group, and 14 patients who were diagnosed with antituberculosis drug-induced hepatotoxicity were classified as the study group.
Statistical analysis revealed that the frequency of a variant haplotype, NAT2*5B, was significantly increased in the study group, compared with those in the control group ($p = 0.04$). Moreover, the combined haplotypes with two mutant alleles NAT2*5A and NAT2*6A was statistically higher in the study group than in the control group ($p = 0.008$). By contrast, the frequency of a wild-type haplotype, NAT2*4, was significantly lower in the study group than in the control group ($p = 0.01$).
Conclusion: The present study shows that NAT2 is one of the determinants of anti-TB drug-induced hepatotoxicity. Moreover, the haplotypes NAT2*4 and NAT2*5B, and combined haplotypes NAT2*5A and NAT2*6A are useful new biomarkers for predicting anti- TB drug-induced hepatotoxicity.

Reference

1. Higuchi N, Tahara N, et al. NAT2*6A, a haplotype of the N - acetyltransferase 2 gene, is an important biomarker for risk of antituberculosis drug-induced hepatotoxicity in Japanese patients with tuberculosis. World J Gastroenterol 2007 December 7; 13 (45): 6003-8

80. Lenograstim-Induced Pyoderma Gangrenosum, an Unusual Side Effect

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Introduction: Pyoderma gangrenosum is a neutrophilic dermatose wich is manifested by intense dermal inflammatory infiltrates composed of neutrophils with little evidence of a primary vasculitis. Aetiology is yet unknown but it is felt to represent a manifestation of altered immunologic reactivity. Approximately 50% of cases of pyoderma gangrenosum are associated with a specific systemic disorder.[1,2] However, pyoderma gangrenosum developing after granulocyte colony stimulating factor administration in patients with solid tumours has been described in the literature and appears in the French summary of product characteristics.[3]
Methods: We report a case of Pyoderma gangrenosum following lenograstim injection spontaneously regressive after discontinuation.
Observation: Pyoderma gangrenosum developed in an 85-year-old woman on the fourth day of SC lenograstim therapy (administered at the dosage of 263 µg/day) for neutropenia following antineoplastic therapy (carboplatin and etoposide) to treat a Merkel cell carcinoma. She had antecedents of gastric tumour, adenocarcinoma, meningioma, angiolipoma, bleeding ulcer and intestinal polyp. Her usual medication included metoprolol, amiloride, omeprazole, allopurinol and atorvastatine. Inflammation of soft skin which started four days after lenograstim's onset has suspected first an infection of the subcutaneous implantable device. IV vancomycin and ciprofloxacin were started. Seven days later, lenograstim was discontinued since normalisation of leukocytes rate. But the patient presented hyperthermia to 38°C despite antibiotherapy, and she presented erythematous, indurated plaque at the device site. She had negative blood and skin cultures and white blood cell count was 13.34 G/L. The plaque progressively worsened to a large erosive and necrotic plaque, pustular in periphery of about 10 centimeters, very evocative of pyoderma gangrenosum. Anothers inflammatory nodules appeared on the forearm evoluting to sweet like lesions. A skin biopsy of the lesion revealed a dense neutrophilic dermal oedema without vasculitis, consistent with pyoderma gangrenosum. Methylprednisolone 30 mg IV was instaured and antibacterials were discontinued. The woman's cutaneous primary plaque rapidly resolved (8 days) on a regimen of oral prednisone 30 mg and remote lesions have completely disappeared. Next chemotherapy cycles were cured by filgrastim without recurrence.
Discussion: The temporal relationship between this treatment and the onset of skin lesions strongly suggests that lenograstim induced a Pyoderma gangrenosum. In addition the symptoms resolved rapidly after the discontinuation of lenograstim. Others pathologies were excluded and a myelogram confirmed absence of hemopathy.
Conclusions: Colony-stimulating factors-induced pyoderma gangrenosum is a rarely reported neutrophilic dermatose. It should be early recognise and treatment must be discontinued in order to limit the morbidity of these adverse events.

References

1. Lear JT, Atherton MT, Byrne JPH. Neutrophilic dermatoses: pyoderma gangrenosum and Sweet's syndrome. Postgrad Med J 1997; 73:65-8

2. Miall F, Harman K, Kennedy B, et al. Pyoderma gangrenosum complicating pegylated granulocyte colony-stimulating factor in Hodgkin lymphoma. British Journal oh Haematology 2005; 132: 114-7

3. Roujeau JC. Neutrophilic drug eruptions. Clin Dermatol 2000; 18 (3): 331-7

81. Pharmacovigilance of Over-the-Counter Products in Community Pharmacies: Pilot Study Conducted in the Canton of Zürich, Switzerland

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Introduction: OTC drugs are widely administered and their use is not under the close control of health professionals. Therefore, monitoring of their safety and efficacy is desirable and could support existing monitoring systems.
Objectives: To determine the feasibility of monitoring adverse drug reactions (ADR) of OTC drugs in community pharmacies by conducting a patient-based survey.
Study design: Prospective observational study without control group.
Methods: From May to July 2006 customers buying an OTC drug containing ibuprofen (200 mg/400 mg) or diclofenac (12.5 mg) were asked to participate in a survey. The pharmacists explained the study and after receiving informed consent the questionnaire including explanatory information was handed out. The participants were to complete the questionnaire on the fifth day after the intake of the first drug dose. Thereafter they sent the questionnaire back. The majority of the questions in this questionnaire were multiple choice questions.

Setting: Five community pharmacies in Zurich and one in Winterthur, Switzerland.
Results: 56 questionnaires were handed out and 38 were sent back (return rate 68%). 26 of the 38 questionnaires concerned ibuprofen, 8 diclofenac and two could not be analysed. Nine participants in the ibuprofen-group (35%) noticed at least one ADR and two in the diclofenac-group (25%). The most commonly reported symptoms for ibuprofen were abdominal pain (4), decreased appetite (4), feeling ill (3), diarrhoea (3), skin rash (3) and numbness (3). For diclofenac the participants reported abdominal pain (2) and diarrhoea (1). The intensity of the reported symptoms was considered to be mild to moderate.
Conclusion: As the sample size of this survey was small the results of the analysis are limited and cannot be generalised. More community pharmacies should participate in subsequent studies and the study period should be much longer. The monitoring of ADRs of selected OTC drugs in community pharmacies using questionnaires is feasible. Limiting time requirements, for both pharmacies and participants, is crucial as well as easy comprehensibility of the questionnaire for the participants.

82. Acute Hepatitis Associated With Chloroquine/Proguanil Use

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Introduction: Savarine® is a combination of chloroquine and proguanil, it has been approved in France since 1996 for the chemoprophylaxis of malaria in selected areas (zone 2) with quinine-resistant *Plasmodium falciparum*.
Aim: To report a case of a patient who developed acute cytolytic hepatitis while using Savarine®.
Case report: A 17-year-old girl was hospitalised on 28-August-2007 for scleral icterus and abdominal discomfort. On 28-July-2007, tree days before her travel she started Savarine® as chemoprophylaxis against malaria. Two weeks later, headache, vomiting, diarrhoea were observed in context of fatigue. She stopped by herself Savarine®. She had no history of previous gastrointestinal disorders or risk factors for liver disease (no alcohol or drug intake, or drug abuse). On admission, liver function tests showed elevated transaminases [ALT: 50-fold the upper limits of the normal (ULN), AST: 25×ULN], bilirubin (6,5×ULN) and alkaline phosphatase levels (AlP : 2×ULN). A full blood count, electrolytes, amylase, lipase, and globulin levels were within normal range. Acute viral hepatitis (A, B, C, E, CMV, and EBV) and autoimmune diseases (autoantibodies not detected) were excluded. Serologic tests for malaria, HIV, HHV-6-to-8 were negative. Wilson's disease was excluded. Abdominal ultrasound showed normal liver, biliary tract, and pancreas. Acute hepatitis related to Savarine® was suspected. Liver enzymes decreased and normalized 15 days later.
Discussion: The combination of chloroquine and proguanil is widely used for current prophylaxis and treatment of malaria. This combination is generally well tolerated, and is very rarely associated with severe adverse reactions with recommended doses.[1] However, several side effects have been described. Gastrointestinal symptoms are the most common adverse reaction in patients receiving chloroquine/proguanil for malaria prophylaxis.[2] The incidence of liver injury caused by chloroquine and proguanil appears to be very low considering their widespread use throughout the world.[3] Recently, a case of acute cytolytic hepatitis related to Savarine® prophylaxis was published. The patient (50-year-old woman) improved within 26 days after Savarine® discontinuation.[4] A French unpublished pharmacovigilance study reviewed 21 cases of hepatotoxicity with this combination including 11 cases with a cytolytic-pattern of liver injury (Technique Comity of Pharmacovigilance 2005).
Conclusion: Physicians should be aware of this rare but potential risk of liver injury related to Savarine® use.

References

1. Luzzi GA, Peto TE. Adverse effects of antimalarials. An update. Drug Saf 1993; 8 (4): 295-311

2. Barrett PJ, Emmins PD, Clarke PD, et al. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. BMJ 1996; 313 (7056): 525-8

3. Høgh B, Clarke PD, Camus D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet 2000 Dec 2; 356 (9245): 1888-94

4. Wielgo-Polanin R, Lagarce L, Gautron E, et al. Hepatotoxicity associated with the use of a fixed combination of chloroquine and proguanil. Int J Antimicrob Agents 2005; 26 (2): 176-8

83. Leflunomide-Induced Pancytopenia

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Introduction: Leflunomide (AravaÓ) is a disease-modifying agent used in the treatment of rheumatoid arthritis. It was introduced on the French market in 1999. Its major adverse effects are gastrointestinal symptoms, abnormal liver function tests, skin rashes, allergic reactions, weight loss, and hypertension. Herein, we report a case of leflunomide associated with pancytopenia.
Case report: A 42-years-old woman with a clinical history of rheumatoid arthritis (RA since 2003) and chronic iron deficiency anemia treated with iron salts since August 2006. She had been treated with corticosteroids and methotrexate. On 20-June-2008, treatment was switched to leflunomide (20 mg daily) due to treatment failure. At that time blood investigations were in normal range, except for a low haemoglobin level (Hb: 7.4 g/dL). Four month later, hematologic control tests revealed pancytopenia with low platelet levels (45 000/mm^3), neutropenia (1300/$mm^{3)}$ and aggravation for her chronic anemia (Hb: 5.3 g/dL). She was hospitalized immediately, and leflunomide was withdrawn. There was no fever or signs of bleeding. Bone marrow biopsy disclosed diffuse hypoplasia without sign of hemopathy. The thrombocytopenia and the neutropenia recovered within 7 days after stopping leflunomide (platelets: 205 000/mm^3 and neutrophils: 2300/mm^3). According to the Naranjo's probability scale, leflunomide-induced pancytopenia is probable in this case.
Discussion: Leflunomide is a pro-drug, rapidly and completely metabolized to the active drug (A771726), which has a half-life of approximately 2 weeks. This active drug was toxic for the haematopoietic system in animal studies. Pancytopenia, thrombocytopenia, and anemia can occur during leflunomide treatment.[1] Chan et al. suggested that the risk of pancytopenia associated with leflunomide was increased in older patients and when used in combination with methotrexate. Its course can be fatal and onset of blood injury ranges from 11 days to 4 years (median: 4 months).[2] Due to the long half-life of the active metabolite of leflunomide, the hematologic side effects can occur several weeks after drug cessation.[3] A recent Australian study estimated the incidence of leflunomide-induced pancytopenia between 1/3698 and 1/4582 exposed patients.[4]

Conclusion: Pancytopenia related to leflunomide therapy remains very rare but physicians should be aware of this potential risk.

References

1. Auer J, Hinterreiter M, Allinger S, et al. Severe pancytopenia after leflunomide in rheumatoid arthritis. Acta Med Austriaca 2000; 27 (4): 131-2

2. Chan J, Sanders DC, Du L, et al. Leflunomide-associated pancytopenia with or without methotrexate. Ann Pharmacother 2004; 38 (7-8): 1206-11

3. Marchesoni A, Arreghini M, Panni B, et al. Life-threatening reversible bone marrow toxicity in a rheumatoid arthritis patient switched from leflunomide to infliximab. Rheumatology (Oxford) 2003; 42 (1): 193-4

4. McEwen J, Purcell PM, Hill RL, et al. The incidence of pancytopenia in patients taking leflunomide alone or with methotrexate. Pharmacoepidemiol Drug Saf 2007; 16 (1): 65-73

84. Perception of NSAIDs Risk in Various Groups of Slovak Population

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Introduction: NSAIDs analgesics as the most widely prescribed drugs worldwide are considered to be one of the most discussed drugs in population use. Previous studies performed in France found major diferences between health and non health professionals in term of risk perception.[1]

Aim: To investigate how perceive physicians, patients and students ADR of NSAIDs and its risk.

Methods: Groups of 568 GPs from 3 regions of Slovakia and non health professionals as patients (n = 72) and students (n = 110) from two regions responded to structured questions. Visual analogue scales (VAS) were used to determine a score of perceived risk of NSAIDs, ranking 0–10.

Results: 74.6% (425/570) of GPs considered NSAIDs analgesics as exactly or probably dangerous. They declared NSAIDs as the safest analgesics. Perceived risk using VAS scale was estimated cumulatively as 3.55 (SD 1.63) by doctors; high school students 4.51 (SD 1.98); patients 4.9*. (21% patients can not declare risk due to VAS). Over 50% patients did not clearly understand an extent of NSAIDs risk.
High school students declared ibuprofen as the most popular and safest analgesics. Limitations of this type of field study should be considered in interpretation of results and need extensive discussion.

Conclusions: Major and significant difference in perception of risk among classes of NSAIDs analgesics and between professionals and non professionals in contrary of previous results from other countries[1] was not found. This study confirmed low extent of information among patient in term of drug risk, which have been revealed in another domestic search.

Reference

1. Bongard V, Ménard-Tache S, Bagherri H et al. Perception of the risk of adverse drug reactions: differences between health professionals and non health professionals. Br Clin Pharmacol 2002; 54: 433-6

85. Colchicine-Induced Acute Neuromyopathy

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Introduction: Colchicine is an efficacious treatment of acute gouty attacks. Chronic renal failure impairs the renal clearance of medicines favouring the occurrence of drug-dependent adverse reactions.

Aim: To report a case of neuromyopathy developing after administration of colchicine to a patient with chronic renal failure.

Case summary: A 68-year-old man with a history of diabetes mellitus, hypertension, chronic renal failure (140 μmol/L) and dyslipidemia has been treated with insulin, telmisartan, furosemide, and atorvastatin (10 mg/day, until November 2007). On 30-June-2007, he was prescribed 1 mg/day of colchicine for exacerbation of gouty arthritis. On 18-July-2007, he experienced weakness with walking difficulty, lasting for 2 days. Examination showed proximal muscle weakness with myalgia, tetraparesis and low reflex levels. Creatinine and creatine kinase (CK) levels were 229 μmol/L and 1385 U/L; respectively. Electromyogram showed axonal-type sensitive-motor peripheral nerve disorders and myopathic changes. Muscle biopsy showed signs of colchicine toxicity. Colchicine and atorvastatin were discontinued on 21-July-2007 due to the suspicion of drug-associated neuromyopathy. The patient's weakness improved over the following days. His CK level decreased to normal range over 4 weeks, and his creatinine level returned to baseline. The Naranjo's probability scale indicated that colchicine was the probable cause of neuromyopathy in this case.

Discussion: Acute neuromyopathy following low-dose colchicine therapy may be potentiated by chronic statin administration. Colchicine is metabolized by the CYP3A4 and mainly excreted by the feces. When colchicine is used simultaneously with a drug which is metabolized by the same CYP450, such as atorvastatin, there is a risk of accumulation of both substrates, as well as occurrence of drug-dependent adverse reaction.[1] Moreover, Kuncl et al.[2] reported 12 cases of neuromyopathy in patients with mild to moderate chronic renal failure while receiving colchicine at normal doses.

Conclusion: Co-administration of colchicine with atorvastatin may accelerate the onset of neuromyopathy in connection with chronic renal failure in this case. Extreme caution and close monitoring of the patient are warranted when a patient with chronic renal failure was treated concomitantly by atorvastatin and colchicine.

References

1. Sahin G, Korkmaz C, Yalcin AU. Which statin should be used together with colchicine? Clinical experience in three patients with nephrotic syndrome due to AA type amyloidosis. Rheumatol Int 2008; 28 (3): 289-91

2. Kuncl RW, Duncan G, Watson D, et al. Colchicine myopathy and neuropathy. N Engl J Med 1987; 316: 1562-8

86. Leucocytoclastic Vasculitis Induced by Ibuprofen

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Introduction: Ibuprofen, a propionic-acid derivative non-steroidal anti-inflammatory drug, is extensively used in the management of pain and fever. Generally, it is well tolerated and does not produce significant adverse effects. We present a patient who developed a leucocytoclastic cutaneous vasculitis induced by ibuprofen.

Case report: A 33-years-old man was admitted for palpable purpura on her lower limbs with not fever. There was no history to suggest any other allergic reactions to drugs or autoimmune disease. Five days before admission he was treated with ibuprofen (Advil® 800 mg daily) for acute dental pain. All standard laboratory tests were normal except for a raised erythrocyte sedimentation rate. Urinalysis was negative for hematuria. Serologic tests for systemic autoimmune,

connectivites and viral infection (hepatitis B, C HIV, EBV and Parvo B19) were negative or normal. Skin biopsy showed leucocytoclastic vasculitis without immune complexes. Ibuprofen was stopped, and skin lesions had completely resolved within 2 weeks. According the Naranjo probability scale, ibuprofen-induced vasculitis was probable.

Discussion: Vasculitis is an inflammation of vessel walls. All ages and sexes are equally affected. Etiologies of LCV include various infections, connective tissue diseases, cryoglobulinemia, malignancies, and drugs (approximately 10% of vasculitis skin lesions). Therapeutic agents from many different pharmacological classes are incriminated in the development of vasculitis. Drug-induced leucocytoclastic vasculitis (DILV) is clinically characterised by inflammation of small vessels and skin alterations, typically palpable purpura. Diagnosis of DILV is based on exclusion of known etiologies of vasculitis, the patient's drug exposure and improvement of the symptoms when the suspected drug is withdrawn. Similar to other NSAIDs, the more common adverse skin reactions that occur with ibuprofen use are morbilliform eruptions, urticaria, and photosensitivity, with rare reports of fixed drug eruption, and TEN.[1] LCV is with ibuprofen is rare but it can be severe.[2,3]

Conclusion: Considering the extensive use to ibuprofen and other members of the propionic acid derivative group, clinicians should be vigilant for the possibility of vasculitis during its use and than drugs should be stopped as soon as possible.

References

1. Halpern SM, Volans GN. Cutaneous toxicity of ibuprofen. Arch Dermatol 1994; 130 (2): 259-60

2. Peters F, Maessen-Visch B, Kho L. Leukocytoclastic vasculitis induced by a nonsteroidal anti-inflammatory drug. J Rheumatol 1996; 23 (11): 2008-9

3. Davidson KA, Ringpfeil F, Lee JB. Ibuprofen-induced bullous leukocytoclastic vasculitis. Cutis 2001; 67 (4): 303-7

87. The Relationship Between Baseline Testing of Serum Electrolytes and Creatinine and Adverse Outcomes in Patients Treated with Antihypertensive Drugs: An Analysis Using Propensity Score Matching Methods

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Introduction: Guidelines have recommended baseline testing of serum electrolytes and creatinine prior to initiation of antihypertensive treatment since the 1990s.[1,2] Baseline testing has two purposes: to detect secondary causes of hypertension, and to ensure that there is no contraindication to the antihypertensive drug chosen. However, there is little evidence for such recommendations, and it is uncertain whether baseline testing reduces the risk of harm in routine clinical practice.

Aim: To examine the relationship between baseline serum electrolyte and creatinine testing and adverse outcomes in patients newly diagnosed with hypertension and treated with antihypertensive drugs.

Methods: Using data from the General Practice Research Database, we identified a cohort of 11 726 pairs of patients, matched on propensity score for baseline testing, with and without any baseline testing in the six months prior to antihypertensive treatment. The components of the propensity score were age, gender, general practice, body mass index, socio-economic status, year of baseline testing, diabetes, smoking status, systolic and diastolic blood pressure, concomitant medications, number of prior practice consultations, and antihypertensive drug class. The primary outcomes were hospital admission, death, and biochemical adverse drug reactions (hyperkalaemia, hypokalaemia, or hyponatraemia) within six months of starting antihypertensive treatment.

Results: Patients with baseline testing were less likely to be admitted to hospital within six months of the start of antihypertensive treatment [190 vs. 232; OR 0.82, 95% CI 0.67, 0.99; p = 0.040], or to suffer a biochemical adverse drug reaction [304 vs. 393 OR 0.77, 95% CI 0.66, 0.89; p = 0.001]. There was large uncertainty for the difference in the rates of death [22 vs. 26; OR 0.85, 95% CI 0.48, 1.49; p = 0.564].

Conclusions: Patients with evidence of serum electrolyte or creatinine tests prior to antihypertensive treatment were at lower risk of hospital admission or a biochemical adverse drug reaction, than patients who had no evidence of baseline biochemical tests, matched by propensity score. The number of fatal events did not differ between the two groups. In a population of 1000 patients, four hospital admissions and eight biochemical adverse drug reactions would have been avoided with baseline testing.

References

1. Ramsay LE, Williams B, Johnston GD, et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. J Human Hypertens 1999; 13: 569-92

2. Smellie WS, Forth J, Coleman JJ, et al. Best practice in primary care pathology: review 6. J Clin Pathol 2007; 60: 225-34

88. Prescribing Pattern And Potential Inappropriate Medications In General Practice

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Introduction: The risk of drug-drug interactions increase (DDI) dramaticaly with the number of medications used.[1] Prevalenaca DDI in patients with several disease can be extremly high from polypharmacy.

Aim: Recognition and warning on polypharmacy with potential DDI of medications that commonly can cause hyperkalemia in ambulatory patients.

Methods: We performed a retrospective evaluation on basis prescribing drugs on sample of 104 ambulatory patients with polypharmacy (5 and more drugs) in city Sarajevo, Bosnia and Herzegowina in period of 8 months. We collected data of prescribing drugs from database in Department of health insurance. Potential DDI were searched in drug interaction book Stockley's Drug Interaction.[2] The description statistics were performed.

Results: We collected sample of 5720 prescriptions of 104 patients with mean age 67 years old. On ambulatory 94% patients were treated with ace inhibitors, 77% with spirinolactone, 76% with digoxin, 51% with potassium supplements, 45% with NSAID and 13% with trimethoprim. We found 32 cases (31%) with potential danger DDI with ACEI + spirinolactone + digoxin + potassium supplements. We found three cases with same combination of drug-drug interactions + trimethoprim. The polypharmacy was observed (average 9 drugs per patients) and most common interacting pairs were ACEI- spirinolactone (75%) and ACEI-digoxin (72%).

Discussion: Keeping current on the many pharmaceutical therapies, their pharmacology, and potential drug interactions currently represents one of the biggest challenges for all medicine practitioners.[1]

Conclusion: Medical doctors need to be particularly vigilant when prescribing drugs for patients who are taking medications with potential for drug interactions leading to serious consequences.

References

1. Prybys KM. Deadly drug interactions in emergency medicine. Emergency Medicine Clinics of North America 2004; 22: 845-63

2. Baxter K. Stockley's Drug Interactions A Source Book of Interactions, Their Mechanisms, Clinical Importance and Management. Pharmaceutical Press. 8th ed. 2007

89. Persistent Mydriasis Associated with the Concomitant Administration of Paroxetine and Cabergoline

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Introduction: Cabergoline is a prolactin inhibitor acting on D2-Dopamine receptors. To our best knowledge, no cases of mydriasis under cabergoline have been yet reported. Mydriasis under serotonin reuptake inhibitors (SSRI) is expected to improve rapidly after withdrawal of the drug. We present here a case of persistent mydriasis associated with the concomitant administration of paroxetine and cabergoline.

Case-report: We report the case of a 37 year old female patient who was started on cabergoline for secondary amenorrhea and galactorrhea with high prolactin levels without pathological findings in the cerebral magnetic resonance imaging. After 6 months of treatment she reported anxiety and depressive symptoms and was then started on lorazepam and paroxetine. Three days later, she developed a remarkable bilateral, slightly reactive mydriasis.

A new cerebral imaging showed then a non compressive pituitary microadenoma but allowed to exclude a compressive cerebral process or other neuro-surgical complications. After one week of antidepressant treatment the patient stopped taking lorazepam but the mydriasis was still present at the following visit.

After 2 weeks of paroxetine treatment and no improvement of the mydriasis, paroxetine and cabergoline were also stopped.

The pupil dilation persisted then for another 15 days before starting improving. Complete normalisation was then achieved within 3 or 4 days. One month later the patient was restarted on cabergoline but no recurrence of the mydriasis was observed after 6 weeks of treatment.

Discussion: Although SSRI-associated mydriasis, especially in overdosage cases, or as part of a serotonine syndrome, has been widely documented, our case report illustrates an unusual persistence of this adverse reaction with prolonged pupil dilation after stopping the suspected treatments. Concurrent use of cabergoline with serotonin agonists may increase the risk of serotonine syndrome. But to our best knowledge no clinical reports of such an interaction are available. In this context the paroxetine/cabergoline association was considered to be the main suspect. The relatively short half-life of paroxetine (about 24h) cannot alone explain the persistence of the mydriasis almost 3 weeks after its withdrawal. Cabergoline has a prolonged half-life (about 79–115h) compatible with this clinical course but has not been classically associated with the occurrence of mydriasis. The clinical course was not suggestive of an implication of lorazepam in this adverse reaction.

Conclusion: The cabergoline/paroxetine association represents the main suspect for this persistent mydriasis. We discuss here several hypotheses like an impaired paroxetine metabolism. Evidences for a potential cabergoline-paroxetine interaction are investigated.

90. Severe Hyponatremia Associated with Lansoprazole Therapy

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Introduction: Proton pump inhibitors (PPI) are generally considered as relatively safe and their adverse effects are probably often overlooked. PPI-associated hyponatremia has rarely been reported and is considered as severe for sodium plasma levels of 120 mmol/L or lower.

Case-report: We report here the case of an 83 year old female patient treated chronically by irbesartan/hydrochlorothiazide, for 2 years, for arterial hypertension. She was also put on lansoprazole for chronic gastritis for 1 year (repeated 1–2 months treatment periods separated by 1–4 weeks of lansoprazole free intervals) but started taking it on a regular daily basis during the last 4 months (30 mg/d). The patient was referred to our outpatient clinic for severe hyponatremia (120 mmol/L) discovered after 2 weeks of asthenia, nausea, intermittent diarrhea and abdominal discomfort. Clinical examination was unremarkable with no neurological findings, signs of cardiac failure, dehydration nor edema. Biological findings revealed a low plasma osmolality (270 mOsm/l) a potassium level within the normal range (4 mmol/L) as well as moderately impaired renal function (plasma creatinine: 163 μmol/L) and indirect signs of hemodilution (hematocrite: 36%) but no signs of impaired hepatic function.

Further investigations ruled out hypothyroidism and adrenal insufficiency. Abdominal and cerebral CT-scans were unremarkable.

An aggressive supplementation therapy (intravenous rehydration with addition of 9 g of NaCl/24h), didn't bring any change for the plasma sodium level, whereas the renal function was improving (plasma creatinine: 120 μmol/L).

A drug induced hyponatremia was thus suspected. Stopping irbesartan/hydrochlorothiazide brought, one week later, only a slight improvement of the plasma sodium level (128 mmol/L). When lansoprazole was stopped, natremia normalized within one week (140 mmol/L). Imputability score for lansoprazole according to Begaud et al. was I2B3.

Discussion: In this context the clinical course and the rapid and complete normalization of the sodium plasma level were clearly in favor of an implication of the PPI. Lansoprazole was then considered as our main suspect whereas the irbesartan/hydrochlorothiazide combination was considered to have only a minor contribution to the reaction as the plasma sodium reached only a level of 128 mmol/L one week after stopping this treatment.

Conclusion: Severe hyponatremia associated to PPIs is rare and remains poorly understood. Our clinical and biological findings are consistent with the hypothesis of a PPI induced inappropriate ADH secretion suggested by some authors. Irbesartan/hydrochlorothiazide may to a lower extent have contributed to the reaction.

91. Prevention Model for Serious Adverse Drug Reactions

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Background: Since many adverse drug reactions (ADRs) are considered preventable, increased efforts should be made to avoid classes of drugs that are problem-prone and to initiate diligent monitoring of drug with predictable toxicities.[1] Any reduction in the occurrence of

adverse event will depend on research into causes.[2] The retrospective study of ADRs in Thai hospitalized patients found that 31.4% were classified as preventable ADRs.[3] This study focuses on shifting attention from process, ADR reporting, to outcome, ADR prevention, with the ultimate goal of improving patient care.

Objective: To develop a prevention model for serious ADR.

Methods: A prospective descriptive analysis was performed. An effective prevention model for reducing ADRs was developed and implemented. An outcome after developing prevention program was analyzed. Incidence of ADRs before and after intervention application was compared. An ''ADR alert card'', the prodomol symptoms and onset of serious skin reaction mini-handbook, was developed as a prevention model for patients who first-time used twenty-six drug items that were reviewed as most commonly associated with serious ADRs. There were 625 patients in the control group and 496 patients in the study group. Preventability of serious ADRs was accessed by following up the serious ADR reports of the study group.

Results: Most patients in both groups got Anti TB drug group at 42.7% and 44.6% respectively. The percentage of male ADR patients was approximately same amount as female patients. Most of ADR reports, in control (96.0%) and study group (72.6%), were classified as Type B ADR. Comparing the percentage of serious reaction patients, in study group (16.1%) was lower percentage than in control group (32.0%). The percentage of non-severe skin reaction diagnosis in study group (79.1%) was higher than in control group (60.0%). The patients in study group showed the percentage of level 2 severity criteria lower than in control group and showed the percentage of level 1 criteria higher than in control group.

Discussion: Patients who first-time use of drugs in the study group got an ADR Alert Card with individual counseling and informed about early awareness of prodomal symptoms and onset of serious skin reaction were more intensive concern about their adverse events after start the drugs.

Conclusion: Implementing strategies to target risk patient and drug group may be early detected and prevented ADR. Various models should be compared to seek the most suitable approach.

References

1. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. Pharmacoeconomics 1999; 15: 445-7

2. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm 1990; 47: 533-43

3. Inpra K, Suwankesawong W, et al. Incidence of Adverse Drug Reactions in 21 selected Thai hospital project. Presented at 26th WHO Annual meeting of the representatives of National Centres. December 7-10, 2003. New delhi. India

92. Adverse Reactions from Coxibs: Reports from Thai-Vigibase

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Introduction: On September 2004, The Food and Drug Administration (FDA) issued an alert for healthcare professionals concerning the voluntary withdrawal from the market of rofecoxib because of an increased risk of serious cardiovascular events, including heart attacks and strokes. After that time, the European Medicines Agency (EMEA) has recommended the withdrawal of the marketing authorizations for all lumiracoxib-containing medicines, because of the risk of serious side effects affecting the liver. Both rofecoxib and lumiracoxib were cyclooxygenase-2 (cox-2) inhibitors drug group. On the basis of these serious adverse reactions reported worldwide, evaluate relation and detect adverse reactions from selective cox-2 inhibitors drug use in Thai patients are interesting to be reviewed.

Objectives: To describe and characterize adverse reactions in patients receiving coxibs in Thailand from Thai-vigibase.

Methods: Spontaneous adverse drug reaction reports associated with coxibs during January 1, 2000 to December 31, 2008 from Thai-Vigibase were included for analyses. The patient demographic data, sources of report and adverse reactions were evaluated. Descriptive statistics were used for data analyses.

Results: A total of 2632 reports with 4237 reactions were reported during study period. Most reports came from respectively.The age range of reported cases was 3–99 years (median 48 years). Of 2632 reports (61.21%.) were male. 22.38% with allergic history information had coxibs associated reaction experience. Mostly 84.92% were non serious reactions. For serious reactions; four patient was died from adverse reaction.The most frequently reported came from celecoxib (49.81%) followed by etoricoxib (49.81%) and parecoxib (7.75%). From 4,237 reactions of coxibs, skin rash was reported mostly (13.92%); followed by pruritus (12.13%). Furthermore, we found serious adverse reaction like myocardial infarction, acute renal failure and fixed drug eruption.

Conclusions: Thai-vigibase has represented serious adverse events from coxibs, Skin rash was the highest reported reactions. The following adverse events were pruritus. Serious adverse reactions from coxibs were found in other organ system like cardiovascular system. Though underreporting, the coxibs adverse events from Thai-vigibase were important for evaluate risk and benefit before prescribing of coxibs drug.

93. Aggravated Penile Psoriasis after Treatment of C Hepatitis with Interferon Alfa-2a and Ribavirin Therapy

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Introduction: Interferon alfa is an immune modulating agent that is used in the treatment of several medical conditions including hepatitis B and C. There have been reports of exacerbations of autoimmune conditions after the therapeutic use of interferon. There have also been case reports of exacerbations of psoriasis during interferon therapy. These flare-ups of psoriasis have usually led to a cessation of interferon treatment. We present a patient who had aggravated his penile psoriasis shortly after starting interferon and ribavirin treatment for chronic hepatitis C.

Observation: A 40-year-old man, with medical history of penile psoriasis, was found to have hepatitis C infection after presenting with abnormal liver function tests. Serum was positive for hepatitis C virus RNA, using the polymerase chain reaction (PCR). The patient was treated with interferon alfa-2a at a dose of 3 MU three times a week, and ribavirin 1200 mg daily. The treatment was initially well tolerated, but few months after, the patient presented a flare up of his psoriasis which remained confined to the penile region. No cutaneous, hair or nail involvement was noted. The patient was treated with emollient and topical corticosteroids without withdrawal of treatment hepatitis with marked improvement of his psoriasis.

Discussion: The first report of aggravated psoriasis following treatment of chronic hepatitis C with interferon alpha occurred in 1993.[1] Than,

several induced or aggravated psoriasis cases have been described suggesting that the drug may act as a triggering agent. The mechanisms by which interferon may cause a flare up of psoriasis are unclear but could involve an interaction between interferon and other cytokines. In our patient, a flare up of psoriasis which remained confined to a penile region did not necessitate withdrawal of hepatitis treatment. In fact, it is possible to continue interferon during a flare-up of psoriasis if the affected region is treated actively.

Reference

1. Garcia-Lora E, Tercedor J, Massare E, et al. Interferon induced psoriasis in a patient with chronic hepatitis C. Dermatology 1993; 187: 280

94. Neuroleptic Malignant Syndrome: Challenging Commonplaces in a Large Dataset

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Neuroleptic malignant syndrome (NMS) is the only acute, life-threatening adverse drug reaction to neuroleptic drugs. Recognition and treatment are still matters of debate because well-powered clinical trials are impossible.

Taking a metanalytical approach, this project has found 749 case reports that supported investigation of risk factors, disease presentation, and what effects clinical outcome. The primary objective of this investigation was putative antidote efficacy as measured in terms of mortality.

Four widely-recognized components of NMS are fever, rigidity, autonomic dysregulation and mental changes. Demographic features of this large dataset are comparable to previously-reported, smaller case series. About 60% of patients are male, mean age is about 40 years and nearly 78% of patients are treated for major affective disorders. However, this analysis demonstrates also that neuroleptics when used acutely (for nausea and vomiting, or preoperative sedation) can still cause NMS. Treatment efficacy is assessed in the complete dataset, as well as in two subsets of increasing diagnostic threshold.

The central measure in this database is mortality (12.0%). Predictors of poor prognosis that are associated with a significantly increased risk of death are age >65 years, renal failure, fever >39°C and CK elevations >3000 iU/L. Rigidity and rhabdomyolysis, a priori thought to be markers of poor outcome, were not associated with increased probability of mortality.

Of twelve putative specific treatments for NMS, only withdrawal of the suspected causative agent was associated with significantly improved survival. In particular, treatment with dantrolene or dopamine agonists is not associated with a better probability of survival, contrary to previous reports. This remains true, when the dataset was stratified by severity of disease using the predictors of poor outcome.

95. Pharmacovigilance Training Needs: An International Survey of Drug Safety Scientists

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Background: Recently the focus of pharmacovigilance has moved from reactive to proactive communication of risks associated with medicines. Accompanying this change is the need to expand the knowledge base of drug safety personnel. Those working in pharmacovigilance are required to have a good working knowledge of the principles of drug safety, its regulations and proactive strategies for risk management.[1] The DSRU is one of the leading providers of training in pharmacovigilance (PV) and is in the process of establishing a higher education institute certified postgraduate qualification to Masters Level in PV. Part of the university application process involved commenting on market need.

Objectives: To assess demand for training by PV professionals.

Methods: An internet (electronic) cross sectional survey of 7000 individuals identified from the DSRU E&R Ltd database was conducted 13th-31st Oct 2008. Enquiries focused on the essential elements to assess market need [product (value of qualification), place and promotion (DSRU as host/course provider) and price]. Summary descriptive statistics and Chi^2 tests of association were calculated using STATA 10.

Results: In total, 415 (5.9%) responded. Of these, 34.2% (n = 142) had attended at least one DSRU course. The majority were pharma industry employees (66.2%, 268/405). The proposed qualification was regarded to be of value (83.1%, 341/410), particularly by some to progress their career (26.5%, 18/109) but there is indication that those with prior experience would be less likely to enrol (50.0%, 20/40). A third held a relevant professional qualification (36.8%, 148/402); the most frequent provider being the University of Hertfordshire in Hatfield, UK (38.6%, 59/153). A high proportion considered the DSRU as an acceptable provider of a certified course (74.1%, 293/395). Cost and time commitments (offsite) were also identified as important factors (93.9%, 371/395; 88.8%, 342/385 respectively).

Conclusions: Current opportunities to undertake vocational training within PV to Masters Level are infrequent. This market research contributes data useful in the evaluation of the feasibility of the collaborative programme. It is likely that the majority of individuals requiring training will stem from the pharmaceutical industry. Such a course is regarded as providing individuals new to the discipline with essential knowledge to perform their duties and to progress their career.

Reference

1. Volume 9A of the Rules Governing Medicinal products in the European Union- Guidelines on Pharmacovigilance for Medicinal Products for Human Use. (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf)

96. The Use of Ivabradine in Primary Care in England: Interim Results of a Modified Prescription-Event Monitoring Study

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Background: Ivabradine is an anti-anginal which inhibits the sino-atrial node's funny current (I_f) to reduce heart rate and myocardial oxygen demand. It is licensed for chronic stable angina in patients with normal sinus rhythm and a contraindication or intolerance for beta blockers.[1] Ivabradine's position as second line therapy and its associated contraindications, require examination of its utilisation as part of ongoing benefit: risk assessment.

Objectives: To examine the utilisation of ivabradine used in primary care in England.

Methods: A post-marketing surveillance study based on the observational cohort technique of PEM.[2] Patients have been identified from dispensed NHS prescriptions issued by General Practitioners (GPs) since November 2005. Study questionnaires are sent to GPs at least 6 months after the first prescription identified for each patient. Information requested includes patient demographics, drug utilisation, indications, contraindications (CI) at time of starting ivabradine, and selected events of interest during treatment (phosphenes and

bradycardia). Descriptive statistics are being used to summarize demographic and other data (based on individual question responses).

Results: Of 5350 new user patients identified, 3743 questionnaires were sent and responses reviewed up to the interim data lock date of 10th October 2008. Of these 3743, 2086 (55.7%) were returned, and 1101 were valid. Median age (n = 1101) was 68 years (IQR 59, 76); 41.2% (454/1101) female. Treatment was initiated by a hospital specialist in 74.9% of patients (825/1101) and a GP in 21.3% (235/1101); (3.8% not specified).The indication was chronic stable angina in 72.3% (796/1101) Pre-existing conditions representing CIs for ivabradine, were frequently said to be present by GPs. These were: unstable angina (17.8%), heart failure (8.4%), arrhythmia (6.8%), acute MI (4.6%), pacemaker (3.2%), hypotension (1.5%); Less frequent (>0.1%, <1.0%) CIs reported included sick sinus syndrome, sino-atrial block, 3rd degree heart block, cardiogenic shock, severe hepatic impairment. Unconfirmed reports of phosphenes and bradycardia during treatment were common (3% and 2.3% respectively).

Discussion: The interim results show ivabradine has largely been initiated by hospital specialists for treatment of chronic stable angina. Reports of pre-existing conditions representing contraindications to its use have occurred. Recognised events with ivabradine (phosphenes and bradycardia) have been commonly reported. This study will continue to collect data to examine utilisation patterns and concordance with the prescribing recommendations in the Summary of Product Characteristics for ivabradine.

References

1. Servier Laboratories Limited. Ivabradine Summary of Product Characteristics. 2006

2. Shakir SAW. Prescription-Event Monitoring. In: Strom BL, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd, 2005: 203-16

97. DRESS Syndrome to Sulfasalazin

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Introduction: DRESS syndrome *(Drug Rash or Reaction with Eosinophilia and Systemic Symptoms)* is an acute and severe drug reaction associating exanthema, fever, lymph nodes, eosinophilia and visceral involvement. Recent reports suggest a combination of immunological reactions to a drug and HHV-6 reactivation.[1] Besides, DRESS syndromes with severe visceral manifestations are responsible for a mortality rate bordering the 10%.We report a case of DRESS syndrome after intake of sulfasalazin and discuss pathogenic and prognostic characteristics of this severe toxic drug reaction.

Observation: A 43-year-old woman with a medical history of seronegative arthritis, has developed 10 days after starting a course of sulfasalazine, an erythroderma with facial oedema, fever and lymphadenopathy. Biological investigations revealed hepatic cytolysis and atypical lymphocytes. Histological examination showed a dermal lymphoplasmocytic infiltrate mainly localized around vessels. Pharmacovigiance enquiry concluded to a probable responsibility of salazopyrin (E2B3 score according to Begaud probability scale). The causative drug was discontinued immediately, but the patient only improved after treatment with prednisone 0.5 mg/kg/day.

Discussion: DRESS syndrome is a rare but severe drug reaction, most commonly to aromatic anticonvulsants with a delayed onset, variable clinical presentation and protracted course. Only few cases of DRESS syndrome induced by sulfasalazine have been reported.[2] Accidental reexposure or drug provocation tests must be avoided in such a potentially life-threatening multisystem adverse drug reaction.

References

1. Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol 2007; 157: 934-40

2. Kardaun SH, et al. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007; 156: 609-11

98. Evaluation of the Safety Information of Beta-Blockers for Ophthalmic Use, Included in the PSUR Work Sharing Procedure

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Background: In France, it is considered that systemic effects of beta-blockers could be observed after ocular instillation even exceptionnally. Therefore, safety information of all beta-blockers has been harmonised in all French SPCs. Since 2007, a European initiative has been introduced related to products registered under mutual recognition, decentralised or national procedure: the EU PSUR Synchronisation Scheme and Work Sharing Procedure (PWSP). The aim of this initiative is to synchronize timetables of PSURs submission for a same substance, in order to share the PSUR assessment workload throughout the EU. A PSUR Reference Member State (P-RMS) is in charge of making a Preliminary Assessment Report (PAR) which will be commented by Member States (MS). At the end of the procedure, a Core Safety Profile (CSP) for the substance, containing the Safety Information (SI) shared by all MS, is approved.

Objective: To assess the feasibility of the harmonisation of SI of beta blockers for ophthalmic use (BBOU).

Methods: During the period from November 2008 to April 2009, we checked BBOU included in the PWSP. A comparison between the CSP proposed by the P-RMS and French safety data has been conducted.

Results: During the period, 4 BBOU were included: levobunolol (P-RMS = Czech Republic), carteolol (Slovakia), timolol (Germany) and one combination timolol + latanoprost (Sweden). For 2 Active Substances (AS) the Marketing Authorization Holder (MAH) was the same. For Levobunolol, none of the systemic effects of beta-blockers are listed in the proposed CSP. For Carteolol, the MAH has not submitted a correct proposal of CSP and is requested to propose one. For Timolol alone or in association, the proposed CSP mentions systemic effects which can occur with this beta-blocker but some are missing or are not listed in the same sections. None of the MS which have sent comments on the PAR of the P-RMS reported this issue.

Discussion: The others BBOU are not included in this 6-month-study. Through the PWSP, we highlighted that the SI is not the same among the different analyzed AS and depends on the P-RMS. Other comments from Member States considered that non-selective beta-blockers effects should also be included in the CSP.

Conclusion: Safety information assessment of the class of BBOU should be organised and led by the same P-RMS, to avoid duplication of work assessment and to facilitate harmonisation. A Non Urgent Information has been circulated by CZ to receive a final opinion from MS concerning beta blockers for ophtalmic use.

99. Cardiac Arrest Probably Induced by Ranitidine in two Patients with Diarrhoea

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Background: H2 blocker ranitidine is widely used EV in hospitals in order to prevent other drugs gastric ADRs and stress-related mucosal damage. Although H2 blockers have a good safety profile, they rarely produce serious cardiac side effects (atrioventricular conduction delay, bradycardia, asystole, ventricular and atrial arrhythmias, prolonged Q-T interval and hypotension).

Case reports: In December 2008, in a University Hospital's ward, two women (52 and 35-year-old) with diarrhoea presented cardiac arrest during ranitidine infusion. None of them had history of cardiovascular disease, and both presented diarrhoea in the previous 3-4 days (irritable bowel syndrome and possible bacterial diarrhoea). **Case 1:** The 52-year-old woman consulted because of abdominal pain and diarrhoea, she had besides Barret's esophagus. She presented cardiac arrest and ventricular arrhythmia during infusion of ranitidine 100 mg and hyoscine hydrobromide 20 mg. She didn't recover after defibrillation and was in coma 14 days, with fatal outcome. **Case 2:** The 35-year-old woman consulted because of a 4-day diarrhoea. She was treated with ranitidine 100 mg altogether with metoclopramide hydrochloride 5 mg and dipyrone in normal saline. During the infusion she presented cardiac arrest and ventricular arrhythmia, but recovered after cardioversion and was hospitalized in order to be monitored.

Discussion: Both women presented non-serious intestinal symptoms, and hadn't other conditions that might have caused their cardiac arrest, but each showed a striking temporal association with the administration of ranitidine. One possible explanation is that subclinical electrolyte disorders induced by diarrhoea (hypokalemia) could have contributed to increase H2 blockage effect. Asymptomatic cardiac arrhythmias reported in elder patients can become symptomatic after H2 blockers administration. Since a third woman presented phlebitis during injection of ranitidine infusion in the same month and hospital ward, a quality problem was suspected and samples of ranitidine used at the hospital were analyzed (HPLC); they passed all quality tests (identity tests, related substances, strength). Remaining questions about possible medication errors (administration faster than recommended, administration of other drugs instead of ranitidine) are not supported by medical records data.

Conclusion: Although ranitidine serious cardiac effects are rare, they must be kept in mind because of the extensive use of this drug. H2 blockers as preventive use should be restricted and rationally administered only in case of gastric bleeding or peptic ulcer disease history or in case of concomitant administration of drugs known to produce serious gastric ADRs.

100. Risk Assessment Study of GHB and its Precursors (GBL, 1,4-BD) in South Korea

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Introduction and Aims: GHB (gamma-hydroxybutyrate) is recently known as a narcotic compound, and UN recommends that national regulatory agency controls it as a psychotropic drug in 2001. But some poisoning accidents by not only GHB but also gamma-butyrolactone (GBL) or 1,4-butanediol (1,4-BD): precursors of GHB have been reported continually. Therefore, the risk assessment, mitigation and management policy of GHB and its precursors are needed.

Methods: First, we collected the reports related to GHB and its precursors & searched the context of drug abuse in USA, European countries & South Korea etc.

Results: GHB has anaesthetic and sedative properties. It has therapeutic potential and preparations containing it are registered medicines in four countries in Europe and in USA as an orphan drug (narcolepsy-associated cataplex). It acts as a central nervous system depressant and hypnotic and is chemically related to the brain neurotransmitter gamma-aminobutyric acid (GABA). It is also abused in recreational settings. The dose margin between the desired and the serious adverse effects is narrow. GHB is absorbed within 10–15 minutes. GBL is rapidly converted to GHB both within and outside the body whereas the precursor 1,4-butanediol is rapidly converted within the body. Several reports indicate that GHB is used for various reasons and by various sections of society. These include: its sexual enhancing effects, increasing muscle bulk, relaxation, antidepressant, anti-aging properties and more recently its apparent euphoric ('high') effects. There have also been reports of GHB allegedly being used in cases of so-called 'date rape', but the extent of this involvement is unclear so far. Because of the effects of the drug, the levels of fatal or non-fatal emergencies and reports of dependency, GHB is considered to pose significant risks to health.

Conclusion: Domestically GHB is controlled as a narcotic compound, it can be obtained on black market only (mainly internet). The precursors of GHB are widely used as industrial solvent and crimes related to GHB and its precursors have been reported constantly. Because limitation on advertisement and marketing based on Act Narcotics Management cannot be sufficient, KFDA will restrict and monitor the precursors of GHB as raw materials for narcotics. Also we noted that biological samples could contain levels of GHB in circumstances where there was no evidence of GHB consumption and recommended that this phenomenon should be the subject of further study with a view to establishing guidance for best practice in the handling and analysis of biological samples containing GHB and its precursors for monitoring.

101. Spontaneous ADR Reports of Drug-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Taiwan

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Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening cutaneous adverse reactions. The estimated incidence of SJS and TEN are 1–7.1 and 0.4–1.3 cases per million person years, respectively.[1,2] The reported mortality varies from 1% to 18% for SJS and from 10% to 70% for TEN.[2-4] The primary lesion of SJS and TEN are flat, irregular,

atypical target lesions. These initial lesions develop into blisters which result in epidermal detachment.[5] The aetiology of SJS and TEN is usually drug-related. The commonly culprits are sulfomamides, anticonvulsants, oxicam NSAIDs, and allopurinol.

Aim: To investigate the pharmacoepidemiology of drug-induced SJS and TEN with Taiwan ADR database.

Methods: We analyzed the cases in Taiwan ADR database from 1998 to 2007. Those reports were reviewed and coded with ATC code for suspected drugs and with MedDRA code (system organ class [SOC], preferred terms [PT] and lowest level terms [LLT]) for the reported adverse drug reactions. The cases with PT coded as Stevens-Johnson syndrome and toxic epidermal necrolysis are retrieved.

Results: There are total 26 077 spontaneous reports in the ADR electronic database from 1998 to 2007. Of which, 627 cases of SJS and 81 cases of TEN were reported. In patients with SJS, comprising 324 males and 303 females, the ages were between less than 1 year and 96 years (mean 53.93 ± 21.83). The outcomes of 30 SJS cases were death. Carbamazepine (25.7%) was the most commonly causative drug, followed by phenytoin (13.3%), allopurinol (9.3%), sulfamethoxazole and trimethoprim (2.8%), and diclofenac (2.4%).

In patients with TEN, comprising 42 males and 39 females, the ages were between 7 and 90 years (mean 59.81 ± 21.19). 13 cases resulted in death. The most commonly culprits were carbamazepine (11.8%), followed by phenytoin (7.9%), allopurinol (6.3%), sulfamethoxazole and trimethoprim (5.5%), and mefenamic acid (3.9%).

Conclusion: In conclusion, according to Taiwan ADR database, the estimated reported incidence of SJS and TEN in Taiwan are 2.7 and 0.4 cases/million person years, respectively. The reported mortality rates in SJS and TEN cases are 4.8% and 16.0%, respectively. However, the limitation of this study is the under-reporting of spontaneous ADR report system. In reality, the data shall be more than estimation. Besides, according to the Taiwan drug relief cases with SJS and TEN from 1999 to 2007, the most causative drugs are carbamazepine, allopurinol and phenytoin,[6] which are consistent with our data.

References

1. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333: 1600-7

2. Letko E, Papaliodis DN, Papaliodia GN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. Ann Allergy Asthma Immunol 2005; 94: 419-36

3. Applied pharmacotherapeutics. P38-15

4. Yamane Y, Aihara M, Ikezawa Z. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. Allergo Int 2007; 6: 419-25

5. Mukasa Y, Craven N. Management of toxic epidermal necrolysis and related syndromes. Postgrad Med J 2008; 84: 60-5

6. Taiwan Drug Relief database in Taiwan

102. Antitubercular Drug-Induced Hepatotoxicity and MDR1 C3435T Polymorphism: A Case Control Study

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Introduction: Hepatotoxicity is a common complication of antitubercular drug (ATD) therapy and often adds to disease morbidity. The first line ATDs causing hepatotoxicity are isoniazid, rifampicin and pyrazinamide. Genetic susceptibility to ATD induced hepatitis could be due polymorphic genes encoding for drug transporters. P-glycoprotein, is an ATP dependent membrane efflux pump that extrudes various intracellular xenobiotics and is encoded by the *MDR1* gene. This gene has various SNPs and one such SNP at 3435 (C > T) results in altered expression and function of P glycoprotein.

Aim: Since the role of P glycoprotein in the transport of ATDs or its toxic metabolites has not been clearly delineated we conducted this prospective case-control study to investigate whether *MDR1* C3435T gene polymorphism is a risk factor for ATD-induced hepatotoxicity.

Methods: Pulmonary tuberculosis patients on isoniazid, rifampicin and pyrazinamide who developed hepatotoxicity using defined criteria were prospectively identified.[1] These cases were then matched with a control on same drugs but without hepatotoxicity. DNA was extracted from peripheral leukocytes[2] and genotyping for *MDR1 C3435T* was done by PCR- RFLP by the method adapted from Bakshi et al.[3] The products were analysed on agarose gel. The Odds Ratios (OR) for the C and T allele frequency amongst cases and controls were calculated to test for association between the allele and hepatotoxicity. Chi square test was done to compare genotype frequencies of CC (wild) CT (heterozygous mutant) and TT (homozygous mutant) amongst cases and controls.

Results: 86 subjects (44 cases, 42 controls) were enrolled. The genotype frequencies of CC, CT and TT were 20.4, 31.8, 47.7% in cases and 26.1, 38.0 and 35.7% in controls respectively. However, there was no statistically significant difference in genotype frequencies ($p > 0.05$). Odds Ratio for C3435 and T3435 alleles was 1.49 (95% CI 0.77, 2.66) respectively showing that the C or T allele were not associated with ATD induced hepatotoxicity.

Conclusion: From this pilot case control study conducted on Indian population it was found that C2435 polymorphism of the MDR1 gene is not associated with ATD-induced hepatotoxicity.

References

1. FDA Working Group. CDER-PhRMA-AASLD Conference 2000: clinical white paper on drug-induced hepatotoxicity, November 2000. [online]. Available at http://www.fda.gov/cder/livertox/clinical.pdf [Accessed January 20, 2006]

2. Johns MB, Paulus-Thomas JE. Purification of human genomic DNA from whole blood using sodium perchlorate in place of phenol. Annals of Biochemistry 1989;180: 276-8

3. Bakshi S, Ramachandran G, RAmesh K et al. Study of ABCB1 polymorphism (C3435T) in HIV-1 infected individuals from South India. Br J Clin Pharmacol 2008; 65 (5): 791-2

103. Real-Time Capacity Building of African National Drug Regulatory Authorities in Analyzing ADR Reports Using a Global Consortium Approach

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Introduction: Drug use in developing countries has grown significantly in both the public and private sectors. A robust national

pharmacovigilance program is therefore vital in managing quality and safety of drugs. However, a large number of national drug regulatory agencies (NDRAs) in developing countries lack the technical resources to implement effective pharmacovigilance programs[1] and traditional capacity-building efforts are slow, often taking several years to have an impact.

Objective: To provide 'rapid' technical support to NDRAs in assessing ADR reports and to submit them to the WHO global database at Uppsala Monitoring Centre (UMC's) for signal detection.

Methods: Six countries in Africa– Botswana, Ghana, Sierra Leone, Sudan, Zambia, and Zimbabwe were selected from different regions of Africa based on the differential capacity of their pharmacovigilance program. Each country was requested to submit 20 or more existing ADR reports to RaPID's collaborating centre at University of Ghana Medical School (UGMS) through e mail, courier, fax, or to directly upload them on to RaPID's website.

The RaPID research team in India, which includes doctors and pharmacists that have been certified by UMC for VigiFlow® data entry, then rechecked the data quality and entered the data into VigiFlow. The team's evaluation included assessment for expectedness, severity and specificity of ADRs as per the standard text of Martindale.[2] The team then wrote a brief medical narrative of each ADR, followed by causality assessment based on WHO's grading system. Finally, line listings and a consolidated summary of ADR assessment were prepared for the ADRs.

Results: The data entry and assessment of 161 ADR reports was completed by four research assistants in 56 hours or the equivalent of seven full days. The assessments and data entry were shared with the countries electronically. The final submission of the data to WHO–UMC database was conducted by the countries themselves, facilitated by RaPID.

The study revitalized country's interest in improving ADR report collection and assessment and catalyzed entry of Sudan as an Official Member of the WHO Program for International Drug Monitoring.

Conclusion: The study examined and successfully demonstrated the viability of a global consortium in providing 'rapid' support in assessment of ADR reports for NDRAs. Although this support is of tremendous value for the NDRAs, the authors acknowledge that 'off-site' support must be complemented with 'on-site' capacity building.

References

1. Lalvani P, et al. Assessment of adverse drug reaction (ADR) reporting in Botswana, Ghana, Sierra Leone, Sudan, Zambia, Zimbabwe. September 200

2. Martindale: The Complete Drug Reference & Physician's Desk Reference, 2008

104. How to Improve Reporting of Adverse Drug Reactions from Hospitals: The Performance of the French PharmacoMIP Network Over a Two-Year Period

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Background: Several examples show that identifying adverse drug reactions (ADRs) over the first 18 months of a drug being on sale leads to protective measures, linked to the mandatory limits set on clinical trials. Collecting information on ADRs depends largely on spontaneous reports which are at the reference method in pharmacovigilance, but limited by 'under-reporting'.

Objective: The purpose of this study was to present a method to improve the collect of ADRs in public non universitary and private sector hospitals and to assess the results of this network over its first two years.

Methods: We set up at the regional level an ADRs gathering system similar to that which exists in University Hospitals: this system involves regular visits of an Assistant in Clinical ReseCRAh Assistant (CRA) from our Regional PharmacoVigilance Centre to public non universitary hospitals and private clinics located in our sanitary area. We compared the total number of ADRs (and the percentage of 'serious' ADRs) reported by these hospitals before (one year) and after implementation of this project. To get this pilot project, we choose 2 departments in our region: Haute Garonne (1 046 338 inhabitants) and Gers (172 335).

Results: During this period of our study (27 months: 3rd quarter 2006-end 2008), 688 reports were collected by the CRA.. Comparison between the number of *spontaneous reports* in 2005 (before the CRA's involvement) and the CRA's *solicited reports* in 2008 showed a clear increase (×4 for Gers et ×1.8 for Haute-Garonne). Similarly, the gap between spontaneous and solicited reports seems to be growing, with an increase in spontaneous reports for the year 2008 compared to the previous years. The total number of ADRs reported (CRA + spontaneous reports) per number of beds in non-teaching hospitals, which was 0.58 in 2008, was not far from that observed in Toulouse University Hospital. Among the reports, 40% were «serious', including two deaths. ADRs by class organ with mainly cutaneous (27%), cardio-vascular (24%), neuropsychic (22%) and metabolic (17%) ADRs observed mainly in women (63%) in aged patients (mean age: 69 ± 17 years).

Conclusion: This simple system appreciably improves collection of ADRs in hospitals and clinics and can contribute towards optimizing the rational use of drugs.

105. Drug-Induced Autoimmune Hepatitis Frequently has a Chronic Course in Spite of Drug Withdrawal

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Introduction: Pathophysiology of autoimmune hepatitis (AIH) remains unknown. The role of a triggering factor in patients with genetic predisposition is strongly suspected. Evolution and treatment of drug-induced AIH may be different.

Aims and Methods: The aim of this work was to compare clinical, biological, histological characteristics and evolution of drug-induced (D+) AIH and non drug-induced (D–) AIH. In a consecutive series of 65 patients with AIH, we identified 8 cases (12%) with D+ AIH and we compared their characteristics with those of the 57 patients with D– AIH.

Results: D+ AIH were due to minocycline (n = 3), nitrofurantoin (n = 2), atorvastatin (n = 1), fenofibrate (n = 1) and isotretinoin (n = 1), taken for a mean of 13 months (extreme: 2–36). The characteristics at the time of presentation the characteristics of the two groups were as summarised in table I.

An overlap syndrome was present in 2 cases of D+ AIH and 6 cases of D– AIH (ns). In the D+ AIH group, drug withdrawal was followed by a spontaneous remission in one patient, without relapse after 36 month follow-up. The 7 other patients received immunosuppressive drugs. Among 3 patients treated by corticoids alone, azathioprine introduction was necessary because of a cortico-dependence (n = 1) or a relapse

Table I. Patient characteristics

	D+ AIH (n = 8)	D– AIH (n = 57)	p
% Female	87%	82%	ns
Age	47 ± 16	47 ± 22	ns
Inaugural symptoms			
Jaundice	50%	31%	0.05
Cytolysis > 10N	87%	35%	0.02
Asymptomatic abnormal liver tests	25%	35%	ns
ALAT (N)[a]	17	8	0.05
GGT (N)[a]	11	4	0.02
Total bilirubin (μmol/L)[a]	71	13	0.03
Gammaglobulin (g/L)[a]	24	22	ns
Positive antibodies	100%	84%	ns
METAVIR Activity A3[b]	75%	65%	ns
METAVIR Fibrosis F3-F4[b]	57%	48%	ns

a Expressed as median. b Liver biopsy.

(n = 2) 2 months after corticoid withdrawal. Remission without relapse was observed among 4 D+ AIH patients first treated by corticoids and azathioprine (plus UDCA in 2 patients with overlap syndrome) after 6 to 86 month follow-up. All patients, D+ or D–, treated by immunosuppressive drugs had a complete biochemical response. There were no more complication or death in the D+ group.

Conclusion: Drug-induced AIH represent 12% of AIH in our series. Clinical and biochemical features at presentation appear to be more severe in these patients. After drug withdrawal, spontaneous remission is rare and immunosuppressive treatment is necessary. The optimal duration of this treatment remains unknown.

106. Statistical Study on Chemical Risk Factors for SJS/TEN

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Introduction: Stevens-Johnson Syndrome (SJS)[1,2] and Toxic Epidermal Necrolysis (TEN) are sometimes classified as a part of Erythema Multi form (EM), though they are definitely the most serious adverse drug reactions.

Aim: Our purpose is to predict the drugs by which EM can progress to SJS/TEN using information analyses of FDA AERS data.

Methods: 2004 version of FDA AERS data, which are available on the website, were analyzed. We analyzed the data in relation to the suspected drugs and prognoses. The logistic regression analysis (LRA) was adopted as a statistical analysis method for the AERS data. In addition, we calculated Maccs_Key Count descriptors,[3] which were derived from 2D-structures. In this study, Partial Least Squares (PLS) was adopted as a supervised learning in order to reveal the structural causes of the adverse events.

Results: Neurologic and antiprotozoan-antibacterial drugs, which indicate combination of antiprotozoan and antibacterial drugs, are highly significantly related to the adverse events of SJS/TEN. And, non-steroid analgesics-antiphlogistics show the similar tendency. Moreover, it is revealed that Z values (Z = b/SE: here, b indicates logarithm of odds ratio) are able to be the index for the prognosis, according to the above-mentioned results about the non-steroid analgesics-antiphlogistics and the neurologic drugs. The analyses using the structural descriptors show good classification results (misclassification rates: SJS/TEN 27.7%, EM 25.9%).

Conclusion: We are able to distinguish the drugs which tend to induce SJS/TEN with higher rates than EM.

References

1. Roujeau J-C, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. New Eng J Med 1995 Dec 14; 333: 1600-8

2. Vanfleteren I, van Gysel D, de Brandt C. Stevens-Johnson syndrome: a diagnostic challenge in the absence of skin lesions. Pediatric Dermat 2003; 20: 52-6

3. Molecular Operating Environment (MOE), Version 2006.08, Chemical Computing Group, Inc.

107. Prescribing of Gastroprotective Agents (GPAs) Among NSAID/COX-2 Selective Inhibitor Users in an Indonesian Hospital

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Background: NSAIDs and cyclo-oxgenase (COX)-2-selective inhibitors have been associated with an increased risk of gastrointestinal (GI) complications, in particular when risk factors are present. It is recommended that gastroprotective agents (GPAs) (i.e. misoprostol, proton pump inhibitors, histamine H2 receptor antagonists or antacids) be taken concomitantly to prevent NSAID-induced GI complications. However, there are concerns that the rate of concomitant use of gastroprotective drugs in NSAID/Cox2 users is too low.

Objective: This study aimed to investigate the prevalence of concomitant GPA among users of NSAIDs/COX-2-selective inhibitors, and to determine the factors associated with concomitant use of GPA and NSAIDs/COX-2-selective inhibitors in a hospital drugs register based.

Methods: We analysed data on age, sex and dispensed drugs for patients between 30–60 years old which were registered in the an Indonesian private hospital prescribed drugs register from 2004–2006 (n = 139 942 prescriptions) and located 31 350 NSAID/COX-2-selective inhibitor prescriptions for 9455 patients. Logistic regression analysis was used for analysing the association between the use of different NSAIDs/COX-2-selective inhibitors and GPA, and between individual characteristics and use of GPAs.

Results: Co-prescribing of GPAs were used by 5550 (17%) of NSAID/COX-2-selective inhibitor users. Celecoxib, meloxicam, ketoprofen, rofecoxib, glucosamien glycan and diclofenac were most commonly used concomitantly with gastroprotective drugs. Celecoxib and meloxicam were most strongly associated with gastroprotective drugs, OR 95% CI 10.09 (8.65, 11.77) and 9.65 (8.08, 11.54), respectively. Concomitant use of GPAs varied among individual NSAIDs. Use of combination NSAIDs (ORadj 1.16; 1.07–1.26), females (ORadj 2.38; 2.24–2.54), age more than 45 years old (ORadj 1.30; 1.21–1.40)), and

concomitant use of corticosteroid (ORadj 1.28; 1.14–1.45). were significantly associated with concomitant prescribing of GPAs during NSAIDs therapy.

Conclusion: The rate of concomitant prescribing gastroprotective agents in NSAID users is low. Furthermore COX-2-selective inhibitors were used with gastroprotective drugs more often than traditional NSAIDs. Use of combination NSAIDs, female, age >45, use of corticosteroid are associated with concomitant use of GPAs in NSAID users. Feedback to prescribers should be given to improve prescribing practices.

108. Study on Adverse Drug Reactions in Tuberculosis Patients in Thailand During 1998–2007

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Introduction: Standard first line therapy of tuberculosis (TB) consists of streptomycin, pyrazinamide, rifampicin, isoniazid and/or ethambutol. The treatment regimen is combination therapy (at least three drug regimens) and must be treated for over 6 month. Although this regimen is effective in treating TB, it is associated with many serious adverse drug reactions resulting in discontinuation or incompliance therapy. Treatment failure and/or fatal outcomes in these patients were detected. Furthermore, concomitant drug therapy, antiretroviral drug, in HIV-positive TB patients could lead to increase serious or unexpected adverse reactions cases. To understand the problem related to adverse reaction in TB patients, a study on adverse effects in Thai TB patients were conducted.

Objective: To ascertain reporting rate and characterize adverse drug reactions in Thai tuberculosis patients during year 1998–2007.

Methods: Adverse reaction reports of patients receiving treatment for TB from Thai-vigibase (National adverse drug reactions database) and TB patient disease surveillance database from Bureau of Epidemiology during year 1998–2007 were retrieved. Descriptive statistic is used for data analyzing including mean, median, frequency and percentage to represent type and characterize data. Reporting rates of developing ADRs were determined using number of TB patients from disease surveillance database as denominator.

Results: During year 1998–2007, the Health Product Vigilance Center received a total of 4315 spontaneous adverse drug reactions reports associated with TB patients using at least one of standard first line therapy. 4237 reports with eligible inclusion criteria were analyzed as TB patients with ADRs. Based on demographic data, 55.86% were male. The majority age group (44.61%) was between 25 and 44 years together with 7.9% reported HIV positive TB patients. Average reporting rate of adverse drug reactions associated with TB patients and HIV positive TB patients were 1.29% and 0.51% respectively. Whereas 1.44% was an average reporting rate of fatal outcome cases.

84.99% of TB patients with ADRs, anti-TB drugs were reported as suspected drugs. Rifampicin was the most commonly reported drugs causing adverse drug reactions (59.25%). 37.69% were reported as serious ADRs. The top 3 adverse drug reactions reports were skin and appendages disorders (45.80%), followed by liver and biliary system disorders (12.14%) and gastro-intestinal system disorders (9.26%).

Conclusions: Serious ADRs were commonly reported in TB patients. Some of these were leaded to fatal outcome. Continuously intensive monitoring of TB patient was needed to early detect adverse drug reactions and decrease failure treatment from bad compliance.

109. Medical Journals and Spontaneous Reporting: Two Complementary Sources of Information on Adverse Drug Reactions

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Introduction: In post-marketing surveillance, publications in medical journals and spontaneous reporting to manufacturers or drug agencies represent two important sources of information on adverse drug reactions (ADRs). These case reports are used for decision-making to minimize patient risk.

Aim: To compare cases published in the literature and those spontaneously reported to the French national agency through a set of cases of lymphoma after treatment by anti-Tumor Necrosis Factor (TNF).

Methods: All cases of lymphoma spontaneously reported to the French Pharmacovigilance system in patients treated with an anti-TNF agent were identified as well as all cases published in the MEDLINE, Cochrane and EMBASE databases. All identified cases of lymphoma confirmed by histopathological diagnosis and with a known delay between the anti-TNF introduction and the lymphoma diagnosis were included. Case reports from both sources were compared on the following characteristics: age and gender, anti-TNF involved, indication for use, type of lymphoma and time to onset of lymphoma.

Results: A total of 61 cases published and 41 cases spontaneously reported to the French Pharmacovigilance system were compared (including 2 duplicates). Characteristics of cases did not significantly differ for age, gender and type of lymphoma. Nevertheless, in published reports, patients were more frequently treated with a single anti-TNF whereas for spontaneous reported cases, a succession of different anti-TNFs ($p = 0.01$) or adalimumab ($p = 0.01$), the most recently available anti-TNF, were more frequently used. Lymphoma in patients treated with anti-TNF for Crohn's disease was prevailing in published cases ($p = 0.0004$) and concerned especially hepatosplenic T cell lymphoma, a rare and serious disease. Conversely, rheumatoid arthritis was the main indication for anti-TNF in spontaneous reports. The time to onset was markedly shorter in published reports (median: 7 months, inter-quartile range: 2–20 months) than in spontaneous reports (median: 27 months, inter-quartile range: 14–43 months) [$p < 0.0001$].

Conclusions: Characteristics of published and spontaneously reported cases markedly differed for several key variables such as type of drug, indication and time to onset. Both sources should be combined when one intends to describe a novel type of ADR or for decision-making purpose.

110. Analysis of Intrinsa® (Testosterone Patch) Utilisation in Prescription-Event Monitoring (PEM): An Interim Report to Support Risk Management

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Background: Intrinsa® is a transdermal testosterone patch, which is indicated for use in hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised (surgically induced menopause) women receiving concomitant oestrogen therapy.

Objective: To describe the utilisation characteristics of the patients prescribed testosterone patch (Intrinsa®) based on an interim analysis of an ongoing PEM cohort and to assess, where possible, if the product is being used within the licensed therapeutic indication.
Methods: Patients from the interim analysis were identified from dispensed prescriptions that had been issued by general practitioners (GPs) for Intrinsa® between May 2008 and November 2008. 'Green Form' questionnaires were sent to GPs six months following the date of the first prescription for Intrinsa® for each individual patient, requesting information including: age, gender, start and stop dates of treatment (if stopped), prescribing indication and reasons for stopping therapy. Additional questions were asked regarding the patient's menopausal status and use of concomitant oestrogen therapy. Summary descriptive statistics were calculated.
Results: The interim cohort consisted of 756 patients. The majority of patients were reported to be female (746, 98.5%) with a median (IQR) age of 50 years (44–55 years). The most commonly reported indication was the licensed indication of HSDD in 580 patients (76.7%). Just under half of the patients (n = 364, 48.1%) were reported to have been hysterectomised and bilaterally oophorectomised (surgically induced menopause) prior to starting Intrinsa®; 127 patients (16.8%) were naturally menopausal and 45 patients were pre menopausal. For 222 (29.4%) patients the GP specified that the patient was not using concomitant oestrogen therapy. Overall, only 219 patients (29.0%) in the cohort were being prescribed Intrinsa® according to the manufacturer's recommendations.
Conclusions: This study has highlighted that some clinicians are prescribing this product outside the recommended terms of the licence, with less than 30% of patients receiving Intrinsa® according to prescribing guidelines. All events experienced by these patients will be analysed to detect any possible adverse events from using Intrinsa® outside of the licensed therapeutic indication. The findings support the ongoing post marketing risk management of the product.

111. Pharmacovigilance Study on Diphtheria, Tetanus and Pertusis (DTP)-Based Combination Vaccines (DTwP-Hib and DTwP-Hib-HepB) in the Asian Indian Paediatric Population

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Introduction: Combination vaccines allow a reduction in the number of required injections, thereby improving compliance to vaccination schedule and higher vaccination coverage. Previous studies[1-2] have demonstrated highly favorable risk-benefit assessment for the use of wP-based vaccines in developing countries. In India Easy four (DTwP-Hib) and Easy five vaccines (DTwP-Hib-HepB) have been introduced by Panacea Biotec Ltd. (PBL).
Aim: To study safety and reactogenicity profile of Easy four and Easy five vaccines.
Material and Methods: An observational study was carried out for safety and reactogenicity profile of Easy four and Easy five vaccines supplied by PBL. The vaccine(s) were administered by intramuscular injection on the anterolateral aspect of the thigh. Suspected Vaccine Adverse Reaction Form was used to capture adverse reactions (ARs). Overall incidence of solicited and unsolicited event(s) reported was calculated. Coding: Medical Dictionary for Regulatory Activities version 11.1 and WHO Drug Dictionary. All reported suspected ARs (numerator) were included. Vaccine usage data (denominator) was derived from the number of doses.
Results: A total of 1 151 146 unit doses for Easy four and 1 863 303 unit doses for Easy five vaccines were administered during the year January 2006 to December 2008. A total of 52 suspected adverse events (AEs) were reported in 25 healthy infants (male = 13 and female = 12). Of the 52 events reported, 30 AE(s) with "Easy four" and 22 AE(s) with "Easy five" vaccine were reported. Fever (8) and convulsion (8) were the most commonly reported suspected ARs (AR rate of 3/1 000 000 dosage units). Other commonly reported events were rash (5), swelling (4), pigmentation (3), abscess (3), itching (2), redness (2), cold and clammy (1), discoloration of hand and feet (1), localized 'scald' (1), irrtitation (1), tenderness (1), lethargy (1), diphtheria (1), temporary respiratory arrest (1), profound bradycardia (1), hypotonia (1), coma (1), bluish color (1), induration (1), limping (1), crying (1), protruding eyes (1), cough (1). Serious adverse event were reported in 14 cases which included therapeutic failure (1) and death (1) as the seriousness criteria. No laboratory adverse event was reported during the entire period (January 2006–December 2008).
Discussion and Conclusion: The safety and reactogenecity profile of the vaccines used in the study was not different as earlier reported with the separate administration of DTwP, Hib and hepatitis B vaccines in literature and other studies.[3-5]

References

1. World Health Organisation. Pertusis vaccine- WHO position paper. Wkly Epidemiol Rec 2005; 80: 31-9

2. Kanra G, Kara A, Demiralp O, et al. Safety and immunogenicity of a new fully liquid DTPw-HepB-Hib combination vaccine in infants. Hum Vaccin. 2006 Jul-Aug; 2 (4): 155-60. Epub 2006 Jul 21

3. Shah R, Raghu MB, Shivananda A, et al. Immunogenicity and safety of an indigenously developed DTPw hepatitis B combination vaccine in Indian infants. Indian Pediatr 2008 Oct; 45 (10): 819-23

4. Riedemann S, Reinhardt G, Jara J, et al. Immunogenicity and reactogenicity of combined versus separately administered DTPw-HBV and Hib vaccines given to healthy infants at 2, 4 and 6 months of age, with a booster at 18 months. Int J Infect Dis 2002 Sep; 6 (3): 215-22

5. Botet Asensi FI, Veronese A, Del Carmen Otero M, et al. Immunogenicity and safety in infants of a DTwPHib full liquid vaccine. Acta Paediatr 2003 May; 92 (5): 541-5

112. Impact of Pharmacist's Interventions on Adverse Drug Event Reductions in Outpatients with Rheumatoid Arthritis

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Introduction: Adverse drug events (ADEs) are common in rheumatoid arthritis (RA) patients.[1] Many studies have proved that ADEs were reduced in hospitalized patients by pharmacists[2] but relatively few studies have been performed in outpatients.
Aim: To study whether pharmacist's interventions could reduce ADEs in outpatients with RA at rheumatology clinic, Ramathibodi Hospital, Thailand.

Table I. Preventable adverse drug event (ADE) rates

	Study group		Control group	
	1st visit	2nd visit	1st visit	2nd visit
Number of patients	72	72	70	70
All ADEs, events	22	25	33	38
Preventable ADEs, events	12	16	16	23
Preventable ADE rates (%)	16.7	22.2*	22.9	32.9*

*0.05.

Methods: Prospective controlled study was performed during April 30th and August 30th 2007. ADEs were detected before (the 1st visit) and after intervention period (the 2nd visit) in study group while no interventions were provided in control group. The pharmacist's interventions consisted of detection and management of prescribing error and providing patient's counseling. All causality assessment and preventability of ADE were validated by rheumatologists. Rates of preventable ADE were the primary outcome. The differences in the rates at the 2nd visit and the 1st visit were compared between the study and the control group. P value ≤0.05 was defined as statistical significance using Chi-squared test.
Results: The number of patients, ADEs, preventable ADEs, and preventable ADE rates in both study and control groups at the 1st and 2nd visit are presented in Table I. The difference in the rates of the study and control group at the 2nd visit was 10.7% (0.05st visit was 6.2% ($p > 0.10$). In both study group and control group, the rates were increased by 5.5% ($p > 0.10$) and 10.0% ($p > 0.10$), respectively.
Conclusions: Despite the difference in the preventable ADE rate between the study group and the control group was not statistical significance, the pharmacist's interventions seem to have some impact on ADEs reduction in outpatients with RA.

References

1. Limsuwan T, Tragulpiankit P, Chulavatnatol S, et al. Prevalence and characteristics of adverse drug events in rheumatoid arthritis and osteoarthritis ambulatory patients at a large teaching hospital, Thailand [abstract]. EJD 2008; 18: 262-3

2. Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care. Arch Intern Med 2006; 166: 955-64

113. Improvement of ADR Monitoring and Reporting by ADRs Community of Pharmacy Practice in Thailand

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Introduction: In Thailand, although the number of individual case safety report (ICSR) has been increased according to the encouragement of national adverse drug reaction (ADR) spontaneous reporting system, the under-reporting and quality of ADR reporting are still challenge probably because of relative insufficient training course for ADR in academic institutions under a global pharmacovigilance trend. The Association of Hospital Pharmacy (Thailand) [Thai HP] is a professional organization which has a role to play in hospital pharmacy improvement in terms of academic and professional activities. Therefore, Adverse drug reaction's Community of pharmacy Practice in Thailand (AdCoPT) was initiated under the auspices of Thai HP and patient safety is a goal of this community of practice.
Aim: To determine characteristics of pharmacists who attended the ADR training courses and to evaluate the effect of them in terms of improvement of ADR monitoring and reporting.
Methods: AdCoPT working team provided the three-days training courses for pharmacists between September 2006 and October 2008. The course consisted of knowledge and skill of ADR monitoring and reporting. ADR case study workshop was also integrated. The mail survey was sent to all pharmacists who used to attend the courses. The knowledge and skill of ADR, ability to ADR causality assessment and reporting were surveyed and graded as five levels and then compared between before and after training. The high level is likely high performance. The data was analyzed by descriptive analysis. The performance which was graded by pharmacists before and after training was compared using McNemar's test.
Results: As a result, 1476 pharmacists out of 7217 Thai HP's member attended total nine training courses which were conducted. Most of attending pharmacists were female (85.6%). The pharmacists from primary hospital attended by 44.6% whereas the pharmacists who work at private hospital attended by 17.1%. The total of 441 responses of survey was received yielding a response rate of 29.9%. Most of the response was female (83.2%). The pharmacists who work at primary hospital and private hospital included in the survey by 58.4% and 9.6%, respectively. The percentage of responses who graded the 4th and 5th level in terms of the knowledge, skill, ability to ADR causality assessment and reporting increased from 7.80% to 76.77% (0.01).
Conclusions: AdCoPT takes part in pharmaceutical education for improvement of ADR monitoring and reporting.

114. Olfactory and Taste Disorders Due to Medicinal Drugs: An Analysis of the French Pharmacovigilance Database

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Introduction: Among Olfactory and Taste disorders, drug-induced aetiology is an uncommon occurrence and poorly studied. In the international literature, no data concerning the respective part of responsible drugs are available, whereas only one (relatively former) study for each sensitive disorder was published in France.[1,2] It seemed interesting to investigated, in the same time, smell and taste complications because of their high degree of interaction. However, such aetiology should be systematically taken into account and investigated, as these disorders may be reversible once the particular treatment has been stopped.
Methods: To carry out this study, we performed a search using the French Pharmacovigilance database for the period January 1985 to March 2009. For case selection, we used "ageusia, dysgeusia, hypogeusia, anosmia and parosmia" as MedDRA preferred terms and "olfactory nerve disorders" as a high level term. All notifications with insufficient information about chronology and outcome were excluded. We therefore obtained 583 notifications: 232 were male and 348 female with an average age of 53.6 (SD 16.37) and 52.6 (SD 16.77) respectively. Descriptive statistics using SPSS software were undertaken.
Results: The results showed that, over the 24 year period, the number of notifications concerning taste or olfactory disorders increased from

3 cases/year to a maximum of 52 in 2008. Quantitative as well as qualitative disorders were observed, with 43% and 38% for dysgeusia and 13.6% and 5% for dysosmia respectively. Only 1 drug was considered suspect in 95% of our cases, 2 drugs in 3.6% and more than 3 drugs in 1.4%. The main pharmacological group involved was anti-infective (38%), then cardiovascular drugs (12.2%), and lastly psychiatric drugs (6.5%). As expected and previously described in the literature, terbinafine is the drug most involved, with 16.3% of cases. Interestingly, we identified 57 notifications with a positive rechallenge with such drugs as telithromycin, palifermin, spiramycin and valsartan. Onset time was 33 days (0.06–1825) on average. In more than 80%, patients stopped their treatment, with recovery without sequelae occurring in 69%. The French Imputability score classified 64% as I1B1, 20% as I2B2 and 13% as I3B3.

Conclusions: It is generally considered that taste and olfactory disorders are not serious side effects and are largely under estimated. These effects can have a serious impact on quality of life and lead to poor compliance with treatment. Increasing physician awareness of smell and taste problems is thus of great importance.

References

1. Norès JM, Biacabe B, Bonfils P. Troubles olfactifs d'origine médicamenteuse: analyse et revue de la littérature. Rev Med Interne 2000; 21 (11): 972-7

2. Ratrema M, Guy C, Nelva A, et al., Association Française des Centres Régionaux de Pharmacovigilance. Troubles du goût d'origine médicamenteuse: analyse de la Banque Nationale de Pharmacovigilance et revue de la littérature. Therapie 2001; 56 (1): 41-50

115. Ten Years of Spontaneous Reporting of Adverse Drug Reactions in Children in Norway

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Background: A new European regulation intends to improve documentation of medicines for children including pharmacovigilance. Consequently, Norway runs a national campaign to stimulate reporting of adverse drug reactions (ADR) in children. Based on an analysis of the Norwegian ADR database of reports concerning children, changes in reporting rate and pattern can be measured and further campaigns planned.

Objective: To analyze the spontaneous reports of ADRs in children in the Norwegian ADR database 1998–2007.

Methods: Spontaneous reports in the Norwegian ADR database 1998–2007 including reports on children ≤17 years and ADRs assessed as certain, probable or possible were analyzed. Reports on ADRs from drug exposure in utero, through breastfeeding, and reports where vaccines were the only suspected drugs were excluded, as were reports of unknown geographic origin. Reporting rate and serious reports in children were compared with all reports in the database.

Results: For the 10-years period, 531 (4.6%) reports involving children met the inclusion criteria. Reporting rate is low, reaching 8 reports per 100 000 children in 2007. However, there was an increase by 2.7 times in ADR reporting rate for children, while the over all reporting rate increased by 2.2 times in the same period. There was a mean of 2.1 ADRs and 1.2 suspected drugs per report. Drugs in the ATC-group N, affecting the nervous system, were most frequently suspected (42%). 52% (n = 276) of the reports involved girls and 48% (n = 253) boys. The majority of reports in the age group 0–14 concerned boys, while ADRs in girls were most frequently reported in the age group 15–17. 45% (n = 240) of the reports involved at least one serious ADR in children, compared to a share of 54% of all reports. Of the reports in children 2.6% (n = 14) resulted in fatality, including 2 reports of suicide. In comparison 8.2% of all reports resulted in fatal outcome.

Discussion: A general increase in reporting rate in Norway with a slight increase in the proportion of reports affecting children was observed. Gender differences in ADR reporting corresponds with more prescriptions being dispensed to boys aged 0–13 and to girls ≥14 years old. Although we excluded reports of vaccines, which often involves non-serious reactions, reporting of serious ADRs is lower in children than in all reports.

Conclusion: Reporting of ADRs in children has a potential of improvement. The present analysis of the Norwegian ADR database can be used to plan, measure and evaluate campaigns of pharmacovigilance in children.

116. Dopamine Dysregulation Syndrome: A Behavioural Manifestation of Pharmacologic Treatment

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Introduction: Treatment of Parkinson'disease (PD) has traditionally focused on the management of motor disability while behavioural disturbances have received less attention. Dopamine dysregulation syndrome (DDS) is a relatively recently described iatrogenic disturbance that may complicate long-term symptomatic therapy of PD.

Aim: To report a case of DDS associated with dopaminergic replacement therapy (DRT) after escalating the dose to treat Parkinson's disease (PD).

Methods: A 57-year-old man had a 15-year history of PD and levodopa therapy. He presented complex motor fluctuations. In order to stabilize the disease, many DRT were instituted successively (levodopa,l, benserazide, carbidopa, bromocriptine, tolcapone, entacapone, pergolide). The patient developed a dopamine abuse with self-medication and a strong compulsion to gamble "uncontrollably" at casinos at age 50, 8 years after the onset of PD. When DRT doses were reduced, behavioural adverse effects improved. At age of 53, the patient underwent bilateral subthalamic stimulation. Parkinsonian symptoms improved markedly and in November 2005 he started therapy with piribedil and pergolide was discontinued. In April 2006, he again reported interest in gambling. His neurologist stopped piribedil and the patient has sustained resolution of symptoms after switching levodopa, levodopa/peripheral dopadecarboxylase inhibitor and combination preparations of levodopa with carbidopa and entacapone. From 2006 to 2009 the patient didn't present any impulsive-compulsive disorders.

Results: Patients with PD may become addicted to their own medication, administering doses in excess of those required to control their motor symptoms and/or develop behavioural addictions like our case.[1,2] The role of DRT in DDS is discussed, with particular reference to models of addiction, suggesting that compulsive drug use is due to progressive neuroadaptation in dopamine projections to accumbens-related circuitry. Persistently elevated dopaminergic stimulation promotes the development and maintenance of addictive behaviours.[2] Dopamine agonists have a high affinity for all dopamine D2 subfamily receptors. Candidate genes affecting the dopamine 'D2-like' receptor family have been associated with impulsive

personality traits in addition to drug and non-drug addiction.[3] The dose of DRT might play an important part in the induction of the adverse effect management primarily requires reduction of DRT, so deep brain stimulation may therefore useful to decrease the treatment.
Conclusions: The mechanisms underlying the DDS are debated but there are current evidence points to specific risk factors: male gender, younger age of PD onset, tardive occurrence, escalated dose.[4] Given the social consequences of these behaviours, neurologists should be aware of the DDS.

References

1. Cabrini S, Baratti M, Bonfa F, et al. Preliminari evaluation of DDS-PC inventory: a new tool to assess impulsive-compulsive behaviours associated to dopamine replacement therapy in Parkinson's disease. Neurol Sci 2009; as supplied by publisher

2. Dagher A, Robbins TW. Neuron 2009; 61: 502-10

3. O'Sullivan SS, Evans AH, Lees AJ. Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS Drugs 2009; 23: 157-70

4. Antononi A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. Drug Saf 2009; 32: 475-88

117. Genetic Polymorphism and Pharmacovigilance: The Warfarin Example

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Introduction: Serious adverse drug reactions (ADRs) due to warfarin treatment constitute an important safety concern. This is due to the narrow therapeutic index of the drug, its potential for interaction, and the wide response inter-individual variability among patients. Thus, inappropriate dosing of warfarin continues to contribute to significant morbidity and mortality causing either blood clotting or bleeding. Clinical trials have revealed that pharmacogenetic-based dosing may be important in active pharmacovigilance in reducing ADRs. Polymorphisms in VKORC1 and in CYP2C9 are strongly associated with unexpected responses to warfarin and testing for these variant alleles allows for personalized dosing during the induction phase and thus a possible reduction of the risk of ADRs.
Aim: To provide an overview of the safety profile of warfarin in relation to CYP2C9 and VKORC1 polymorphisms, and subsequent actions taken by different Regulatory Authorities in such context.
Methods: Data sources included the English language literature using PubMed searches from selected articles published in the last three years and including key words as warfarin, genetic, and adverse events. In addition, U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMEA) websites were scrutinised in order to identify any released information including the same key words.
Results: Pharmacogenetic based warfarin dosing could increase accuracy, shorten the time to achieve stable and therapeutic INR, and subsequently reduce ADRs.[1] However, it has not been fully established whether this dosing approach could significantly reduce the frequency of major bleeding events.[2] According to the results from some clinical trials, the FDA has recognized the importance in pharmacovigilance of a proper initial warfarin dosing by approving in August 2007 an update of the warfarin labelling which included pharmacogenetic information. Further, in September 2007, the FDA has also cleared a genetic test for warfarin sensitivity.[3] Currently, three genetic biomarker tests are recommended by the FDA, even if the routine use of warfarin genotyping is not endorsed. The EMEA has so far not yet expressed its opinion about updating the warfarin labelling or recommending any pharmacogenomic test. However, the International Conference on Harmonisation (ICH) has issued a proposal for a new harmonized ICH guideline on important aspects for the qualification of pharmacogenetic biomarkers.
Conclusions: Pharmacogenetic may play an important role in the safety and efficacy profile of warfarin; however, prospective clinical studies are necessary to fully evaluate the effectiveness of genotype-guided therapy in daily medical practice, and subsequent implications in active pharmacovigilance.

References

1. Canadian Agency for Drugs and Technologies in Health. Issues in Emerging Health Technologies-Pharmacogenomics and warfarin therapy. October 2007; Issue 104

2. Bacquemont L. Evidence for a pharmacogenetic adapted dose of oral anticoagulant in routine medical practice. Eur J Clin Pharmacol 2008 Oct; 64 (10): 953-60

3. Kim MJ, Huang SM, Meyer UA, et al. A regulatory science perspective on warfarin therapy: a pharmacogenetic opportunity. J Clin Pharmacol 2009; 49: 138-46

118. Semantic Interoperability and Standardization Enable an Integrated Evaluation of Safety Data

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Background: Establishing the safety profile of a medicinal treatment and proper risk mitigation demands the access and evaluation of ALL safety data that are being collected. These data are not available in an integrated way, but scattered around the globe in very diverse databases.

- Standardization of scientific approaches to drug related problems are being addressed by multiple initiatives (FDA/Sentinel, IMI, ICH, ENCePP, others).
- Standardization of data exchange are being established through open standard setting organizations (e.g. collaboration between HL7, CDISC, BRIDG, ISO, CEN) to implement standards that support interoperability within the pharmaceutical industry and with healthcare.
- The new ICSR model developed through HL7 will provide a solution across all aspects of patient safety, supported by the Medicinal Product Identification.
- Assuring optimal drug utilization is an integrated risk management effort of the entire company that needs to be championed by Safety.
- Planning and executing risk management activities requires much better integration of safety into development and medical affairs activities as well as collaboration with outside stakeholders.
- Pharmacovigilance has the opportunity to actively contribute to value creation by providing strategically relevant information.
- Increasing budget constraints require a new approach for higher efficiency in drug safety operations.
- An integrated evaluation of safety data across all data sets (clinical, observational, spontaneous, etc.) can be achieved efficiently within and across organizational boundaries.
- A neutral partner'' can facilitate a broader collaboration and data exchange across internal and external stakeholders (e.g. between different domains and companies of a pharmaceutical corporation, with development or marketing partners, with owners of large data bases [regulatory, academic, payers], etc.).

- In addition, a drug safety solution based on standardization and modern Service Oriented Architecture technology is much more flexible to adapt to processes and system changes of a pharmaceutical company and its partners than currently used hard-coded and heavily customized systems.

Conclusion: Semantic interoperability and standardization enable an integrated evaluation of safety data-and a ''neutral partner'' role facilitates a broader collaboration.

119. ADR Networking: An Empowering Tool for Excellence

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Background: The high quality adverse drug reaction (ADR) monitoring process was recognized as one of the most important parts to achieve the effectiveness of drug therapy. High quality ADR monitoring process can be accomplished via a combination of knowledge, skill and positive attitude of ADR pharmacists. Thus, pharmacist plays an important role in the development toward the high quality ADR monitoring process.

Objective: To excel and empower pharmacists in ADR monitoring via establishment of network developing system.

Methods: A three-party network consisting of the Faculty of Pharmacy, the Provincial Public Health Office and Community Hospitals was established under the name ''Chiang Mai Adverse Drug Reaction Monitoring Committee'' in order to continually motivate clinical and professional skills, as well as knowledge of ADR pharmacists working in community hospitals with relation to their settings.

Results: The Chiang Mai ADR Monitoring Committee has been developing 24 community networks across Chiang Mai province. The development was carried out according to drug quality criteria for hospital via self assessment, 5 academic conferences, ADR case study presentation, provincial ADR database compilation, establishment of electronic community information, development of ADR record cards, intensive ADR monitoring system, vaccination follow-up monitoring, and ADR data transfer within the network system and preliminary agreement on the academic-base cooperation.

Conclusion: The development of pharmacists and network system of Chiang Mai led to the improvement of the quality of ADR monitoring process which benefited the patients. The process also elevated the professional standard of hospital and served as quality sites for ADR training.

120. The Use of Time to Event Models in Signal Detection

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Introduction: The rate of occurrence of adverse drug reactions (ADRs) after starting a drug varies with time. The onset of some ADRs are rapid after starting treatment, whilst for others the onset may be delayed. Plotting a hazard function over time can be a useful method to subjectively determine whether it is increasing or decreasing and statistical modelling can be applied. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. Prescription Event Monitoring (PEM) observational cohorts are able to be used to study possible ADRs.[1]

Aim: To examine the usefulness of a statistical approach to time to event modelling for evaluation of ADRs.

Methods: Two clinical examples involving eight PEM studies were used; events of hypoglycaemia in four oral antidiabetic (AD) treatment cohorts and events of deafness in four erectile dysfunction (ED) treatment cohorts. The patterns of these events over time were examined by plotting a smoothed hazard function, then a parametric survival model was then fitted to each cohort. The model parameters and 95% confidence intervals were used to test for a non-constant hazard function and then the fit of the model was assessed.

Results: The number of hypoglycaemic events observed ranged from 43–85 for each antidiabetic treatment cohort (cohort size range n = 4557–14 418), and 8–18 deafness events were observed for each ED treatment cohort (cohort size range 11 177–28 056). For both examples, time to event analysis was performed for a maximum of nine months. Due to the PRN nature of ED treatment, the exact exposure time was not known, so patients were assumed to be 'on' treatment, except when it was reported by GP that the patient had stopped the treatment. From smoothed hazard function plots, it was felt that monotonically increasing or decreasing hazards could be assumed for all cohorts. A Weibull model was fitted and the estimated shape parameter indicated significant decreasing hazards over time in three of the four AD treatments and none of the ED treatments using this approach.

Conclusion: Parametric models may be a useful method to determine the significance of non-constant hazard functions. The sensitivity of the analysis will clearly be low with small numbers of events but it seems to have utility for PEM and other cohorts in databases. The validity of this signal detection method for PRN drugs is questionable.

Reference

1. Shakir SAW. Prescription-Event Monitoring. In: Strom BL, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd, 2005: 203-16

121. Effect of Antihypertensives in Hypertensive Patients' Symptomatology

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Introduction: The role of drug tolerability in adherence to antihypertensive medication remains a topic for debate.[1] Patients who experience adverse drug effects are significantly more likely to be noncompliant.[2] Outside the context of clinical trials, there is still a lack of information about patients' experiences and chronic therapy tolerability.[3]

Aim: To evaluate the relationship between perceived symptoms by hypertensive patients and the antihypertensive therapy in Primary Health Care.

Methods: We performed an observational study in Primary Health Care Unit of São Mamede de Infesta, Matosinhos. We interviewed 124 patients with essential hypertension, under antihypertensive therapy for over six months, using an original validated questionnaire about perceived symptoms. Patients were selected by consecutive sampling. They were asked to bring all their medicines used in the last 3 months. Collected data were compared with information from clinical files. Logistic regression model were used to study the relationships between drugs and symptoms (SPSS 15.0).

Table I. Relationships between antihypertensive drugs and perceived symptoms

Antihypertensive	Symptom	OR*	Effect
Indapamide	*Itching*	7.517	Enhancer
	Swollen or red face	10.456	Enhancer
Thiazide Diuretics	*Swollen or red face*	7.344	Enhancer
ACE inhibitors	*Swollen feet or legs*[a]	0.145	Protector
	Dry mouth[b]	0.203	Protector
Calcium channel blockers	*Constipation*	2.949	Enhancer
	Nausea	0.262	Protector
Cardioselective beta blockers	*Constipation*	0.204	Protector
	Palpitation	0.136	Protector
Trimetazidine[c]	*Palpitation*	0.166	Protector

*95% CI, Wald test sig.<0.05, adjusted for age and gender.

a Adjusted also for Diabetes Mellitus and Peripheral Vascular Disease.

b Adjusted also for Diabetes Mellitus.

c The analysis was extended to other cardiovascular drugs.

Results: See data in table I.

Conclusion: Some of the symptoms reported by patients are significantly related to antihypertensive therapy. These results are consistent with the pharmacological effects of the different groups of antihypertensives drugs. The data show the importance of this systematically approach for tracking patient's signals and underdiagnosed adverse reaction events.

References

1. Sabaté E. Adherence to long-term therapies: evidence for action [e-book]. Switzerland: World Health Organization; 2003 [cited 2009 May 14]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/index.html

2. Jokisalo E, Kumpusalo E, Enlund H, et al. Factors related to non-compliance with antihypertensive drug therapy. J Hum Hypertens 2002; 16: 577-83

3. Ambrosioni E, Leonetti G, Pessina AC, et al. Patterns of hypertension management in Italy: results of a pharmacoepidemiological survey on antihypertensive therapy. Scientific Committee of the Italian Pharmacoepidemiological Survey on Antihypertensive Therapy. J Hypertens 2000; 18 (11): 1691-9

122. Haematological Reactions by Vaccines: Data from the Italian Spontaneous Reporting System

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Background: Routine vaccination is now provided in all developing countries against the most common pediatric infectious disease. Vaccines are very safe, however adverse reactions (ADR) can occur, generally mild. As for the other drugs the risk profile of vaccines, especially for rare adverse effects, may not be clear until a vaccine is given to millions of people with different backgrounds and medical histories.Among serious reactions many vaccines have been associated to haematological reactions. They include thrombocytopenic purpura mainly associated to measles, mumps and rubella vaccination (MMR) or Henoch-Schönlein purpura associated to meningococcal vaccination.

Aim: Aim of this study is to analyze the report with haematological reactions associated to vaccines in the Italian Spontaneous Reporting database.

Results: Up to December 31 2008, 12 022 reports related to vaccines were present in the database. Vaccine spontaneous reporting rate in Italy in 2008 was 33.2 report per million inhabitant, with an increase of 13% compared to 2007. High variability is however present in the different Italian regions. Most of the vaccine reports (72%) refer to pediatric age (age <18 years). Fifty-three percent of reports were related to females, as expected with a great difference between children (47%) and adults (69%). Sixty-four percent of reports came from physicians working in vaccination Districts, 11% by General Practitioners, 11% by Hospital doctors, 6% by pediatricians and only 1% by nurses. Only a small part of the reports were serious (14%).Five hundred and three vaccine reports (4.1%) include at least one haematological reactions, with a slight predominance of females (55%). The most reported vaccines with haematological reactions were MMR (186 reports, 9.8% of total MMR reactions), hexavalent (64 reports, 2.4%), tetanus-diphtheria-acellular pertussis (59 reports, 3.2%), influenza (40 reports, 4.1%), tetanus (39 reports, 4.9%) and pneumococcal (37 reports, 2.9%). The most frequent reported haematological reactions were lymphadenopathy (233 reports), purpura (146 reports) and thrombocytopenia (44 reports). The analyses of serious haematological reactions highlighted thrombocytopenia or thrombocytopenic purpura by MMR with an higher incidence of these reactions when this vaccine is associated with the varicella vaccine (combined in a single preparation -MMRV- or separate), thrombocytopenia as well as haemolitic anemia and Kawasaki disease by hexavalent vaccine (respectively 9, 3 and 2 reports).

Conclusion: The risk-benefit ratio evaluation of immunization should be evaluated at a population level. For this reason efficient spontaneous reporting systems devoted to the surveillance of adverse reactions by vaccines are essential. MMR vaccine is the vaccine with the highest incidence of haematological reactions.

123. Bortezomib: Prospective Pharmacovigilance Follow Up

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Introduction: Bortezomib is approved for multiple myeloma treatment. Its safety profile has been well characterised through clinical trials in a targeted populations.

Aim: To describe adverse effects of bortezomib and its predisposing risk factors using a prospective six-months' follow-up in a "real life" cohort of patients treated for multiple myeloma.

Methods: Risk factors predisposing to adverse reactions were identified through literature review and analysis of the national database of French pharmacovigilance. Clinical information and risk factors were collected into a standardised data sheet. At each administration, adverse reactions were recorded (severity, management and outcome) and evaluated by WHO toxicity grading scale.

Results: 26 patients were included from October 2006 to March 2007 and received 627 administrations of bortezomib during this period. 294 adverse effects were reported. Reversible and transient thrombocytopenia (n = 68 events, 73% of patients), peripheral neuropathy (n = 32 events, 77% of patients), asthenia (n = 55 events, 77% of patients), gastrointestinal disorders (n = 48 events, 62% of patients), and infections (n = 36 events, 56% of patients), were the most frequently reported adverse effects. Grade 4 toxicities reported were thrombocytopenia (19% of patients), neutropenia (1 case) and hepatotoxicity (1 case). Other serious adverse effects included one case of cardiac failure and a grade 3 disabling peripheral neuropathy. History of thrombocytopenia, peripheral neuropathy and cardio-pulmonary disorders were identified as risk factors predisposing to adverse reactions to bortezomib.

Conclusion: These results confirm that the safety profile of bortezomib is comparable to literature and potential risk factors identified should be confirmed in a larger study population. Once all cases will be recorded in the national pharmacovigilance system, this information will help identify patients at higher risk of developing adverse events while treated by bortezomib.

124. NSAID Use and Safety in Italy: Variation After the Change of the Supply Status of Nimesulide

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Introduction: For many years nimesulide was largely the most used NSAID in Italy. In 2003 a signal related to a higher risk of hepatotoxicity by nimesulide in comparison with the other NSAIDs raised in Finland and Spain. A new signal on hepatotoxicity by nimesulide was raised in 2007 in Ireland. In both situations the signal was not confirmed by the Italian data. However the Italian National Authority decided on November 2007 to change the supply status of nimesulide containing products from ''renewable'' to ''not renewable'' prescription, as a measure to reduce the potential inappropriate use of nimesulide.

Aim: Aim of this study was to evaluate changes in the Italian NSAIDs market after this decision, together with data from spontaneous reporting.

Results: During the period 2000–2008 in the market of NSAIDs in Italy the main variations were related to the coxibs (marketing of rofecoxib and celecoxib, withdrawal of rofecoxib, marketing of etoricoxib). In the same period the use of nimesulide was almost stable up to 2006 (17.9 DDD/1000 inhab/die in 2000 and 18.2 in 2006, ranging from 16.9 to 19.0). The use decreased in 2007 (14.2 DDD/1000 inhab/die, –22%) and again during the 2008 (10.6 –25%, –42% on the whole in the 2 years). In the last two years, among the most used NSAIDs, the drugs with the highest increase were ketoprofen (+52%, 8.3 DDD/1000 inhab/die in 2008), ibuprofen (+57%, 5.1) and diclofenac (18%, 6.7).

Nimesulide had in 2006 the lowest spontaneous reporting rate (5.1 reports/DDD/1000 inhab./die) compared to ibuprofen (9.5), diclofenac (11.5) and ketoprofen (12.4). The spontaneous reporting rate increased in 2008 for nimesulide (14.7) as well for ibuprofen (24.2), diclofenac (19.4) and ketoprofen (24.8). Nimesulide remained the NSAID with the highest number of reports with hepatotoxic reactions, even if proportionally reduced with the decrease of sales. The percentage of reports with gastrointestinal reactions in the whole NSAIDs class showed a slight increase in the last two years (22% in 2006, 27% in 2007 and 25% in 2008).

Conclusion: Drug use data show that the alerts and the diffusion of the signal related to the nimesulide hepatotoxicity in 2003 did not have an effect on the use of this drug in Italy. On the other hand the restriction of the supply status induced a 42% reduction of the use in the following the years. Ketoprofen, ibuprofen and diclofenac showed the highest increase of use. The percentage of reports with GI reactions showed only a slight increase after the restriction.

125. Statins and Tendon Rupture

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse reaction reports to medicines from 94 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at the UMC perform periodic analyses of VigiBase to look for previously unrecognized adverse effects of medicines. An association between the use of simvastatin/ezetimibe combination therapy and subsequent tendon rupture was highlighted by routine screening of VigiBase. This was extended to a review of all reports of tendon rupture following statin use.

Aim: Analyse reports in VigiBase of an association between statin use and subsequent tendon rupture.

Methods: Clinical review of all reports of tendon rupture possibly attributable to statin use.

Results: VigiBase contained 119 reports of tendon rupture following the use of one or more statins. Reports also describing fluoroquinolone use were excluded from this review. Only one report was confounded by use of another drug (steroid) associated with tendinopathy. Four reports described concomitant use of diltiazem, a CYP3A4 inhibitor likely to increase bioavailability of the coadministered statin. Where sex was stated, 84% of reports were in males, whereas statin reporting in VigiBase is generally similar between the sexes, and female sex has been described as a risk factor for statin-associated myopathy.[1] Where duration of statin use could be determined, it was greater than one year in nearly all reports.

Discussion: There are only isolated reports in the medical literature of tendon rupture following statin use,[2] although it is apparent that many cases have been reported to regulatory authorities worldwide.[2,3] The reaction may represent a class effect for statins, but is inconsistently described in product labelling.[4,5] The mechanism for the reaction may be similar to that involved in statin-associated myopathy.[2] In this VigiBase cases series it was generally not possible to calculate the dose of statin use.

Conclusion: Tendon rupture may be a underrecognised adverse reaction to statin use.

References

1. Jacobson TA. Toward ''Pain-Free'' Statin Prescribing: Clinical Algorithm for Diagnosis and Management of Myalgia. Mayo Clin Proc 2008; 83: 687-700

2. Pullatt RC, Gadarla MR, Karas RH, et al. Tendon Rupture Associated With *Simvastatin/Ezetimibe* Therapy. Am J Cardiol 2007; 100: 152-3

3. Marie I, Delafenetre H, Massy N, et al. Tendinous Disorders Attributed to Statins: A Study on Ninety-Six Spontaneous Reports in the Period 1990-2005 and Review of the Literature. Arthritis & Rheumatism (Arthritis Care & Research) 2008; 59: 367-72

4. UK SPC, at the electronic Medicines Compendium. URL: http://emc.medicines.org.uk/ Accessed 5 March 2009

5. Micromedex healthcare series; Physician's Desk Reference. URL: http://www.thomsonhc.com/ Accessed 5 March 2009

126. Montelukast and Photosensitivity Reactions

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse reaction reports to medicines from 94 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at the UMC perform periodic analyses of VigiBase to look for previously unrecognized adverse effects of medicines. Review of VigiBase highlighted a possible association between use of montelukast, a selective leukotriene receptor antagonist used primarily in the management of asthma, and the subsequent development of a photosensitivity skin reaction. This reaction has not been previously described in the medical literature.

Aim: Analyse all reports in VigiBase of photosensitivity following use of montelukast.

Methods: Clinical review of all reports in VigiBase where photosensitivity was possibly attributable to use of montelukast.

Results: To April 2009, VigiBase contained 16 reports of photosensitivity following use of montelukast, received from eight countries. In 15 reports montelukast was the only suspected drug. The ages of the patients ranged from 4 to 72 years. Four patients were noted to improve on withdrawal of the drug, and two of these patients experienced a recurrence when montelukast was reintroduced (positive rechallenge). Coreported drugs were mainly antiasthmatic agents (for example, salbutamol, fluticasone, beclometasone), which have not been previously described to cause photosensitivity,[1] and there was no consistent pattern of other drugs that may serve as an alternative explanation for the reaction.

Discussion: Reports in VigiBase provide support for an association between use of montelukast and development of a photosensitivity skin reaction. There are no published case reports of photosensitivity following montelukast use, and no information on photosensitivity in the labelling for montelukast.[1-3]

Conclusions: Montelukast use may be associated with the subsequent development of a photosensitivity reaction.

References

1. The electronic Medicines Compendium. Datapharm Communications Ltd. [online]. Available from URL: http://www.medicines.org.uk/ [Accessed 2009 April]

2. Martindale. Thompson Micromedex database [online]. Available from URL: http://www.thomsonhc.com [Accessed 2009 April]

3. Physician's Desk Reference. Thompson Micromedex database [online]. Available from URL: http://www.thomsonhc.com [Accessed 2009 April]

127. Gender Distribution in International Adverse Drug Reaction Surveillance

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Background: The susceptibility to certain adverse drug reactions (ADRs) differs between males and females.[1,2] Males and females also use different types of drugs[3] and the nature of ADRs experienced diverges.[4,5] Limited information is available on how this affects routine monitoring of large collections of individual case safety reports (ICSRs).

Aim: To investigate the pattern of reported gender distribution in different subsets of data in international collections of ICSRs.

Methods: Data was extracted from the WHO global ICSR database, VigiBase,[6] currently with more than 4.7 million reports from over 90 countries (June 2009). The WHO adverse reaction terminology system organ classes (SOC) were used in the grouping of adverse reactions, and the WHO Anatomical Therapeutic Chemical (ATC) classification was used in the groupings of drugs using the 1st level, anatomical main group. Data from 1968 to 2008 was used to evaluate gender distribution over time, while the analyses of the following subsets of data were limited to the years 1998 to 2008: gender distribution by country, age group, type of reporter, SOC, and ATC.

Results: A female dominance of around 60% was shown to have been constant since the international drug monitoring started in 1968. Among the 49 countries with at least 500 reports during the study period, only three had a male dominance: China, Macedonia, and India. Slovakia had the greatest proportion of female reports (66%). A female dominance among the reports was seen in patients aged 15 years and up. Consumers reported most commonly for females (68%), while pharmacists reported almost equally for males and females (50.6%). In all SOCs, a female dominance was seen except for the male reproductive disorders SOC. In all ATC groups, a female dominance was seen apart from the blood and blood-forming organs group where the female proportion was 48%.

Conclusions: This investigation showed a higher reporting rate for females across most studied subsets in the international collection of ICSRs in VigiBase. The heterogeneous pattern of gender distribution by type of reporter seen in this study needs further investigation.

References

1. Kando JC, Yonkers KA, Cole JO. Gender as a risk factor for adverse events to medications. Drugs 1995; 50 (1): 1-6

2. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol 2008; 83: 1-10

3. Rademarker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001; 2 (6): 349-51

4. Domecq C, Naranjo CA, Ruiz I, et al. Sex-related variations in the frequency and characteristics of adverse drug reactions. Int J Clin Pharmacol Ther Toxicol 1980; 18 (8): 362-6

5. Tran C, Knowles SR, Liu BA, et al. Gender differences in adverse drug reactions. J Clin Pharmacol 1998; 38 (11): 1003-9

6. Lindquist M. Vigibase, the WHO Global ICSR Database System: Basic Facts. Drug Information Journal 2008; 42 (5): 409-19

128. International Reporting Pattern of Individual Case Safety Reports in Children

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Background: Drug safety problems in children deserve particular focus in international monitoring. This is because each individual nation has relatively few reports for children. The WHO global individual case safety report (ICSR) database VigiBase,[1] containing over 4.7 million

ICSRs from more than 90 countries (June 2009), makes a valuable source for international monitoring.

Aim: To investigate the reporting pattern of the most commonly reported suspected Adverse Drug Reactions (ADR) for different age groups.

Methods: Reports from VigiBase, received between 2004 and April 2009, were extracted. The following age groupings were used: <1 months (neonates), 1–23 months, 2–11 years, 12–16 years, and ≥17 years.[2] The top 10 reported reactions for each age group were reviewed using WHO-adverse terminology reaction critical preferred terms. Medicines reported in suspected connection to the top reactions were also reviewed. Reports with unspecified age and reports listing vaccines were excluded from the analysis. Due to a published review on paediatric data for ICSRs originating from the US by the food and drug administration,[3] US reports were excluded.

Results: During 2004 to April 2009, after having excluded reports with unspecified age, US, and vaccine reports, 566 032 reports had been entered into VigiBase. 8.3% of the reports concerned patients ≤16 years old and 91.7% listed ages of ≥17 years. 0.3% of the reports were issued for <1 month olds, 1.4% for 1–23 month olds, 4.1% for 2–11 year olds, and 2.4% for 12–16 year olds.

In all age groups, except for the neonates, face oedema and angioedema were listed as the most commonly reported serious reactions, or as the second and third reaction as for the adolescents and adults, most commonly in connection to antibiotics, NSAIDs, and other analgesics/antipyretics. Among the top 10 reported reactions, granulocytopenia and thrombocytopenia were reported in all age groups in connection to various medicines in the different age groups.

Stevens-Johnson Syndrome was only reported among the top reactions in the 2–11 year old group, most commonly with antiepileptic and antibiotic medicines. Hallucination and aggressive reaction were common for the 2–11 and the 12–16 year olds, mostly in connection to psychostimulant medicines. The most reported reactions for the neonates were reported in connected to antiretroviral medicines.

Conclusions: Serious allergic reactions in children issued during recent years are reported for commonly used medicines that have been on the market for decades and continue to represent a great burden of disease for a vulnerable population like children.

References

1. Lindquist M. Vigibase, the WHO Global ICSR Database System: Basic Facts. Drug Inf J 2008; 42 (5): 409-19

2. European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. January 2001 CPMP/ICH/2711/99 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf: [Accessed 2009 June 10]

3. Johann-Liang R, Wyeth J, Chen M, et al. Pediatric drug surveillance and the Food and Drug Administration's adverse event reporting system: an overview of reports, 2003-2007. Pharmacoepidemiol Drug Saf 2009; 18 (1): 24-7

129. A Temporal Association Between Prescriptions of Antipsychotic Drugs and Pneumonia in Electronic Health Records

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Background: Electronic health records are a valuable source of clinical information that can highlight possible safety signals.[1] In screening out-patient records in the IMS Health Disease Analyzer database from the United Kingdom, a temporal pattern had been identified of increased registrations of pneumonia subsequent to the prescribing of some antipsychotic medicines. An increased risk of pneumonia has been identified in hospitalized patients in the Netherlands with current use of antipsychotic medicines.[2]

Aim: To further characterize the temporal association between antipsychotic prescriptions and pneumonia in out-patient records, with respect to age, type of pneumonia, and antipsychotic class.

Methods: ICD10 terms relating to pneumonia and prescriptions within the Ephamra ATC atypical (N05A1) or conventional antipsychotic (N05A9) groups were included in the study. A separate analysis was carried out for patients 65 years and older. Further analysis was done for groups of pneumonias classified as "acute pneumonia" (ICD10 codes J110, J12x-16x, J181,188,189, J220), "bronchopneumonia" (ICD10 code J180), and "hypostatic pneumonia" (ICD10 codes J182, J69x). The observed rate of pneumonia registrations in different time periods, relative to antipsychotic prescription, was contrasted to the overall registration rate of pneumonia relative to prescriptions of other drugs in the same dataset. Statistical shrinkage and uncertainty intervals around the computed observed-to-expected ratios were used to reduce the risk of highlighting spurious associations.

Results: Recordings of pneumonia occurred more frequently than expected among all ages within a month of receiving antipsychotic prescriptions compared to the expected rate of pneumonia in the same population prior to the prescription. An increased registration of "acute pneumonia" subsequent to atypical antipsychotic prescriptions was identified in the elderly, which was not observed after the conventional antipsychotic prescriptions. Bronchopneumonia, on the other hand, showed a striking and persistent increase after both atypical and conventional antipsychotic prescriptions in this age group. Few registrations of "hypostatic pneumonia" were noted.

Conclusions: This exploratory study showed a trend of a higher frequency of pneumonia recorded very soon after antipsychotic prescriptions, especially for bronchopneumonia. Further research is needed to investigate if undiagnosed pneumonia is a frequent cause of antipsychotic use, or if there is indeed a direct mechanism by which the antipsychotic medicines result in an increased risk of pneumonia.

References

1. Norén GN, Bate A, Hopstadius J, et al. Temporal pattern discovery for trends and transient effects: its application to patient records. Proceeding of the 14th ACM SIGKDD international conference on Knowledge discovery and data mining 2008: 963-971; http://doi.acm.org/10.1145/1401890.1402005

2. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008; 56 (4): 661-6

130. Deafness in Drugs for Erectile Dysfunction

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Background: Over the last decade the treatment of erectile dysfunction (ED) in men has been revolutionised by the availability of phosphodiesterase 5 (PDE5) inhibitors. ED is a common disorder in males with increased prevalence associated with age and presence of cardiovascular disease.[1] A published case report of sudden deafness associated with sildenafil[2] led FDA and EMEA to update the safety information in this product class, raising concerns regarding its potential ototoxicity.[3] Prescription-Event Monitoring studies of ED treatments PDE5 inhibitors (sildenafil, vardenafil, tadalafil), as well as apomorphine

have been conducted in England during its immediate post-marketing period.

Objective: To examine the possible association between the PDE5 inhibitors and deafness and to quantify the incidence rate.

Methods: All cases of deafness were identified. Because of the 'as required' (PRN) nature of these treatments, the exposure time was calculated using observation time (date of first prescription to end of study period) unless the prescriber specified a stop date. Incidence Rate Ratio (IRR) comparing the PDE5 inhibitors with apomorphine (control) for the first nine months was calculated using a Poisson Regression model. The incidence rate (IR) for the PDE5 inhibitors was also calculated for the first two years data where available.

Results: During the nine month study period, there were 45 cases of deafness reported for 66 125 patients (36 846 person-years) in three PDE5 inhibitors cohorts, the IR was 1.22 deafness per 1000 years. In the apomorphine cohort there were 8 cases of deafness reported for 11 185 patients (8266 person-years), the IR was 0.97 deafness per 1000 years. The mean age (SD) was slightly greater in the apomorphine cohort compared to the PDE5 inhibitor cohorts, 60.1 (0.22) and 59.1 (0.10), respectively. The estimated IRR adjusting for age was 1.33 (95% CI: 0.62, 2.85). Although that ratio is not suggesting important differences, the deafness rate increases by 33% when taking PDE5 inhibitors compared with apomorphine. Over the two year observation period, the IR of deafness in patients prescribed PDE5 inhibitors increased (95 cases, 61 518 person-years; 1.54 deafness per 1000 years).

Conclusions: There was no evidence of an increased risk of deafness in patients taking PDE5 inhibitors compared to those taking apomorphine over the first nine months of observation after starting treatment. Use of observation time at exposure time will bias the result to the null hypothesis of no difference. However, there was some evidence the incident rate for the three PDE5 inhibitor cohorts increased over time.

References

1. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54-61

2. Mukherjee B, Shivakumar T. A case of sensorineural deafness following ingestion of sildenafil. J Laryngol Otol 2007; 121: 395-7

3. Almanza A, Navarrete F, Vega R, et al. Modulation of voltage-gated Ca2+ current in vestibular hair cells by nitric oxide. J Neurophysiol 2007; 97: 1188-95

131. Integrating Effective Safety Risk Management into Clinical Programmes

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There is increasing regulatory focus on both sides of the Atlantic on effective safety risk management in both drug development and marketing. In the EU and USA this regulatory attention is focussed most closely on the submission for marketing authorisation, where approvals are now effectively conditional on the completion of risk management commitments. The FDA has additionally made it clear that they expect to have an ongoing dialogue with companies during development where the drug is likely to require risk management activities after registration.

Companies have responded to these demands by committing to risk management activities during the submission process, wherever these are required by the product concerned.

Commitments at submission can, however, be very time consuming for a team already heavily committed to the launch process and substantial levels of investment will be needed to set up and run late phase studies to fill product knowledge gaps.

As the requirements for the EU RMP are clearly stated, there is an obvious advantage to integrating the safety risk management needs from the regulators into the drug development process. This will ensure that the submission package is as complete as possible and will reduce the impact of post authorisation commitments.

In many companies, however, Pharmacovigilance has an image problem when it comes to its relationship with Clinical Development and other colleagues. PV departments must find a way to build an understanding of their new proactive role across their organisations to ensure that the business benefits of a robust, lifecycle-long, safety risk management process are delivered.

The specific demands of safety risk management therefore require the development of an integrated set of solutions, building new cross-functional processes and relationships across the organisation.

Successful safety risk management hinges on four critical solutions:

- A safety risk management process that defines actions and accountabilities across the product development lifecycle.
- Cross-functional forums for assessment of safety risks and determination of risk management actions.
- Governance to ensure that safety risks are appropriately integrated into development programmes and that actions committed to are effectively carried out.
- Skills development for PV staff to ensure that they can meet the new demands of safety-focussed team leadership.

Lessons from the implementation of a lifecycle-long safety risk management system will be discussed with a specific focus on the success factors in integration with the existing drug development processes.

132. Drug Interactions Programs: Clinician's Needs and Program's Realities

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Electronic programs to aid the physician with prescribing drugs can be valuable tools for the safety of patients and may become part of the quality assurance in medical practice. Drug interactions programs give risk estimations of drug combinations, which dependent on the factors considered-also patient characteristics-will be more or less accurate. Currently there exists no program which is able to predict the outcome of a drug (combination) treatment, the interplay of a multitude of influencing variables being too complex.

Clinician's needs: Clinicians wish a precise risk prediction of a drug combination therapy, this not only for the combination of 2 but also for many drugs. The program should also take into account patient factors such as renal or hepatic insufficiencies, age, gender, illnesses, pharmacogenetic polymorphisms, diet, and lifestyle.

Today's program's abilities: The following analysis is based on the 5 programs: Drug Reax,[1] genelex,[2] pharmavista,[3] mediQ,[4] PSIAC[5] which all reference the source of their information (see table I).

Conclusion: The complexity of the interplay between drugs and the patient variables represent a seemingly insurmountable challenge at least as per today. One can imagine that new mathematical models to combine all these variables will make a more precise outcome prediction one day possible. The clinician has to be aware of the advantages but also of the shortcomings of today's drug interaction programs.

Table I. Analysis of the 5 programs

Abilities	Yes	Partly	No
Risk estimation of combination >2 drugs		Genelex, mediQ	Drug Reax, pharmavista, PSIAC
Pharmacokinetic information	Genelex, mediQ	PSIAC, Drug Reax, pharmavista	
Pharmacodynamic information	Drug Reax, Pharmavista, mediQ, PSIAC	Genelex	
Side effect profile	Drug Reax, Pharmavista, mediQ, PSIAC	Genelex	
Pharmacogenetics	Genelex, mediQ		Drug Reax, pharmavista, PSIAC
Age, gender, comorbidities			None, sometimes in the text a warning
Diet/lifestyle	Genelex, mediQ, PSIAC		Drug Reax, pharmavista
Recommendations to the clinician	Drug Reax, pharmavista, mediQ, PSIAC		Genelex
Risk estimation without clinical cases	mediQ, PSIAC	Genelex for pharmacokinetics, Drug Reax and pharmavista for class effects	

References

1. www.micromedex.com
2. www.GeneMedRx.com
3. www.pharmavista.net
4. www.mediQ.ch
5. www.psiac.de

133. Serotonin Syndrome Following Varenicline Use

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse reaction reports to medicines from 94 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at the UMC perform periodic analyses of VigiBase to look for previously unrecognized adverse effects of medicines. Routine screening of VigiBase highlighted an association between varenicline, a non-nicotine medicine used as an aid for smoking cessation in adults, and development of serotonin syndrome. Serotonin syndrome, often the result of an inadvertent drug interaction,[1] has not been previously described in association with varenicline.

Aim: Analyse reports in VigiBase of an association between varenicline use and subsequent development of serotonin syndrome.

Method: Clinical review of all reports of serotonin syndrome possibly attributable to varenicline use.

Results: VigiBase contains seven reports of serotonin syndrome following varenicline use. In six of the reports varenicline was used in combination with antidepressants known to be associated with serotonin syndrome. Time from initiation of the drug to onset of the reaction ranged from 1–13 days.

Discussion: Symptoms of serotonin syndrome usually occur within minutes to hours after drug exposure.[1] The relatively late onset in two cases (after 8 and 13 days) could be explained by the dosing regime for varenicline, which involves a stepwise dose increase over two weeks. The specific term 'serotonin syndrome' is not listed in varenicline labelling,[2,3] however, most of the symptoms of serotonin syndrome (nausea, vomiting, diarrhoea, muscle spasms, tremor, restlessness, increased blood pressure) are listed. Varenicline is reported to have no clinically meaningful pharmacokinetic drug interactions,[2,3] however this does not preclude the possibility of a pharmacodynamic interaction resulting in increased serotonin levels.

Conclusion: Reports in VigiBase suggest that varenicline may have an additive effect when used together with antidepressants and thereby result in an increased frequency of adverse effects, including serotonin syndrome, in some patients. These effects may not become manifest until the dose of varenicline is increased in the second week of treatment.

References

1. Boyer E W, Shannon M. The Serotonin Syndrome. N Engl J Med 2005; 352: 1112-20
2. Chantix (varenicline) product information [online]. New York: Pfizer 2008. Available from: URL:http://www.pfizer.com [Accessed 2009 Feb 02]
3. The electronic Medicines Compendium (eMC) [online]. Available from: URL:http://emc.medicines.org.uk/ [Accessed 2009 Feb 02]

134. Signal Detection in a Global Database of Reports of Suspected Adverse Drug Reactions

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse reaction reports to medicines from 94 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at the UMC perform periodic analyses of VigiBase to look for previously unrecognized adverse effects of medicines. The reports are statistically analysed using the Information Component (IC). Each report lists at least one medicine and one suspected adverse drug reaction (ADR), giving rise to a number of potential drug-ADR pairs ("combinations"), any of which may represent new, clinically significant signals. A combination of automated and manual techniques is used to examine VigiBase for new signals.

Aim: To detect new signals of drug safety issues in VigiBase.

Method: All combinations entered in VigiBase during the previous quarter are screened automatically on the basis of statistical disproportionality ($IC_{025} > 0$), global relevance (number of reporting countries > 1) and the presence of either an emerging signal (delta-IC > 1) or a serious signal for a new drug (critical ADR term and drug first entered in the database within the last 5 years). Combinations selected by the automated method are further screened by UMC staff for expectedness (based on labelling, standard drug references, and further literature searching as required) and confounding factors (particularly disease under treatment, concomitant medical condition, or concomitant drugs). Those combinations judged to potentially represent new safety issues are sent for detailed review by experienced pharmacovigilance experts. Those combinations assessed as being new, clinically interesting signals, may be published in the Restricted WHO document "SIGNAL", which is circulated to all members of the WHO programme.

Results: As of 1 June 2009, there were 4 725 231 reports in VigiBase. During 2008, a mean of 113,046 combinations were entered into VigiBase each quarter. Of these, 2521 (0.56% per quarter) were flagged via the automated triages. 372 (18%) of these were sent for detailed evaluation, resulting in the publication of 17 items in "SIGNAL" to date.

Conclusions: A combination of automated and manual techniques continues to find new signals in a spontaneous ADR database. It is worth noting that all WHO programme members now have direct access to VigiBase, including its statistical functionality.

135. Automated Text Extraction as an Aid to Signal Evaluation

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Background: The WHO Programme for International Drug Monitoring coordinates the collection of spontaneous adverse drug reaction (ADR) reports to medicines from 94 member countries. These reports are entered into a global database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC). Staff at the UMC perform periodic analyses of VigiBase to look for previously unrecognized adverse effects of medicines. As many as half of the reported reactions have been previously documented in the medical literature, so a method was sought to prefilter established reactions, preferably using a widely-available drug information database.

Aim: To investigate the use of automated text extraction from a database of previously described ADRs as a tool to aid routine signal detection work in VigiBase.

Method: Martindale,[1] a widely-used source of drug information, was used as the free text source, from which adverse reaction terms were extracted. Before matching, both the free text and the ADR terms were pre-processed; importantly, all words were replaced by their stems. All terms consisting of more than one word were permuted, that is, all possible orders of the individual words were matched against the free text. A lexicon of common synonyms, such as 'bleeding' for 'haemorrhage' was also incorporated. Extracted terms from Martindale were compared to a list of 708 potential new ADR signals generated from VigiBase. Independently, two pharmacovigilance experts reviewed Martindale to determine if the VigiBase signals could be considered listed there. Their findings were classified as not found, found, or an equivalent clinical term found. The results of the text mapping and clinical review were compared.

Results: See table I. Automatic searching detected 28% of reactions found by manual methods, and only 8% of reactions where it was considered that a clinically equivalent term was found manually. The specificity of the automatic method was quite high, with a rate of false discoveries of 7 out of 55 (13%).

Table I. Results

	Not Found	Found	Equivalent term found
Manual results	408	117	183
Found automatically	7	33 (28%)	15 (8%)

Discussion: Manual checking for known ADRs is time-consuming when screening a large ADR database. The usefulness of drug information databases in this respect could be improved by incorporation of a standardised ADR terminology.

Conclusion: Automated text mapping may be a useful tool in filtering out known ADR signals. A highly specific automatic method may be very useful in sparing much manual work.

Reference

1. Martindale. Thompson Micromedex database [online]. Available from URL: http://www.thomsonhc.com [Accessed 2009 April].

136. Pregnancy Outcome in Women Exposed to Atypical Antipsychotics

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Introduction: Few prospective studies are available on the safety of the new atypical antipsychotics olanzapine and risperidone in the first trimester of pregnancy.

Aim: To evaluate the rate of major malformations after first-trimester exposure to risperidone and olanzapine in comparison to conventional antipsychotics (chlorpromazine, cyamemazine and haloperidol) or non teratogenic agents. Other outcomes of interest included the rate of spontaneous and elective abortions and neonatal characteristics at birth.

Methods: From 1997 to 2007, pregnant patients were included following risk evaluation request and followed up prospectively. Patients from the antipsychotic groups should have been exposed during embryogenesis for a psychiatric indication. Patients from the control group were matched to those of the atypical antipsychotic group based on maternal age (±2 years) and gestational age at the time of the first request (±2 weeks).

Results: Data on 89 women exposed to olanzapine (n = 62), risperidone (n = 26) or to both drugs successively (n = 1) were compared to those of 143 women exposed to conventional antipsychotics and 178 control group women. There were 66 live births (74.2%, 1 set of twins) in the atypical antipsychotic group compared to 159 (89.3%, 2 sets of twins) in the control group ($p < 0.05$), and 111 (77.6%, 3 sets of twins) in the conventional antipsychotic group ($p = 0.55$). Elective termination of pregnancy was found in 13 (14.6%) patients in the atypical antipsychotic group vs. 7 (3.9%) in the control group ($p < 0.05$), and 21 (14.7%) in the conventional antipsychotic group ($p = 0.99$). Spontaneous abortion occurred in 8 pregnancies (9%) in the atypical antipsychotic group vs. 12 (6.8%) in the controls ($p = 0.51$), and 10 (7%) in the conventional antipsychotic group ($p = 0.58$). After exclusion of chromosomal anomalies (2 in the conventional antipsychotic group), 2 major malformations were found in the atypical antipsychotic group (3%, both in Olanzapine-exposed fetuses) compared to 3 (1.9%) in the control group (RR: 1.63; 95% CI: 0.27, 9.99) and 8 (6.8%) in the conventional antipsychotic group (RR: 0.42; 95% CI: 0.09, 2.03). Birth weight in full-term babies was

higher in the atypical antipsychotic group (3467 ± 497 g) than in the conventional antipsychotic group (3244 ± 496 g) (p = 0.015), but was not significantly different with the control group (3356 ± 430 g, p = 0.14).
Conclusions: Despite limitations due to sample size, our study suggests that exposure to olanzapine or risperidone is not associated with an increased risk of major malformations.

137. Adverse Cutaneous Reactions to Drugs. First Case Series in the Uruguayan University Hospital

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Background: Cutaneous drug adverse reactions (CDRs) are of particular interest within all adverse drug reactions (ADR) due to their frequency, potential severity and because of the importance of an early diagnosis. There is scarce data about ADR in Uruguay, and no data about CDRs. Antimicrobial agents, anticonvulsivants and non-steroidal anti-inflammatory drugs (NSAID) are the drugs associated to the highest risk of CDRs; however, any pharmacologic group of drugs may cause this kind of ADR.[1-3] Only a small proportion of CDRs are severe but we emphasize the importance of knowing the drugs related to potentially severe CDRs.
Objectives: To promote and continue the development of Pharmacovigilance in the University Hospital. To identify and characterize CDRs in hospitalized patients and the drugs involved.
Methodology: All the patients hospitalized in the Hospital de Clínicas for suspected CDRs between 11/01/08 and 04/30/09 were included. The information was obtained from the clinical record and patient interview. The imputability was established using the Karch and Lasagna algorithm. We analyzed age, gender, drugs involved, caused disease, and evolution.
Results: Six CDRs were identified; 5/6 were female, the age media was 39 years. Three morbilliform exanthemas were diagnosed, two Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS) and one Stevens Johnson (HIV infected patient). The drugs involved were: Sulphonamides (Trimethoprim–Sulfamethoxazole and Phthalylsulfathiazole) (n = 2), antituberculous drugs (Rifampicin, Isoniazid and Pirazinamide) (n = 1), Allopurinol (n = 1), Aspartic Insulin (n = 1) and Carbamazepine (n = 1). Three patients had a life threatening reaction; one of them was admitted to the intensive care unit. No deaths occurred. All of them recovered after the withdrawal of the drug. Two of the ADR were categorized as probable and four as possible. Polypharmacy was detected in 4/6 cases.
Conclusions: Even though our data are still limited, CDRs were more frequent in women with polypharmacy and half of the cases were caused by antimicrobial agents, as reported in other series.[2] It is worth to mention that the severest reaction was suffered by an HIV infected patient, which is another risk factor for this kind of ADR.[4] In spite of the low frequency of severe CDRs and their unpredictable behavior, we emphasize the importance of an early diagnosis and the withdrawal of the drug involved, which are the most effective therapeutic measures. It is important to continue this kind of studies in order to know the local frequency of this health problem.

References

1. Roujeau Jc, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331(19): 1272-85

2. Svensson C, Cowen E, Gaspari A. Cutaneous Drug reactions. Pharmacological Rewies 2000; 53: 357-79

3. Revuz J, Valeyrie- Allanore L, Reacciones medicamentosas. In: Bolognia J, Jorizzo J, Rapini R, editors. Dermatología. Elsevier, 2003: 333-54

4. Coopman S, Johnson R, Platt R y cols. Cuatneous Disease and Drug Reactions in HIV infection. N Engl J Med 1993; 328: 1670-3

138. Interstitial Pneumonia Induced by Fluoxetine

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Introduction: Fluoxetine-induced lung disorders have been rarely reported and only five cases have been so far published.[1-5]
Aim: To describe a case of interstitial diffuse pneumonia associated with prolonged fluoxetine treatment and to review other cases recorded in the French pharmacovigilance database as well as published case reports.
Case report: A 86-year old woman was hospitalized in November 2008 for a history of progressive worsening dyspnoea for 1 year. She had no history of smoking or allergic disease, but underwent surgery and a successful 6-month course of chemotherapy for colon cancer 10 years before. The patient had been treated for 20 years with fluoxetine 20 mg/day. Clinical examination found diffuse crackles bilaterally, most prominently over the posterior lung bases. A chest computed tomography scan evidenced ground-glass opacities in both lungs. Resting gasometry was normal, but oxygen desaturation was found during a walking test. The FEV_1 was normal and diffusing capacity for carbon monoxide was moderately reduced. Bronchoscopy was normal with no specific findings on the bronchoalveolar lavage. Other investigations ruled out an autoimmune, cardiac, neoplastic or infectious etiology. Two months after the cessation of fluoxetine, her dyspnoea and pulmonary testing improved.
Other data sources: Selection of relevant cases from the French pharmacovigilance database with fluoxetine among the suspected drugs retrieved 9 other cases of pulmonary disease including 4 cases of diffuse interstitial pneumonia and 5 cases of pulmonary fibrosis (6 males, mean age: 64 years). Fluoxetine was the only suspected drug in 3 cases. In four cases, the treatment duration ranged from 3 to 34 months (mean 18 months) whereas a prolonged exposure not otherwise specified was noted in 3 cases (no data in 2 cases). Six patients recovered or improved within 10 days to 5 months after fluoxetine withdrawal, and one died from pulmonary complications (outcome unknown in 2 cases). The five published cases consisted of interstitial pneumonitis in 4 patients and pulmonary granulomatosis in 1.
Conclusion: Our case as well as other cases extracted from the French pharmacovigilance suggest that fluoxetine is a possible cause of interstitial pneumonia. This is further exemplified by a published case report with recurrence of the symptoms after fluoxetine readministration.[2]

References

1. Bass SP, Colebatch HJH. Fluoxetine-induced lung damage. Med J Aust 1992; 156: 364-5

2. Gonzalez-Rothi RJ, Zander DS, Ros PR. Fluoxetine hydrochloride (Prozac)-induced pulmonary disease. Chest 1995; 107: 1763-5

3. de Kerviler E, Trédaniel J, Revlon G, et al. Fluoxetin-induced pulmonary granulomatosis. Eur Respir J 1996; 9: 615-7

4. Vandezande LM, Lamblin C, Wallaert B. Interstitial lung disease linked to fluoxetine. Rev Mal Respir 1997; 14: 327-9

5. Braun D, Nippert B, Loeuille D, et al. Interstitial pneumopathy induced by fluoxetine. Rev Med Interne 1999; 20: 949-50

139. A Prescription Protocol to Prevent Intravenous Immunoglobulin-Related Serious Adverse Drug Reaction

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Introduction: Intravenous immunoglobulin (Ig IV) is now being used to treat humoral immune deficiency, several chronic inflammatory and autoimmune diseases.[1,2] Adverse drug reactions (ADRs) can occur during or after treatment and some of these are serious and potentially preventable.[3,4]

Aim: To assess Ig IV related-ADR and whether a prescription protocol directed by a risk-factor profile would reduce the occurrence of immunoglobulin related-ADR.

Design: Monocentric, French prospective study in an internal medicine unit of a teaching hospital. Two periods were undertaken. During the first period (4 months), each physician prescribed Ig IV without standardized protocol, based their prescription on the usual use. A systematic monitoring of risk factor for ADR was undertaken for each patient treated. During the second period (twenty months), a prescription protocol determined by a standardised questionnaire permitting identification of ADR risk factors was completed at each visit. A prescription protocol (as such hydratation, reduced dose…) directed by a risk-factor profile (chronic renal failure, diabetes, arterial hypertension, migraine, Ig A deficiency, sepsis, dehydratation, cardiovascular and thrombosis risk factors)[3,4] was created and information was given to nurses and each new prescriber of immunoglobulin in the ward.

Population: All patients treated with Ig IV were prospectively included. Patients included in the first period were not included in the second period.

Collected data: For each potential Ig-associated ADR, clinical pharmacologists assessed causal relationship between the reaction and the immunoglobulin treatment. Frequency of immunoglobulin related adverse drug events was compared before and after protocol use.
Statistical tests were performed to describe population and compare risk factors and ADR between the two periods using STATA 8.0

Results: During this twenty-four month-study, 59 patients were included and 307 courses of immunoglobulin were prescribed. Half of patients were treated for humoral deficiency (0.4 g/kg/course) and the others for auto-immune diseases (2 g/kg/course). During the first period, 55 courses of immunoglobulin were prescribed to twenty-one patients. Eleven adverse drug events occurred to nine patients (20% of all 55 courses). In six cases patients presented with acute renal failures during the treatment and two thromboses. Whereas, during the second period, 252 courses were prescribed to thirty-eight patients and only nine adverse drug events occurred (3.6% of of all 252 courses). One renal failure occurred and one thrombosis.

Conclusion: Use of risk-factor directed prescription protocol, for Ig IV treatment, respecting summary of products recommendations, greatly reduced ADR, particularly acute renal failure and acute thrombosis.

References

1. Hamrock D. Adverse events associated with intravenous immunoglobulin therapy. Int Immunopharmacol 2006; 6 (4): 535-42

2. Orbach H, Katz U, Sherer Y, et al. Intravenous immunoglobulin: Adverse effects and safe administration. Clin Rev Allergy Immunol 2005; 38 (2): 123-37

3. Itkin YM, Trujillo TC. Intravenous immunoglobulin-associated acute renal failure: case series and literature review. Pharmacotherapy 2005; 25 (6): 886-92

4. Dalakas MC, Clark WMC. Strokes, thromboembolic events, and IVIg. Rare incidents blemish an excellent safety record. Neurology 2003;60:1736-7

140. Eleven Cases of Epileptic Seizures Closely Related to the Administration of Thiocolchicoside: Data from the French Pharmacovigilance database

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Background: Thiocolchicoside, a semi-synthetic derivative of an analog of colchicine, colchicoside is widely used as a muscle relaxant in orthopedic, traumatic and rheumatological conditions. This drug is generally well tolerated.

Methods: Recent spontaneous notifications of seizures associated with this drug led us to search similar cases in the French pharmacovigilance database.

Results: Eleven cases of epileptic seizures associated to the use of thiocolchicoside (considered as a suspect drug) and not related to self-poisoning were found and evaluated.The patients were 5 women and 6 men with a mean age of 43 y (13-94). Three of them had a previous history of seizures but were controlled by their anti-epileptic treatment. In seven cases, the duration of treatment varied from some minutes to 3 days. The route of administration was oral in all cases except 2 cases with periarticular infitrations and 1 case with an intramuscular injection. In seven cases, NSAIDs were also administered as well as in two cases lidocaïne. These drugs were considered as concomitant suspect drugs. The two cases with non concomitant suspect drugs and no clinical condition compatible with blood-brain barrier disruption occurred in the first case several minutes and in the second one the second day after the instauration of the thiocolchicoside treatment.

Discussion-Conclusion: These results are in accordance with experimental data demonstrating a significant interaction of thiocolchicoside with GABA-A receptors (with marked antagonism of various subtypes of these receptors) in spinal cord and cerebral cortex leading to focal and secondary generalised convulsions when the drug is applied topically to the cerebral cortex. Only a clinical series of three cases of epileptic seizures has been published.[1]
These cases emphasize the potential neurotoxicity of thiocolchicoside which must be taken into account when determining the risk-benefit ratio of the drug when treating patients with muscular contractures. Then this drug must not only be avoided but contra-indicated in patients with an history of seizures or with clinical conditions leading to blood-brain barrier disruption and convulsions must be mentioned in the SPCs.

Reference

1. De Riu PL, et al. Epileptic seizures after treatment with thiocolchicoside. Epilepsia 2001; 42: 1084-6

141. The Benefits to a Pharmacovigilance Department of Having a High Quality, Efficient Medical Information System

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Being one of the primary means for health care professionals and consumers to contact a pharmaceutical company, the medical information department has an important role to play in the collection of

accurate safety information relating to a company's products. With rapidly advancing technology in communications improving the speed, quality and accessibility by which we communicate data, there is the opportunity for pharmaceutical companies to become more readily accessible to health care professionals and consumers, and provide comprehensive, timely and accurate support on their products and therapeutic areas of interest. With advancing communications technology, it is important that companies ensure that any new technology is fully validated and checked regularly so as to ensure that important safety information can be relayed to the pharmacovigilance unit and other key stakeholders. As small and mid size Pharma start to take advantage of global markets it is important to consider language barriers which may hinder the communication of important safety information. Language difficulties may be overcome by the use of company affiliates or outsourcing the medical information service. Continuous training of the medical information unit on the company's product information, and evolving safety profile is important to ensure that important new safety information which may arise during initial contact is fully documented to ensure ultimately that as much information can be gathered and communicated to authorities. Getting as much information during the initial contact is critical saving time for all stake holders as less follow up may need to be performed. Solid training and deployment of tools such as approved Frequently Asked Questions (FAQs) can be helpful. The medical information unit provides health care professionals with the opportunity to tap into the knowledge and resource of Pharma, and as such the unit may potentially be used as a part of a risk minimisation strategy (education). The use of the medical information service in the provision of a risk minimisation strategy deserves further evaluation. Collecting quality metrics from the medical information department on service delivery is critical to ensure that potential safety information can be communicated to the pharmacovigilance unit rapidly and effectively. Collection of key medical information metrics ensures a seamless transfer of data from health care professionals and consumers, and reassures customers that Pharma are listening and value feedback received on its service and products. Consequently, with a high quality medical information service health care professionals may be more prone to communicating ADRs.

142. Safety Issues of HIV Drugs, Regulatory Consequences

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Background: Pre-marketing research is limited in establishing the full safety profile of any new drug. As a result regulators have to communicate serious adverse drug reactions (ADRs) that are identified post approval urgently to health care providers through Direct Healthcare Professional Communications (DHPCs). Half of all HIV drugs registered in the EU required at least one DHPC in the past 10 years. It is unclear to what extent regulators could have identified these ADRs pre- approval and how they applied this knowledge when assessing subsequent marketing applications of new HIV drugs.

Objectives: The aim of this study is to explore the effect of serious ADRs of an HIV index drug on the subsequent approval of similar HIV drugs in terms of thoroughness of safety assessment.

Methods: Centrally registered HIV drugs that received DHPC between 1999-2008 were identified as index drugs. Each index drug was paired with a follow-on HIV drug in the same ATC-4 class. DHPC's and European Public Assessment Reports (EPARs) were reviewed with regard to symptoms and incidence rates of ADRs. Thoroughness was assessed as the safety population being in accordance with ICH/EMEA guidelines, and attention paid to ADR-symptoms in pre-clinical-, pharmacokinetics- and clinical trials and in post marketing commitments.

Results: We identified six index with one to six follow-on HIV drugs; totalling twelve different drugs. Three ADRs were drug-drug interactions (DDIs); the other three were intracranial haemorrhage, neuromuscular weakness and severe skin/hepatic reactions. Eight drugs were registered under exceptional circumstances (EC) or conditional approval (CA).
All but one follow-on drug had information in the EPAR on the ADR, using different approaches. The DDIs were addressed by pre-clinical trials and in the Summary of Product Characteristics or with DDI studies. Two of the other ADRs were addressed by postmarketing surveillance commitments, intracranial haemorrhage was not addressed.
Short-term safety population was adequate for four index and seven follow-on drugs, whereas long-term safety population was adequate for one respectively three drugs. The rest was not assessable from the EPARs, five of these eight were registered under EC/CA.

Conclusion: In general, safety issues of HIV index drugs are taken up in the registration process of follow-on drugs using different approaches determined by the nature of the ADR. The little information in EPARs on long-term safety population seems partly explained by the EC/CA registration.

143. Knowledge About Reporting System of ADRs and Reasons for Their Underreporting in Croatia

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Introduction: The importance of adverse drug reactions (ADRs) monitoring was recognized in Croatia already in 1974 when the National Centre for Adverse Drug Reaction was instituted in the University Hospital Zagreb. In March 2005, after new legislation came into force, the obligation of pre- and post- marketing drug surveillance was delegated to the Agency for Medicinal Products and Medicinal Devices.

Aim: As to date there is no published work in this area, we wanted to identify reasons for pharmacists' and physicians' underreporting of ADRs in Croatia and to measure their knowledge about the reporting system.

Methods: Closed, pre-coded questionnaire was developed. Content validity was established using a panel of experts and a field test following which the questionnaire was piloted to ensure reliability. Following testing and change of initial questionnaire, 814 questionnaires were distributed to pharmacist and physicians in the period from April 2006 to April 2009 across 8 Croatian towns. Data from the questionnaire were entered into PAWS 17. and were analysed descriptively and inferentially.

Results: The response rate was 78.9%. It was found that physicians' knowledge about reporting system in Croatia is greater than pharmacists' knowledge ($t = -4679$ $p < 0.05$).Pharmacists who reported ADRs differed in knowledge from pharmacist who did not report ADR ($t = -3291$, $p < 0.05$) in contrast to physicians whose reporting did not depend on knowledge about reporting ($t = 0{,}326$, $p = 0.745$). Lack of time was considered as a constraint for not reporting ADRs by more physicians than pharmacists ($\lambda = 41{,}08$, $p < 0.05$), whereas lack of knowledge was a reason for not reporting for more pharmacists than physicians ($\lambda = 4{,}39$, $p < 0.05$). Most valuable predictors for

underreporting are lack of time, lack of knowledge about reporting, not reporting expected ADRs and fear of revealing identity of reporter (R^2=0.225, $p < 0.05$).

Conclusion: Results suggest that targeted education can increase reporting of ADRs in pharmacists, whereas less time consuming reporting system would achieve the same with doctors.

144. Seizures Induced by Ketoprofen

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Introduction: Ketoprofen is a propionic non steroidal anti-inflammatory drug (NSAID). The commonest side-effects of these drugs are generally gastro-intestinal disturbances such as discomfort, nausea and diarrhoea. Central Nervous System (CNS) adverse reactions are rare and include headache, vertigo, dizziness, nervousness and insomnia.

Aim: In this study, we report a case of an infrequent NSAID adverse reaction of young man who experienced seizures after the intake of Ketoprofen, notified to the National Centre de Pharmacovigilance of Tunis and validated according the French method of imputability.[1]

Observation: RM, a 16 years-old young man with a history of asthma in childhood, received a punch on his chest wall and presents a thoracic pain, on the 20 febrary 2009; he didn't get any injury on his head. He received one tablet of Ketoprofen® and 2 tablets of Panadol®.

On the 21 febrary 2009 at midday, he received again one tablet of Ketoprofen® and 2 tablets of Panadol®. Around 21h30 of the same day (9 hours and a half later), the patient presents loss of consciousness, tonic extension of the members, hypersialorrhea without urinary incontinence. The symptoms resolved within 2-3 min without any treatment, with slow return to complete lucidity: after seizures, the patient was confused and uncooperative for several minutes before full recovery. Neurological examination showed no abnormalities. General analyses were normal, as was the cerebral tomodensitometry and the electroencephalogram (EEG). The patient was followed up to 4 months, and during this time he didn't receive any medication, and he didn't represent any type of seizures again.

The intrinsic sore of the two drugs were plausible.

Discussion: We retained the responsibility of ketoprofen in this case in front of:

- The normality of the analysis, the radiological examination and the electroencephalogram.
- The absence of similar clinical picture 4 months later,
- The bibliographic data: seizures are rather reported with ibuprofen, and other NSAID.[2-4]

We haven't retained the responsibility of Panadol because there haven't been reported any seizures with this drug yet.

We couldn't perform any oral rechallenge with Ketoprofen® nor with Panadol®, because of the gravity of the reaction.

In this case, the seizures appeared after a therapeutic dosage of drugs, and weren't followed by any symptoms suggesting an overdosage. These features indicate that the drugs were a trigger factor.

This case must lead to more attention to seizures appearing after ingestion of NSAID.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Hoppman A, Peden JG, Ober SK. Central Nervous system side effects of nonsteroidal anti-inflammatory drugs. Arch Intern Med 1991; 151: 1309-13

3. Sanchez-valiente S. Encefalopatia mioclonica originada por el tratamiento con Diclofenac. Rev Neurol 1995; 23: 1226-7

4. Sanchez–Hernandez MC, Delgado J, Navarro AM, et al. Seizures induced by NSAID. Allergy 1999; 54: 78-92

145. Do Adverse Drug Reaction Reports Differ Between Consumers And Healthcare Professionals?

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Introduction: The primary procedure for reporting suspected adverse drug reactions (ADRs) in the UK is the Yellow Card (YC) scheme. Since 2005, consumers (patients/their representatives) have been able to submit YC reports.[1,2] Consumer reporting may avoid the filtering effect of reporting via healthcare professionals (HCPs) and increase knowledge of suspect medicines.[3]

Aim: To compare the patient characteristics, suspected drugs, and suspected ADRs associated with patient submitted YCs with those submitted by HCPs.

Methods: The Medicines and Healthcare products Regulatory Agency (MHRA) electronically records information from all submitted YC reports. They provided data for all YCs submitted during October 2005-September 2007 (excluding industry reports). Data included information on category of reporter (e.g. consumer, doctor, pharmacist), age and gender of person experiencing the ADR, number and names of suspect drugs, anatomical drug classification, date drug commenced, reaction terms coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the date, seriousness and reported outcome of the suspected ADR. These variables were compared between HCP and consumer YC reports using chi-squared tests for categorical data and Mann-Whitney tests for continuous data. Differences significant at $p < 0.001$ are reported.

Results: There were 26129 YC reports received from the MHRA (80.2% from HCPs and 19.8% from consumers). Compared to HCPs, consumers reported significantly higher numbers of reactions per report (median 3 vs 2), and more reactions involving nervous system (40.5% vs 20.4%), general (38.4% vs 22.9%), and gastrointestinal disorders (32.5% vs 19.5%). Overall consumers reported significantly higher numbers of different suspect drugs per report; they specifically reported significantly more distinct suspect drugs than HCPs for the nervous (33.2% vs 26.2%) and cardiovascular system (21.8% vs 13.5%), whereas HCPs reported significantly more anti-infectives for systemic use (19.4% vs 13.6%) and antineoplastic/immunomodulating agents (9.5% vs 2.5%). Compared to consumers, HCPs reported significantly more ADRs that caused hospitalisation (18.8% vs 12.9%), were life-threatening (11.1% vs 6.2%) or caused death (2.6% vs 0.7%).

Conclusions: Consumers tend to report more reactions and more suspect drugs than HCPs, but less of these reactions resulted in serious events. This suggests that consumers may be less knowledgeable or specific than HCPs about ADRs and may therefore tend to include all possible reactions. HCPs may also report more serious ADRs because the consumer was perhaps too ill to report it themselves.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Download reporting forms and promotional material for the Yellow Card Scheme. http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reportingsuspectedadversedrugreactions/Downloadreportingformsandpromotionalmaterial/index.htm (Accessed 11th June 2009)

2. House of Commons Health Committee. The influence of the pharmaceutical industry. Fourth report of session 2004-5

3. Hammond IW, Rich D. Consumers usurp spontaneous adverse event reporting in the United States. Pharmacoepidemiol Drug Saf 2005; 14: S8-9

146. Hyperglycemia as a Side Effect of Tacrolimus in Renal Transplant Patients

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Introduction: Tacrolimus is an immunosuppressant agent used for organ transplantation. Its therapeutic drug monitoring (TDM) is essential because of the narrow therapeutic windows of this drug. Blood levels are monitored routinely by enzyme linked immunoassay (ELISA). It has a great variability of pharmacokinetics parameters and one of its main adverse effects is hyperglycemia.

Aim: The aim of this study is to seek for a correlation between tacrolimus blood concentration and hyperglycemia.

Methods: It consists on a retrospective study (2008-2009), 480 TDM was carrying out by enzyme linked immunoassay (ELISA). A total of 135 subjects were evaluated, all renal transplanted.

Results: The average age was 31.7 years (9 to 61 years) and the sex ratio M/W was 2.

Our results show a mean blood tacrolimus concentration (Cm) about 8.65 ng/mL (thérapeutic interval: 8-12 ng/mL). Results show also that 50.6% were under the therapeutic range; 31.25% were in therapeutic interval and 18.15% have a toxic concentration.

A hyperglycemia was found in 16.3% of patients with a Cm about 11.84 ng/mL. It was 8.4 ng/mL in patients with normal glycemia. The difference was statistically significant between Cm tacrolimus and occurrence of this side effect ($p < 0.001$).

Analysis of renal function show no difference between the two groups ($p = 0.69$). Analysis of dose show a significant difference between the two groups (0.08 mg/kg/j in group with normal glycemia and 0.1 mg/kg/j in group with hyperglycemia, $p = 0.001$).

Conclusions: Our results support interindividual variability of biodisponibility of tacrolimus and show that hyperglycemia due to this drug is not rare, and closely related to blood concentration. Hyperglycemia is due to reduced insulin secretion but the mechanism remains unknown.

147. Assessment of the Risk Factors of Bleeding Due to Oral Anticoagulant Treatment: A Prospective Study in Patients with an INR≥5 Admitted to the Amiens University Hospital

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Introduction: Bleeding due to vitamin K antagonists (VKA) occurs more frequently when the INR is over the therapeutic range. An INR≥5 is associated with an excessive bleeding risk. However, in many observations with high INR, there is no apparent bleeding. The fact that other factors should be combined to lead to bleeding is questioned.

Methods: This prospective, epidemiological, analytical and descriptive study was carried out from 13/01/206 to 09/04/2007. In order to assess the main risk factors (RF) leading to bleeding, patients taking oral VKA, admitted to the Amiens University Hospital with an INR≥5, were studied. Two groups of patients were identified:

1. patients with bleeding, and
2. patients without bleeding.

These two dependant variables (bleeding or not) were compared in relation with potentially explanatory variables linked to the patients (gender, age, glomerular filtration rate, history, compliance…) or linked to the treatment (INR, dosage, clinical indication, treatment duration, contraindication, drug interactions..).

Results: In this study, 600 patients were included. There was a bleeding in 27% and 80% of them were serious. Bleeding led directly or took part in the death of patient in 17%. The half of these haemorrhages was considered as avoidable or potentially avoidable. Patients with an INR>10.5 were 21%. Such a high INR was the RF that emerged with the greatest power from this study. The other significant RF were: previous high INR not managed, chronic alcoholism, recent trauma or digestive lesions, prescription off the indications of the Summary of the Product Characteristics (SPC), drug interactions (acetaminophen,heparin,allopurinol), recent patient mistake (lack of compliance, misunderstanding of the instructions). Age, gender, severe kidney failure, other drug interactions were not RF. However, some of these factors could explain the INR increase, particularly the kidney function and some recent drug interactions.

Conclusion: Different points emerge from this study. A big part of patient had INR sometimes very high. The close control of the INR is essential for trying to reduce the bleeding risk. This critical situation is probably underestimated (the half of the bleedings was avoidable). An action seems to have to be led:

1. with patients in order to improve the compliance by repeated therapeutic education actions with an assessment of the patients,
2. with the health care professionals, with respect to the SPC, in order to ensure the continuity of health care (coordination between health professionals) and a real therapeutic education (When? Where? By whom? How?).

148. Corneal Toxicity Caused by Hydroxychloroquine

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Introduction: Hydroxychloroquine has been used for the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other inflammatory and dermatologic diseases. This drug can cause ocular toxicity, mainly retinal toxicity. Corneal toxicity is an exceptional adverse effect.[1] We report a case of hydroxychloroquine-induced photophobia resulting from corneal complications.

Case report: A 40-year-old woman was treated by hydroxychloroquine at a dose of 7,27 mg/kg per day for autoimmune disorder, since June 2008. In August 2008, she started complaining from blurred vision, halos around lights and photophobia. Electroretinography and visual evoked potential were performed and showed no damage in the retina and optic nerve. Hydroxychloroquine was discontinued in September 2008. All symptoms resolved in 2 months after drug cessation.

Discussion: In this case, the imputation score of hydroxychloroquine evaluated by *the French* Method of p*harmacovigilance*was plausible C2S2I2.[2]

Corneal toxicity is largely dose-related. The risk of ocular damages of hydroxychloroquine is small with daily doses of up to 6.5 mg/kg ideal (lean) body weight; if absolute body weight is used as a guide to dosage, it could result in an overdosage.[3] Exceeding the recommended daily dose increase the risk of ocular toxicity, and may reflect the potential risk for lenticular or retinal changes.[4] Cessation of the drug is the only effective management of the toxicity.

Conclusion: Appropriate examinations should be performed regularly in order to decide whether to reduce or stop this medication when damage is still mild, preclinical, or reversible.

References

1. Tehrani R, Ostrowski RA, Hariman R, et al. Ocular toxicity of hydroxychloroquine. Semin Ophthalmol 2008; 23: 201-9

2. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments : actualisation de la méthode utilisée en France. Thérapie 1985; 40: 111-8

3. Ingster-Moati I, Bui Quoc E, Crochet M, et al. Severe chloroquine- and hydroxychloroquine-induced retinopathy. 2006; 29: 642-50

4. Tripp JM, Maibach HI. Hydroxychloroquine-induced retinopathy: a dermatologic perspective. Am J Clin Dermatol 2006; 7: 171-5

149. Fixed Drug Eruption to Pheniramine

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Introduction: Pheniramine is a histamine H1-receptor antagonist that is primarily helpful in treating allergy symptoms. It is mostly included in combination with other drugs and can be used for symptomatic treatment of nasal congestion.

A few skin reactions to H1-antihistamines have been described in the literature.[1] FDE with H1-antihistamines was exceptional. We report a case of fixed drug eruption with pheniramine in male genitalia.

Case report: A 54 year-old man had a history of two episodes of cutaneous eruption in the glans penis. The lesion occured in 2006 and in 2007, 3 days after taking Fervex® (paracétamol, vitamin C and pheniramine) for nasal congestion. This eruption was circular, erythematous and oedematous. At each episode, lesion persisted two weeks and then fade slowly to residual hyperpigmented lesion.

On July 2008, 24 hours after taking Fervex®, he presented a reactivation of the old lesion on the same site. The eruption cleared completely with residual pigmentation in 2 weeks. The diagnosis of fixed drug eruption was retained.

A several reexposure to paracetamol and vitamin C (contained in Efferalgan®) in 2008 and 2009 did not reactivate this lesion.

Discussion: The imputation score of pheniramine was valuted to C3S3I4 (very likely) because of *suggestive* chronology (positive rechallenge) and *suggestive* semiology (FDE is specific to drugs).[2] Skin reactions provoked by antihistaminic are rare.[3] FDE are mainly linked to piperazine-derived compound such as cetirizine, lévocétirizine and hydroxyzine.[1]

Conclusion: To the best of our knowledge, this is the first report of FDE to pheniramine.

References

1. Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. Am Acad Dermatol 2004; 50: 953-6

2. Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputabilité des effets inattendus ou toxiques des médicaments: actualisation de la méthode utilisée en France. Thérapie 1985; 40: 111-8

3. Epstein E. Dermatitis due to antihistaminic agents. J Invest Dermatol 1994; 12: 1512

150. Fixed Drug Eruption Due to Miconazole

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Introduction: Fixed drug eruption (FDE) caused by systemic azole antifungals is extremely rare.[1] Some cases of FDE were described with fluconazole, tinidazole, itraconazole, and ketaconazole.[2] We report a case of FDE due to miconazole in the male genitalia with positive oral provocation test.

Case report: A 55-year-old man developed two episodes of circular, erythematous and oedematous eruption on the glans penis since miconazole gel was started for oral fungal infection. The first episode appeared on January 2009, 2 weeks after an initial exposure to miconazole oral gel. Lesions persist two months and then fade slowly to residual oval hyperpigmented patches. The second episode appeared on April 2009, 6 hours after reexposure to miconazole gel, resulting in a reactivation of the old lesions with development of new lesions at other sites on the glans penis. The eruption cleared completely with residual pigmentation in 2 weeks. An oral challenge test to miconazole reproduced the same eruption at the same site.

Discussion: The imputation score of miconazole was very likely, C3S3I4, because of *suggestive* chronology (positive rechallenge) and *suggestive* semiology (FDE is specific to drugs).

Cross sensitivity with the azoles drug, such as fluconazole and itraconazole,[1] have been described.[3] Patients sensitive to one azole drug should be advised to avoid all other azole drugs.[4]

Provocation test is the only reliable method to confirm the causative drug.

Conclusion: To our knowledge, this is the first case of FDE to miconazole confirmed through oral provocation.

References

1. Gurvinder P, Thami MD. Fixed drug eruption caused by itraconazole: Reactivity and cross reactivity. J AM Acad dermatol 2008

2. Ghislain PD, Ghislain E. Fixed drug eruption due to fluconazole: a third case. J Am Acad Dermatol 2002; 46: 467

3. Khandpur S, Reddy BS. Fixed drug eruptions to two chemically unrelated antifungal agents. Indian J Dermatol 2000; 45: 174-6

4. Arika Bansal, Rashmi Kumari, M Ramam. Fixed drug eruption due to cross reaction between two azoles used for different indications. Indian J Dermatol 2008; 74: 81-81

151. Survey of Adverse Drug Reaction Reporting by Medical Practitioners in the Midi-Pyrénées Area of France

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Introduction: General practitioners (GPs) have an important role in detection and reporting of suspected ADRs. However, underreporting is a major limitation of spontaneous reporting system. The aim of the study was to assess the knowledge and attitudes associated with ADR reporting in a group of GPs and to evaluate their interest in online ADR reporting.

Methods: The survey was conducted among a sample of 382 GPs in the Midi-Pyrénées area of France, from October 2008 to January 2009. A first postal questionnaire about social demographic characteristics, years of experience and knowledge with ADR reporting was sent by mail. A second phone contact assessed their expectations of an online ADR reporting.

Results: The response rate was 50.3% after the first questionnaire and 27.4% following the phone contact. Respondents were 72% male and

28% female. The median age was 53 years [25th–75th centiles: 46–57]. Physicians were located in rural (23%), small urban (36%) and urban (41%) areas. Half of GPs had practising for 26 years. 46% of them have never reported ADR and 47% have a incorrect knowledge about ADR reporting. They believed that ADR reporting is not mandatory for unexpected (19% of GPs) or serious (16%) ADRs. GPs mainly reported ADR by mail (80%). They have not experienced online reporting. 80% of them believed that online reporting system will be useful and 44% have confirmed its use in the future.

Conclusion: Knowledge of GPs in ADR reporting system remains limited. Education and training will be important in increasing ADR reports from GPs. A website of online reporting could contribute to improve spontaneous ADRs reports and communication with Pharmacovigilance centres.

152. Anaphylaxis to Iobitrodol

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Introduction: Iobitridol is a low-osmolar, non-ionic monomers, contrast medium (CM) used for urography and intravascular. It is a safe CM with minor adverse effect compared with high osmolarity and ionic CM.[1] We report a case of anaphylaxis induced by iobitridol with severe positive rechallenge.

Case report: ZN, a 46-year-old man, has a history of hypertension, renal failure, hypercholesterolemia and coronary disease. He had in 2005 coronary arteriography for coronary artery disease.

On April 2009, he had a new coronary arteriography, performed with an injection of iobitridol. The patient had no side effects during the exam. Six hours later, the patient developed dyspnea, cough and agitation. He was immediately given oxygen with intravenous corticoids. All symptoms resolved within 20 minutes.

On May 2009, the patient had another coronary arteriography with an injection of iobitridol. During cardiac catheterization, the patient developed violent chest tightness, nausea, vomiting, epigastric pain, and a decline in blood pressure with tachycardia. He was immediately intubated for artificial respiratory. His clinical status gradually improved over the next several hours with intravenous infusions of corticoids.

Discussion: The diagnostic of anaphylaxis caused by iobitridol was retained because of compatible delay in the first episode and, mainly, the severe positive rechallenge. The first adverse reaction presented by the patient was classified as mild delayed anaphylaxis.[2] The second reaction was classified as severe anaphylaxis (grade 3).[2]

The frequency of mild anaphylactic reactions ranges from 0.7% to 3.1% in patients receiving low-osmolar non-ionic contrast material.[3] The risk for serious or severe reactions has been estimated to be 0.02–0.04% with non ionic contrast material.[4]

Conclusion: This case reported an exceedingly uncommon adverse event with a low-osmolar non-inonic CM, iobitridol.

References

1. Esplugas E, Cequier A, et al. Comparative Tolerability of Contrast Media Used for Coronary Interventions. Drug Safety 2002; 25: 1079-98

2. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004; 114: 371-6

3. Lieberman PL, Seigle RL. Reactions to radiocontrast material: anaphylactoid events in radiology. Clin Rev Allergy Immunol 1999; 17: 469-96

4. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175: 621-8

153. Teratogenesis with Antiepileptic Polytherapy: Is It Topiramate?

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Introduction: Risk of malformation in epilepsy is two to three fold higher than in general population, mainly attributable to Antiepileptic drugs (AED). Polytherapy is more critical.

We describe one case of birth defects with 4 AED.

Similarity between experimental animal data and clinical developmental side effects are noteworthy for topiramate.

Description: A 25 years old woman, epileptic since the age of 9, was treated during all pregnancy with lamotrigine 400 mg/day, topiramate 1g/day, clonazepam 20 mg/day, and only during the two first months oxcarbazepine150 mg/day, associated with folic acid 0.4 mg/day.

Despite this treatment, maternal seizures occurred regularly during the pregnancy.

Detailed ultrasound examination at 23 weeks after the last normal menstrual period (LNMP) showed developmental defects: craniofacial anomalies including retrognathism, microtia, low- set ears, long filtrum and short femurs. Parents refused prenatal diagnosis and a girl was born at 41 weeks after the LNMP, height of 49 cm for a weight of 3480 kg.

Discussion: Interpretation of birth defects in infants born to mother exposed to anticonvulsant medications is difficult, mainly in polytherapy. In this case, two drugs are considered to be safe during pregnancy: clonazepam and lamotrigine.

Premarketing study in animals with Oxcarbazepine found craniofacial, cardiovascular and skeletal abnormalities in the offsprings of rats, clinical data are safe.

Topiramate is teratogenic in mice, rats and rabbits. At low dose, craniofacial malformations and reduced fetal body weight can occur, whereas, at higher dose, limb reduction defects are described.

Conclusion: Similarity between experimental and clinical effect is rare. Responsibility of topiramate can be evoked because craniofacial malformations and limb reductions are described in our case report and in animal data.

154. Keloids During Isotretinoin Therapy: A Case Report

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Introduction: Isotretinoin, a retinoid, is given by mouth for the treatment of severe cystic acne. The initial oral dose is 0.5 mg/kg daily. The adverse effects are generally reversible and dose-related. The most common are dryness of the skin with scaling, fragility and erythema, especially of the face. Keloids associated with isotretinoin therapy have arisen after dermabrasion or laser therapy but there are isolated reports of spontaneous appearance of keloid.[1,2]

Method: A case report of keloid was notified in March 2009 in our Pharmacovigilance Center.

Results: This report describes a 19 years old man who was admitted in outpatients' department of Dermatology. He was given isotretinoin 30 mg daily for acute acne and after 3 months he developed keloid formation. Isotretinoin was not stopped but initial dose was reduced to 20 mg daily. Ten weeks later, keloid lesions persisted and increased. Clinical examination revealed more than 200 hypertrophic, keloidal

scars. These were most predominant on the patient's back and shoulders. Isotretinoin was stopped. Cryotherapy and siliconed dressing were administred without effect. Patient was treated by compressive clothes. After withdrawal of isotretinoin, no more lesions appeared. There was no family or personal past history of keloid formation in this patient.

Discussion: Retinoids are known to modulate connective tissue metabolism. They inhibit collagenase synthesis leading to excessive accumulation of collagen. Keloids are abnormal growths of fibrous tissue that develop after form due to excess collagen deposition in the dermis and subcutaneous tissue.

Conclusions: Chronologic criteria are compatible with the role of the drug. No treatment-induced keloid was reported and the patient has not past medical history. These results suggest that isotretinoin might be the cause of keloids.

References

1. Dogan G. Possible isotretinoin-induced keloids in a patient with Behcet's disease. Clin Exp Dermatol 2006; 31 (4): 535

2. Ginarte M, Peteiro C, Toribio J. Keloid formation induced by isotretinoin therapy. Int J Dermatol 1999 Mar; 38 (3): 228-9

155. Adverse Reactions Associated with Interferon

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Introduction: Interferons are glycoproteins involved in blocking viral replication in newly infected cells and are cytokines that modulate the body's immune response. Alpha interferon is used as a treatment for viral hepatitis and certain cancers, such as leukemia. Beta interferon is used as a treatment for some types of multiple sclerosis. The aim of this study was to assess adverse reactions related to interferons and notified to the Centre National de Pharmacovigilance.

Methods: It was a retrospective study involving all the reports of adverse reaction associated with interferons from December 1991 to December 2007. We considered the cases where the interferons has the most important imputation score alone or in association with other drugs. We collected the age, the sex, the medical history, the indication, the type of adverse reaction, the delay, the outcome and the imputation score. The cases were analysed according to Begaud method of imputation.[1]

Results: There were 7 cases including 2 men and 5 women. The age varied form 26 to 57 years. The patients had no history of hypersensitivity to drugs. Pegasys® (interferon alpha 2A) was implicated in 4 cases, Avonex® (interferon beta 1a) in 2 cases and Rebif® (interferon beta 1a) in 1 case. Pegasys® was indicated for chronic hepatitis C and Avonex® and Rebif® were indicated for multiple sclerosis plaques. In 2 cases, interferon was administered alone and in the other 5 cases, interferon was associated with other drugs. Skin eruption occurred in 4 cases, haematological effect in 2 cases and anaphylaxis in 1 case. The skin eruption healed spontaneously without stopping the interferon in 2 cases. The eruption healed in the 2 other cases after stopping the interferon. The 3 other adverse reaction required interferon withdrawal. In 1 case, interferon was implicated with an imputation score of I3 (likely), in 3 cases with I2 (likely) and in 3 cases with I1 (doubtful).

Discussion: There was a predominance of the skin eruption (4/7). These adverse reactions are usually mild and transient. They occur with an incidence of about 1–10%. Hematological effects occurred in 2 cases. These effects are serious and require regular haematological monitoring. There was no report of flu syndrome which is generally a frequent adverse reaction and seems to occur in about more than 50% of treated patients.

Conclusion: Our study reported 7 notifications of adverse reactions related to interferon with a predominance of cutaneous effect.

Reference

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

156. Adverse Reactions Associated with Macrolides

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Introduction: Macrolides are antibiotics which are usually considered as save alternative in case of hypersensitivity to penicillin. The aim of this study was to assess adverse reactions related to macrolides and notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all the reports of adverse reaction associated with macrolides from December 1991 to December 2007. We considered the cases where the macrolide has the most important imputation score alone or in association with other drugs. We collected the age, the sex, the medical history, the type of adverse reaction, the delay, the outcome and the imputation score. The cases were analysed according to Begaud method of imputation.[1]

Results: There were 34 cases including 15 men and 19 women. The age varied form 7 months to 66 years, with a mean of 31 years. Six patients had a history of hypersensitivity to penicillin and two others had previous reaction to macrolides. Except in one case where the macrolide was administered intravenously, the other 33 cases the macrolide was administered orally. Spiramycin was implicated in 17 cases, erythromycin in 11 cases, clarithromycin in 3 cases, roxithromycin in 2 cases and azithromycin in 1 case. Adverse reaction were skin eruption in 29 cases (including a case of fixed drug eruption and a case of polymorph erythema), gastro-intestinal effects in 3 cases, anaphylactic shock in 1 case (with clarithromycin) and liver test abnormalities in 1 case. In 3 cases, macrolides were implicated with an imputation score of I3 (likely), in 15 cases with I2 (likely) and in 16 cases with I1 (doubtful).

Discussion: There was a predominance of the skin reaction (29/34). These reactions are usually rare with a frequency less than 1%.[2] Gastro-intestinal effects which are reported in literature to be the most common untoward adverse reaction related to macrolides (between 4% with roxithromycin to 27% with erythromycin) were reported in only 3 cases in our study.[2] Anaphylactic reactions to macrolides are exceedingly uncommon. We reported in our study one case of anaphylactic shock with clarithromycin.

Conclusion: Our study reported 34 spontaneous notifications of adverse reactions related to macrolides with a predominance of skin reaction.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Ruef C, Blaser J. Miscellaneous antibacterial drugs: aminoglycosides, chloramphenicol and thiamphenicol, fluoroquinolones, glycopeptides. In: Dukes MNG, Aronson JK, editors. Meyler's side effects of drugs. 14th ed. Amsterdam: Elsevier, 2004

157. Adverse Reactions Associated with Streptokinase

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Introduction: Streptokinase can be responsible of hypersensitivity reaction, cardiovascular and neurological effects. The aim of this study

was to assess adverse reactions related to streptokinase and notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all the reports of adverse reaction associated with streptokinase during 2008. We collected the age, the sex, the medical history, the indication, the type of adverse reaction, the delay, and the outcome and the imputation score. The cases were analysed according to Begaud method of imputation.[1]

Results: Six cases were collected including 5 men and 1 woman. The age varied from 45 to 64 years. Four patients had a history of coronaropathy and the two others had no medical history. In the six cases, streptokinase were infused for myocardial infarction. There were one case of anaphylactic shock, one case of seizures, and 4 cases of hypotension without tachycardia. The delay varied from 10 minutes to 30 minutes after starting the infusion of streptokinase. Except the case of the anaphylactic shock, the infusions were not stopped. The signs resolved after infusions and correct monitoring of the blood pressure. All the cases had an imputation score of I2 (likely).

Discussion: Only six notifications of adverse reactions related to streptokinase during one year were collected despite the widespread use of this drug. This low number of notification emphasise the limitation of spontaneous notification in estimating the incidence of such events. Two serious adverse events were observed. Anaphylaxis is not an exceptional event with streptokinase. Seizures are a rare event. Symptoms such as hypotension or bradycardia are frequent and are not related to anaphylaxis. They are induced by the reperfusion and don't need stopping streptokinase infusion.

Conclusion: Our study reported six notifications of adverse reactions related to streptokinase, during a year emphasising, the limitation of the spontaneous notification.

Reference

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

158. Adverse Effect Following Immunization Associated with Diphtheria-Tetanus-Pertussis and Oral Poliomyelitis Vaccine

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Introduction: Diphtheria–tetanus–pertussis (DTP) and oral poliomyelitis vaccine (OPV) are included in the Tunisian vaccination Program. It is administered at the age of 2 months and 3 months. The common reported adverse effects are local reactions and skin reactions. The aim of this study was to assess adverse reactions related to DTP and OPV and notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all the reports of adverse reaction associated with DTP and OPV from December 1992 to December 2007. We considered the cases where the vaccine has the most important imputation score alone or in association with other drugs. We collected the age, the sex, the medical history, the type of adverse reaction, the delay, the outcome and the imputation score. These cases were analysed according to Begaud method of imputation.[1]

Results: There were 14 cases including 6 men and 8 women. The age varied from 3 months to 34 years: 11 cases in infants and 3 cases in adults. The patients had no history of hypersensitivity to drugs or vaccine. Adverse reactions were local reactions in 8 cases, skin eruption in 2 cases, neurological effects in 3 cases and myalgia in one case. The delay was immediate in 5 cases, less than 12 hours in 6 cases, and more than 12 hours in 3 cases. The outcome was favourable in all the cases. The imputation score was I3 (likely) in 5 cases, I2 (plausible) in 3 cases and I1 (doubtful) in 6 cases.

Discussion: There was a predominance of the local reaction (8/14). The incidence of such reaction is reported in literature to be more than 10%.[2-4] Three serious neurological effects were reported, including one case of encephalitis. Encephalitis is an exceptional adverse effect with DTP and OPV.

Conclusion: Our study reported 14 notifications of adverse reactions related to DTP and OPV, with 3 serious neurological effects.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Nikkels AF, Nikkels-Tassoudji N, Pierard GE. Cutaneous adverse reactions following anti-infective vaccinations. Am J Clin Dermatol 2005; 6: 79-87

3. Tapiainen T, Cherry JD, Heininger U. Effect of injection site on reactogenicity and immunogenicity of acellular and whole-cell pertussis component diphtheria–tetanus–pertussis vaccines in infants. Vaccine 2005; 23: 5106-12

4. Cassidy WM, Jones G, Williams K, et al. Safety and immunogenicity of concomitant versus non concomitant administration of hepatitis B, tetanus–diphtheria, and measles–mumps–rubella vaccines in healthy eleven- to twelve-year-olds. Journal of Adolescent Health 2005; 36: 187-92

159. Tongue and Lips Hyperpigmentation with Dysgeusia During Imurel® Therapy for a Crohn Disease

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Azathioprine, the 6-mercaptopine precursor is an immunosuppressive drug commonly used in inflammatory bowel diseases. The most frequent side effects of this drug are known to be dose-related bone marrow depression and liver damage. Cutaneous side-effects are usually rashes or alopecia.

Hyperpigmentation was reported in literature with immunosuppressant therapy but as a naevi eruption. Dysgeusia can be related to either azathioprine or the Crohn disease.

We report a case of tongue and lips hyperpigmentation with dysgeusia in a patient undergoing chemotherapy with azathioprine for a Crohn disease.

ZL is 45 years-old, with a history of face oedema three hours after ingestion of blue fish on 2006.

On mars 2008, she was diagnosed a Crohn disease and started a treatment with azathioprine. A year later, she developed an hyperpigmentation of the tongue and in the junction between the lips and the skin. The palate, the gums, and the internal mucosa of the cheeks were normal pigmented. She also described a dysgueusia after the intake of the azathioprine tablets which disappear a few hours later. A lingual biopsy was done and found a keratose without dysplasia.

The patient was given a Dalibour cream for her lips and the treatment wasn't stopped. The evolution was characterized by a little improve in the hyperpigmentation of the lips whereas the hyperpigmentation of the tongue became cyclic: sometimes it eases and sometimes it becomes more marked.

We retained the role of azathioprine in front of:

- an absence of such clinical features in the past,
- a compatible delay (around one year after the onset of the azathioprine therapy) with an iatrogenic cause,

- the persistence of the symptoms under azathioprine therapy,
- the absence of other aetiology.

In literature, some case-reports were found in which hyperpigmentation (multiple melanocytic naevi) was observed with immunosuppressive treatement. The most plausible theory is that an intact immunological state normally inhibits the proliferation of melanocytic lesions.[1,2] In our case the hyperpigmentation was only mucous (tongue and the junction between the lips and the skin). Besides, tongue and skin hyperpigmentation were reported during PEG-Interferon-α/Ribavirin therapy.[3]

The dysgeusia which appears just after the drug intake and disappear a few hours later suggests the role of azathioprine. We found one case of reversible dysgeusia related to azathioprine in literature.[4]

This case is interesting because of the mucous site and the type of the eruption associated with dysgeusia. It hasn't been reported such clinical picture with azathioprine yet.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Woodhouse J, Martin EV. Eruptive nevi of the palms and soles. J Am Acad Dermatol 2000; 52 (5 Suppl. 1): S96-100

3. Gurguta C, Kauer C, Bergholz U, et al. Tongue and skin Hyperpigmentation during PEG-Interferon-α/Ribaverin Therapy in dark skinned non Caucasian patients with Chronic Hepatitis C. Am J Gastroenterol 2006; 101: 197-8

4. Richert S, Bloom EJ, Flynn K, et al. Widespread eruptive dermal and atypical melanocytic nevi in association with chronic leukaemia: case reportand review of the literature. J Am Acad Dermatol 1996; 35: 326-9

160. BCG Vaccination - Experience in France: Risk Minimiation Tools

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Introduction: BCG SSI vaccine, administered by intradermal route (ID), became the sole antitubercular vaccine available in France following withdrawal of the mutipuncture vaccine currently used until decembre 2005. In January 2006, an increase in the number of locoregional Adverse Drug Reactions (ADR) was observed. One hypothesis of these locoregional ADR was that paediatricians and general practitionners were not familiar with the ID injection technique. As a result, since February 2006, on request of the French Health Products Safety Agency (Afssaps), the regional pharmacovigilance center (RPVC) of Saint-Etienne has been in charge of the review of ADRs associated BCG SSI vaccine use, and reporter to the RPVC network or to the marketing authorisation holder (MAH).

Methods: All ADRs and misuses spontaneously reported in France after use of BCG SSI vaccine to RPVC network or to MAH between January 2005 and June 2008 were analysed. The notification rate was estimated by evaluating th ratio of ADR reports and the vaccine sales for the same period. Misuse associated with locoregional ADRs was defined as wrong injection site, administration route or dose, inapropriate schedule of vaccine administered.

Results: From 2005 to mid-2008, 1529 notifications were collected and analysed. 1050 locoregional ADRs were retained. The most frequent locoregional ADRs were abscesses at the site of injection (n = 764), then injection site reactions or adenopathies exceeding 10 mm (n = 266), then suppurative adenitis (n = 20). The mean rate of misuse associated with abscesses was 35.3%. Afssaps decided to set up a Risk Management Plan in April 2006 in order to reduce the occurence of these ADRs and improve their handling: information released for healthcare professionals (HCP) and patients (press release, ''Dear doctor Letter'', recommendations), poster, box stickers, change of the box needle.

Conclusion: Since September 2006, a rapid decrease of the spontaneous notifications and rate of abscesses occured.

161. Afebrile Seizures Associated with Measles Vaccine

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Introduction: Measles vaccine is included in the Tunisian vaccination Program. It is administered at the age of 18 months in association with mumps-rubella vaccine (MMR). Neurological reactions are common adverse events following immunisation (AEFIs) especially febrile seizures and encephalitis. Afebrile seizures are an exceptional neurological AEFI.[1,2] We report a case of afebrile seizures in an infant following measles vaccine.

Case report: N.H., an 18-month-old girl, with no personal of family history of seizure, has already received a correct vaccination as recommended by the Tunisian vaccination Program. On May 15th 2009, she received Rouvax® (measles vaccine). In the evening, about 9 hours after immunisation, she developed tonico-clonical seizures, which lasted 90 minutes. She was transferred to a paediatric emergency where she received anticonvulsive drugs. She had not fever, nor focal neurological signs. After seizures cessation, she had not had severe alteration in level of consciousness. Biological investigations including glycaemia and calcaemia were normal. CSF was normal. Cerebral tomodensitometry showed no abnormalities. The infant was discharged after 2 days of monitoring, and was prescribed Depakine® (valproic acid). This case was notified to the Centre National de Pharmacovigilance and was analysed according to Begaud method of imputation.[3]

Discussion: The implication of measles vaccine in the genesis of these afebrile seizures was retained because of the compatible delay (9 hours after vaccination) and especially the negative investigations.

Living measles vaccines can produce febrile convulsions or other central nervous symptoms. The incidence of febrile convulsions varied between 0.04 and 1.9/1000 with a peak between 8 and 9 days after vaccination.[1,2] Afebrile seizures are exceptionally reported. D'Souza et al have reported 4 cases of afebrile seizures among 1.7 million vaccinated children with MMR vaccine.[1] The 4 cases were classified as possible according to the WHO scale of imputation. The onset was less than 24 hours after vaccination for 1 of the 4 cases. The latter was a 7 year old child who had a seizure lasting 20 minutes the day after receiving MMR vaccine. The child had no previous history of epilepsy and was taken to hospital. The afebrile seizures in the other 3 children occurred at 12, 15 and 28 days respectively after administration of the MMR vaccine.[1]

Conclusion: This case reported an exceptional AEFI associated with measles vaccine administered alone and which occurred in a brief delay.

References

1. D'Souza RM, Campbell-Lloyd S, Isaacs D. Adverse Events Following Immunisation associated with the 1998 Australian Measles Control Campaign. Commun Dis Intell 2000; 24: 27-33

2. Nolan T, McIntyre P, Roberton D. Reactogenicity and immunogenicity of a live attenuated tetravalent measles–mumps–rubella–varicella (MMRV) vaccine. Vaccine 2002; 21: 281-9

3. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111

162. Bullous Fixed Drug Eruption Induced by Indomethacin

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Introduction: Indomethacin is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. Indomethacin can be responsible of hypersensitivity reaction such as skin reaction. Fixed drug eruption (FDE) is an exceptional cutaneous adverse effect of this drug.[1] We report a case of bullous FDE induced by indomethacin with positive patch test.

Case report: A.G., a 64-year-old man, used to take for recurrent back pain paracetamol and indomethacin. In February 14th 2009, he took for about 4 days Indocine®$_{100}$ (indomethacin), 1 suppository per day, and Analgan®$_{500}$ (paracetamol) 2 or 3 times a day. In February 17th, the patient presented 4 red erythematous plaques in his hands (2 plaques in each hand) of about 3 cm of diameter, with pruritus and a burning sensation. Each plaque exhibited tense bulla in the center. After indomethacin and paracetamol withdrawal, the patient's lesions resolved completely within 3 weeks with residual pigmentation. One month later, the patient took Doliprane (paracetamol) for headache, without recurrence of the lesions. In May 21st, a patch test with indomethacin was placed on one residual pigmented lesion. Twenty four hours later, the patient presented reactivation of the 4 initial lesions, with appearance of new lesions in his hand, feet and thigh.

Discussion: The role of indomethacin in the genesis of this bullous fixed drug eruption is retained because of the negative rechallenge of paracetamol, and especially the positive patch test with indomethacin.

FDE to indomethacin is exceptional. Mahboob et al have reported 3 cases of FDE to indomethacin in a study of 450 cases.[1] There is no report of bullous FDE with this drug.

Conclusion: This study reported a case of bullous FDE, an exceptional cutaneous adverse effect of indomethacin, which was confirmed by positive patch test.

Reference

1. Mahboob A, Haroon TS. Drugs causing fixed drug eruptions: a study of 450 cases. International journal of dermatology 2008; 37: 833-8

163. Superficial Thrombophlebitis Induced by Loxitalamate

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Introduction: Ioxitalamate meglumine is an ionic, high-osmolar, contrast media (CM) which is indicated in different radiologic exams such as tomodensitometry or intravenous urography. Its most common adverse effects are allergic reaction, and renal effects. Thrombogenic effects are not reported with ioxitalamate meglumine. We report 2 cases of superficial thrombophlebitis induced by ioxitalamate.

Case report 1: G.B.M., an 18-year-old man was admitted in medicine ward for Hodgkin disease. Cerebral and thoraco-abdominal tomodensitometry was performed in January 6th 2009. At 10am, he received an infusion of Telebrix®$_{35}$ (ioxitalamate meglumine), 100 mL intravenously. The perfusion was performed in the cephalic vein of the right wrist. Immediately, the patient felt warm and pain in his wrist. A few minutes later, there was a local swelling in the cephalic vein. An echo Doppler performed two days later, showed thrombophlebitis in the cephalic vein of the right wrist. The patient was prescribed local heparin and analgesics. The pain resolved totally within 2 weeks. One month later, the Doppler showed persisting thrombophlebitis.

Case report 2: A.O., a 23-year-old man, with a recent history of Hodgkin disease, had a first cerebral and thoraco-abdominal tomodensitometry. Telebrix®$_{35}$ was infused without problems. On December 12th, a second tomodensitometry was performed. Immediately after Telebrix® infusion in the cephalic vein of the left wrist, he felt warm and pain. Analgesics and local care were ineffective to relieve pain. A Doppler showed thrombophlebitis in the cephalic vein of the left wrist. The pain resolved totally within 2 or 3 weeks. On January 13th 2009, the Doppler showed persisting thrombophlebitis.

The two cases were reported to the Centre National de Pharmacovigilance and were analysed according to Begaud method of imputation.[1]

Discussion: The role of Telebrix® was retained in the genesis of the two cases of thrombophlebitis because of a compatible delay and especially the occurrence of the adverse effect in the target of the vein where the CM was injected.

Thrombogenic Effects are reported with the different types CM especially the high-osmolar ones.[2] These effects result mainly from a direct activation of platelets and secretion of prothrombotic agent by the endothelium.[2] Even if ioxitalamate meglumine is a high-osmolar CM, there are no reports of thrombophlebitis in English literature with this drug.

Conclusion: these two cases reported superficial phlebitis, which is an exceptional adverse effect of ioxitalamate.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Esplugas E, Cequier A, et al. Comparative tolerability of contrast media used for coronary interventions. Drug Safety 2002; 25: 1079-98

164. Adverse Effect Following Immunization (AEFI) Associated with Hepatitis B Vaccine

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Introduction: Hepatitis B vaccine is included in the Tunisian vaccination Program. It is administered at birth, at the age of 2 months and 6 months. Its also administered to young and adults. This vaccine can be responsible of skin reactions, local reaction and rarely neurological effects. The aim of this study was to assess adverse reactions related to hepatitis B and notified to the National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all the reports of adverse reaction associated with hepatitis B vaccine from December 1996 to December 2007. We considered the cases where hepatitis B has the most important imputation score alone or in association with other drugs. We collected the age, the sex, the medical history, the type of adverse reaction, the delay, the outcome and the imputation score. The cases were analysed according to Begaud method of imputation.[1]

Results: There were 12 cases including 4 men and 8 women. The age varied form 1 month to 32 years: 9 cases in infants and 3 cases in adults. The patients had no history of hypersensitivity to drugs or vaccine. Adverse reaction were skin eruption in 7 cases, neurological effects in 3 cases, haematological effects in 1 case and local reaction in 1 case. The delay was less than 12 hours in 6 cases, and more than 12 hours in 6 cases. There was a case of neurological sequella in one infant. The outcome was favourable in the other cases. The imputation score was I3 (likely) in one case, I2 (plausible) in 7 cases and I1 (doubtful) in 4 cases.

Discussion: There was a predominance of the skin reaction (7/12). Skin eruption is common with hepatitis B vaccine and is mild and transient

reaction.[2,3] Neurological effects are uncommon adverse reaction associated to hepatitis B vaccine and consist in peripheral neuropathies or optic nevritis or multiple sclerosis plaques. The relation between these neurological effects and the vaccine has never been established.

Conclusion: Our study reported 12 notifications of adverse reactions related to hepatitis B vaccine, mainly skin reaction.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Cassidy WM, Jones G, Williams K, et al. Safety and immunogenicity of concomitant versus nonconcomitant administration of hepatitis B, tetanus–diphtheria, and measles–mumps–rubella vaccines in healthy eleven- to twelve-year-olds. Journal of Adolescent Health 2005; 36: 187-92

3. Nikkels AF, Nikkels-Tassoudji N, Pierard GE. Cutaneous adverse reactions following anti-infective vaccinations. Am J Clin Dermatol 2005; 6: 79-87

165. A Study on Efficacy and Adverse Effects of Antibiotics Used in Treatment of Urinary Tract Infection During Pregnancy

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Background: Urinary tract infection (UTIs) is the most common bacterial infection during pregnancy. There are various antibiotics commonly used in UTI in pregnancy their efficacy and adverse reaction in such situation is not known yet in Nepalese women.[1-3]

Objective: This study aims to ascertaining the efficacy and adverse reaction of commonly used antibiotics in treatment of UTI during pregnancy.

Methodology: 82 pregnant patients diagnosed of UTI were enrolled. Midstream urine was collected and sent to laboratory for routine investigation, culture and sensitivity. According to the causative organism detected and sensitivity pattern, patients were given either amoxicillin 500 mg TDS (n = 45), cephalexin 500 mg QID (n = 33) or norfloxacin 400 mg BD (n = 4) for one week. To assess success or failure of prescribed antibiotics next urine culture was done one week after completion of the therapy. Then the patients were asked about the adverse effect they have experienced after starting the drugs therapy. Adverse effects were noted on the Data collection form.

Results: During the study period of 5 months, highest incidence of UTI was found in the second trimester (13–24 weeks, 42.6%) of pregnancy followed by third trimester (25–36 weeks, 39.0%) and least to first trimester (4–12 weeks, 18.2%). Common presenting symptoms were burning micturition (75.6%) followed by increased urinary frequency (70.73%), suprapubic pain (64.6%) and fever (40.20%). Overall bacterial cure rates were 100% in antibiotic groups after one week of drug therapy. The safety profile of amoxicillin was similar to that of cephalexin. However, based on the tolerability of these adverse effects (e.g. nausea, vomiting, rashes, headache, dizziness, confusion etc), amoxicillin was better tolerated than cephalexin. So, from the result of this study it seems that amoxicillin is equally effective to cephalexin with added advantage of being cheaper and also having higher patient compliance due to less severity of adverse effects.

References

1. Goddard J, Turner AN, Cumming AD, et al. Kidney and urinary tract disease. In: Boon NA, Colledge NR, Walker BR, Hunter JAA, editors. Davidon's Principle and Practice of medicine. 20th ed. International Edition. New York: Churchil Livingstone, 2006: 467-82

2. Chowdhary SK, Kolar M, Yeung CK. Urinary tract infection: The urological perspective. Indian J Pediatr 2004; 71: 1117-20

3. Which antibiotics are apprariate for treating bacteriuria in pregnancy. Journal of Antimicrobial Chemotherapy 2000; 46

166. Implementation of Pharmacovigilance Activity in a Mental Hygiene Department

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Background: For the first time, a pharmacovigilance activity was carried out in an ambulatory consultation unit in Mental hygiene Dispensary in Abidjan. The objective was to collect and notify any adverse events occurred during psychotropic drug use.

Method: It was about an exploratory study of monitoring adverse events over six months (January 1 to June 31, 2007) in order to have routine activity. Before collecting data, seventeen (17) personals were trained about concepts, methods in pharmacovigilance and transmission of report reform.

Results: The incidence of adverse events was 9.4% (174 ADRs notified). It concerned mostly female (58%). The sex-ratio was 0.72. The means age was 35.5 years ±14.4. The neurological events were most common (44.3%) followed by neurovegetative (20.7%) and Metabolic and endocrine events (16.7%). Eighty-seven percent patients did not have any extraclinic check up. The neuroleptics were most responsible for ADRs (67.3%) particularly Penfluridol (22.7%) and Haloperidol (13.3%). The hypnotics were responsible for 10.5% of the ADRs. In more than half cases, the onset of ADRs was started beyond one day (55.2%). The duration of theses events was inferior to one month in 38.7% of the cases or ranged between one and six months in 12.9% of the cases. The event regressed in the quasi-totality of the cases when drug was withdrawn (45.2%), after corrective treatment (20.4%) and after dose reduction (16.1%). The outcome of ADRs was unknown in 18.3% of the cases. The drug rechallenge was observed in 18% of the cases. Our study did not highlight the interest of preventive use of anticholinergics. The chronological score was better (suggestive or possible) in 65.3% of the cases but semiological one was dubious in 82% of the cases. More than half of the intrinsic imputabilities were dubious (63.3%). The extrinsic imputability was dominated by well-known adverse effects (76%).

Conclusion: This preliminary study of ADRs monitoring in an ambulatory clinical psychiatry department showed that the setting up of this activity is possible. It could be useful in the monitoring of psychotropic drugs prescription because our population sample ''applicant of psychiatric care'' is representative. Also, the integration of notification reform in patient medical files of would help to fight against the under-notification.

167. The Cardiovascular Risk of Sulfonylureas on Newly Diagnosed Type II Diabetes Mellitus Patients

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Introduction: Since the UGDP (university group diabetes program) study,[1] the cardiovascular risk of sulfonylureas has not been clarified. Although many findings from animal studies concluded that these

drugs could prevent the ischemic preconditioning during ischemia, the long-term effects on human in clinical practice have still not been confirm yet.[2] Since sulfonylureas remains the mainstay in the treatment of type-2 DM. So we conduct a pharmacoepidemiological study based on the National Health Insurance database in Taiwan.

Aim: To identify whether sulfonylureas increase the risk of cardiovascular events on type-2 DM patients.

Methods: This is a retrospective cohort study with the out-patient and in-patient registered records in National Health Insurance Research Database (2000–2007) of Taiwan. New users of medications for diabetes during Jan 2001–Dec 2007 were included. Patients under 18 years-of-age or patients with any records of CV events in the past 1 year were excluded. The primary endpoint was hospitalization for acute myocardial infarction (MI). And there were 2 secondary endpoints, hospitalization for heart failure (HF) and ischemic stroke (stroke). Cox's proportional hazard regression was performed to test the model of drug exposure during 1 year before events. All the prescriptions of the diabetic and cardiovascular medications were recorded as time-dependent variables for calculation of the adjusted hazard ratio in the stepwise selection procedure.

Results: Patients' ID who were first prescribed with DM medications during 2001–2007 were identified (n = 37290). About 76% of them (n = 28340) had ever used sulfonylureas (SU group) and 24% (n = 8950) had never exposed to sulfonylureas (Non-SU group) in the follow-up period. The mean age of SU and Non-SU group were 56.6 ± 13.2 yrs and 53.7 ± 17.4 yrs ($p < 0.0001$), and the percentage of male were 54.2% and 41.7% ($p < 0.0001$). In the survival analysis, the adjusted hazard ratio (HR) of MI events for sulfonylureas was 1.147 (95% CI: 0.995, 1.321, $p = 0.0578$). In HF and stroke events, sulfonylureas were not included in the model, i.e., they did not meet the criteria of $p < 0.15$.

Conclusions: Usage of sulfonylureas in the past 1 year was not associated with increased CV risk for new users of DM medications in our study. Since the safety of sulfonylureas remains a question, it depends on more well-designed study to be answered.

References

1. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970; 19: Suppl.: 789-830

2. Riveline JP, Danchin N, Ledru F, et al. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. Diabetes Metab 2003; 29: 207-22

168. Pharmacoeconomic Assessment of Black Water Fever in Abidjan

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Background: Black water fever related to antimalarials constitutes a major public health issue. Its morbimortality is very high, ranging between 15 and 35% of the cases. This high morbimortality is due to diagnostic and management delay.[1] This pathology constitutes an over cost in the management of malaria. Objective was to assess the direct costs of the management of black water fever.

Material and Method: this retrospective study concerned intravascular haemolysis related to antimalarials occurred in intensive care, medicine and paediatric units of private clinic Polyclinique Internationale Sainte Anne Marie (PISAM) from 1996 to 2006. The surveys selected were the ones with information about billing. We determined direct medical and non-medical costs.

Results: This study concerned 18 cases. Patients' means age was 35 ± 18 years (extremes: 9–67 years). Masculine sex represented 83.3% and sex ratio was 5. Patients with no insurance accounted for 44.4%. The onset was within 5 days and the mean admission time was 4 ± 5 days. The global cost of management of black water fever was on average 1162 672 ± 758 474 Fcfa (1euro = 655.957 Fcfa) for a mean hospitalisation time of 7 days (extremes: 281 840 et 2 570 751 Fcfa). Laboratory costs accounted for 28.8% followed by the hospital stay charges (19.1%), those of the nursing staff (15.7%) and the charges in intensive care (15.6%). Therapeutics accounted for just 9.9% of the global cost. The patients with no insurance paid more than the ones with insurance, just as men paid more than women. Charges in the intensive care unit were the highest.

Conclusion: this pharmaco-economy study about black water fever was a preliminary study which shows the way to control and reduce expenses in public health to poor in developing countries. Indeed, the management of black water fever in private hospital remains inaccessible to the middle class Ivorian without social security cover.

Reference

1. Daubrey-P Th, Die-Kacou H, Kamagate M, et al. Fièvre bilieuse hémoglobinurique au cours du traitement antipaludique à Abidjan: à propos de 41 cas. Bull Soc Path Exot 2004; 97: 325-8

169. Analysis of Individual Case Reports in the WHO Database of Suspected Drug-Induced Hepatic Injury in Children

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Objective: In the last decades, many medications have been withdrawn from the market because of drug-induced hepatic injury.[1] Little is known, however, about drug-induced liver injury in the pediatric population.[2] A hypothesis-generating study to identify which drugs are associated with the highest risk of reported liver injury in children.

Methods: A case/non case design was conducted based on all individual case safety reports of suspected adverse drug reactions (ADRs) occurring in children 0–18 years of age, as registered in the WHO database until 2006. Cases were all reports in which hepatic ADRs were documented, non-cases were all other reports of ADRs. Reports regarding topically administered drugs were excluded from both groups. The association between drug and suspected hepatic ADRs was calculated using the reporting odds ratio (ROR) as a measure of disproportionality.

Results: Overall, 867 405 ADRs in children were reported to the WHO database during the study period, of which 624 673 reports remained after excluding those in which topically administered drugs were suspected of causing the reported ADR. 6595 reports (1.1%) concerned liver injury. Most of the reported liver injuries occurred in children 12–18 years of age, the most frequently involved drugs were isotretinoin, followed by paracetamol, valproic acid, carbamazepine, methotrexate, minocycline, lamotrigine, zidovudine, pemoline, and ceftriaxone. In comparison to all other ADRs, the adjusted RORs for liver injury were above 30 for oxymetholone, the combination

norethisterone-ethinylestradiol, milrinone, retinol, atazanavir, pemoline, pyrazinamide and isoniazid.

Conclusions: Liver injury was infrequently reported as ADR in children, but the rate increased with age. Known adult hepatotoxic drugs (paracetamol, antiepileptic, and anti-tuberculosis agents) were associated with reported liver toxicity in children as well. A new association was identified for which the summary of products characteristics did not yet list hepatic events. Further analytic investigations are needed to confirm whether this safety signal is real or spurious.

References

1. Lasser KE, Allen PD, Woolhandler SJ, et al. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287: 2215-20

2. Le J, Nguyen T, Law Av, et al. Adverse Drug Reactions Among Children Over a 10-Year Period. Pediatrics 2006; 118: 555-62

170. Annual Safety Reports from a Medical Writer's Perspective: Lessons Learnt

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Introduction: Sponsor companies are increasingly outsourcing preparation of pharmacovigilance documents to Contract Research Organisations (CROs) who have the advantage of document experience and data objectivity. PAREXEL Medical Writing Services often prepares pharmacovigilance documents including annual safety reports (ASRs) and periodic safety update reports (PSURs). I will present some of the issues medical writers encounter during document preparation, using the ASR as an example, and explain how medical writers play a key role in ensuring document quality.

Lessons learnt: Key issues in ASR preparation are time management and communication. The sponsor should ensure someone in the CRO knows when the ASR is due (ASRs have a fixed deadline) and that well-defined and tested processes are in place to meet the deadline. Ensure familiarity with the content of an ASR and that there is a well-defined template, either from the sponsor or CRO. Document key contacts for review, approval and submission of the ASR. The ASR hinges on the listings and summary tabulations of serious adverse reactions (SARs); agree or be aware of the format in advance to make sure the necessary data will be included. Data quality is essential and medical writers may need to verify that listings and tabulations have undergone quality control checks. It is also important to ensure that complete safety information, not just the listings and tabulations, is available, including all the studies being conducted globally with this product. A CRO may only be aware of studies for which they are responsible for safety reporting or other aspects of the study, so communication and availability of this information is essential. One critical issue with ASRs is the handling of unblinded data. Since ASRs may contain unblinded information, you may need to decide how the data will be handled in the report and ensure that both CRO and sponsor team members who are providing input or reviewing the report are allowed to see unblinded data. Avoid unwitting distribution to study personnel who must remain blinded. Finally, if you are involved in pharmacovigilance document preparation, be prepared to participate in pharmacovigilance inspections.

Conclusions: Involvement of medical writers from CROs in ASR preparation ensures smooth interaction between the sponsor and CRO teams and provides expertise in the content and preparation of these documents. This ultimately ensures the highest quality document is prepared in the time available.

171. Treatment Pattern of Pulmicort HFA® in Spain: Preliminary Results from an Observational Study

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Introduction: The use of chlorofluorocarbons (CFC) as propellants, currently known as environmental toxics,[1] has been usual in the inhaled pharmaceuticals. The change to an alternative propellant, the hydro fluoroalkane (HFA) with magnesium stearate as excipient, in a new formulation of inhaled budesonide, Pulmicort HFA® 100 µg & 200 µg,[2] made necessary to perform a utilization study as part of the Risk Management Plan in Spain.

Aim: To identify the treatment pattern of the new formulation of Pulmicort® HFA during short/mid term in adults and children and describe associated factors.

Methods: Prospective observational, multicenter study with a 6 months follow-up period performed in 3 different outpatient settings in Public Healthcare System in Spain: Primary Care, Paediatrics and Pneumology. Patients with an asthma diagnosis (according to Spanish guideline-GEMA[3]) who were previously treated with Pulmicort CFC and changed their treatment to Pulmicort® HFA were included in the study. A compliance evaluation was done, consider as good ones those patients with more than 80% of inhalations accordingly to authorized posology in previous 7 days. An initial evaluation of asthma control was performed at baseline and after 3 and 6 months using the Asthma Control Questionnaire[4] (ACQ).

Results: 260 patients were recruited, 230 of them were available at the three month visit (89.2%) and 227 at the final visit (87.3%) after six months. 53.9% were women and mean age was 39.8 years old (SD 26.5). A 48.6% came from Primary Care, 42.0% from Pneumology and 9.3% from Paediatrics. The mean duration of the disease was 4.8 years (rank: 0.25–48). At baseline, 93.1% of the patients had good compliance (95CI%:89.7%, 96.4%); with no significant changes at 3 and 6 months (93.6% [95% CI: 90.2%, 96.9%] and 94.8% [95% CI: 91.8%, 97.8%], respectively). Regarding the asthma severity:

1. In adults (n = 165) was: 5.3% intermittent, 46.8% mild-persistent, 42% moderate-persistent and 5.9% severe;
2. Among paediatric population (n = 62): 34.3% occasional-episodic, 50% frequent-episodic, 11.4% moderate-persistent and 4.3% serious-persistent.

After 6 months, 56.8% of the patients were well controlled (ACQ lower than 0.75), 27.6% partially controlled (ACQ between 0.75 and 1.5) and 15.6% poorly controlled (ACQ higher than 1.5).

Conclusions: The introduction of new Pulmicort® HFA formulation, instead of former CFC, did not produce any change in asthma diagnosis and management in Spain, based on the preliminary results available.

References

1. United Nations Environment Programme. The 1987 Montreal Protocol on Substances that Deplete the Ozone Layer (as agreed in 1987). [Internet monograph] Ozone Secrétariat; 1987. Available at: http://ozone.unep.org/spanish/Ratification_status/montreal_protocol.shtml [Accessed June 2007]

2. AstraZeneca Farmacéutica Spain, S.A. Pulmicort® 100 y 200 mg/inh suspensión para inhalación en envase a presión. summary of product characteristics. March 2008

3. Plaza V, Álvarez FJ, Casan P, et al. GEMA Executive Committee. Spanish Guide for Asthma Management [Guía Española para el Manejo del Asma - GEMA]. Arch Bronconeumol 2003; 39 Suppl 5: 1-42

4. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999 Oct; 14 (4): 902-7

172. TRAMADOL-Induced TICS: A Case Report

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Introduction: Tramadol hydrochloride is a widely prescribed, central opioid analgesic drug. Abnormal movements are not described as a possible adverse event in the summary of product characteristics.
Aim: To report and discuss a case of Tramadol-induced tics.
Methods: We report the case of a 40 years old man who experienced facial tics while abusing Tramadol. This case is discussed with the French pharmacovigilance causality assessment method.
Results: This case was rated as a plausible adverse event of the drug (score of imputability: C2S2I2B1).
Discussion: Tics in this patient are thought to be related to the serotonin stimulation caused by the inhibition of serotonin re-uptake by Tramadol. The literature on serotonin syndrome associated with Tramadol is reviewed.

173. Interaction between Paroxetine and Adrafinil: A Case Report

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Introduction: Polypharmacy is common when psychotropic drugs are regarded, leading to potential drug-drug interaction.
Aim: To report and discuss a case of clinically relevant interaction between paroxetine and adrafinil: an adrafinil overdose when paroxetine was stopped.
Method: We report the case of a 35 years old man with depressive disorder and adult ADHD. He was maintained under paroxetine 40 mg per day and adrafinil 900 mg per day for one year. Twenty-four hours after stopping paroxetine on his own, the patient started to experiment irritability, insomnia, tachypsychia and muscle twitches. This stimulant syndrome lasted for 7 days when he consulted again. He was rechallenged with paroxetine 20 mg per day. All symptoms resolved in 48 hours. During this time, adrafinil dosage was maintained at 900 mg per day.
Results: This case was rated as plausible, with a score of imputability: I3 C3S2B1.
Discussion: This case is discussed with the French pharmacovigilance causality assessment method.
The possible underlying pharmacodynamic and pharmacokinetic mechanisms of this interaction are reviewed, including a competitive interaction between the two drugs at the level of CYP 3A4 disposition.

174. Reccurent Hypotonic-Hyporesponsive Episodes after Whole Cell Pertusis Vaccine

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Introduction: Hypotonic-hyporesponsive episode (HHE) has been defined as a sudden onset of limpness, unresponsiveness, and pallor or cyanosis occurring within 48 hours after immunization.[1] HHE are rare and serious adverse events after immunization. HHE usually follows administration of a pertusis containing vaccine.
We report here a case of 2 accesses of HHE occurring after multiple vaccinations (DTP, Hepatitis B, HIB, and oral Polio vaccine) reported to the Tunisian National Centre of Pharmacovigilance and validated according the French method of imputability.[2]
Case report: HM, is a three months-old boy whose brother experienced febrile seizure at the age of 7 months. On the 10 of October 2008 (3 months and 20 days) he received Hepavax® (hepatitis vaccine), Hib (haemophilus vaccine) and DTP (diphtheria, tetanus, pertusis) and OPV (oral Polio Vaccine). An hour later he got a 37,8°C temperature and he was given a dose of paracetamol.
One to 2 hours after the vaccination the baby was crying and shouting and developed pallor, cyanosis of the extremities and hypotonia. Those features resolved about 2 min later. The next day, on the 11 October 2008, HM, developed a second access with pallor, cyanosis of the extremities, binding of the glance, apnea. All these symptoms resolved within 2 min. The baby was driven to emergency and on his way on he presented again apnea. He was hospitalized during 3 days. The clinical examination was normal (no local reaction was noted on the site of vaccination), the biological analysis and an abdominal echography were also without any abnormalities. When he get 8 months old, HM received DT vaccine with Hepavax® and developed a pallor which disappeared rapidly (2 min). Until today, the patient has not had further adverse events.
Discussion: The responsibility of the pertusis vaccine was retained in front of:

- Compatible delay. In fact, the two episodes occur within the 48 hours after the vaccination.
- Bibliography: most published reports on HHE focus on the incidence of episodes after immunization.[3] Although, statistically HHEs most often follow the administration of pertusis containing vaccine.
- the absence of recurrence of cyanosis, apnoea after the DT and Hepatitis vaccine.

This case is interesting since the HHE occur twice after the vaccine administration whereas in literature, HHE are benign and self limited syndrome. This may be explained by the familial history (the febrile seizures of the brother) which can be considered as a risk factor.

References

1. Braun MM, Terracciano G, Salive ME, et al. Report of a US Public Health Service Workshop on Hypotonic-Hyporesponsive episodes (HHE) after pertusis immunization. Pediatrics 1998; 102

2. Bégaud B, Evreux JC, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

3. Tracy S, Duvernoy M, Miles Braun, and the VAERS Working Group. Hypotonic-Hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. Pediatrics 2000; 106

175. Provocation by Alcohol of Violence as a Side Effect of Antidepressants

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Introduction: Based on case-reports and epidemiological data, we reported the rare induction of serious violence by antidepressant treatment.[1] Given the prevalence of alcohol and its tendency to disinhibit behaviour, we studied its association with SSRI-induced violence.
Methods: We analysed some 200 cases drawn from our medicolegal practices, web-based patient discussion lists, and ADR reports to government authorities in Canada and the USA. Assessment was based on standard criteria for drug-effect causality (CIOMS), taking into account apparent sources of bias.

Results: A distinct syndrome of uncharacteristic disinhibition with alcohol was detected in 40 men and women during treatment with an SSRI or venlafaxine. Outcomes included 12 homicides (2 of them double), suicide, serious assault, unintended sexual intercourse and other damaging or markedly embarrassing social behaviour. In the majority of cases, memory for the episode was lacking, often completely so. In most of the people modest or usual amounts of alcohol were involved, with evidence that these had been well tolerated before antidepressant treatment, and after its discontinuation (challenge-dechallenge). In several cases, re-exposure to the same or a related antidepressant reproduced the phenomenon (rechallenge).
Conclusions: We identify a distinct and forensically important interaction between alcohol and SSRI antidepressants. Aggregated pharmacovigilance data (in preparation) corroborate the existence of this phenomenon. We suggest that antidepressant product warnings about alcohol-both to prescribers and to users-need to be reconsidered and strengthened. Until now they have been non-specific and unhelpful.

Reference

1. Healy D, Herxheimer A, Menkes D. Antidepressants and violence: problems at the interface of medicine and law. PLoS Medicine 2006; 3 (9): e372

176. Risk of Hepatotoxicity Associated with Nimesulide use in Thailand

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Introduction: On 15 May 2007, the Irish Medicines Board (IMB) announced the decision to withdraw nimesulide (a non-steroidal anti-inflammatory drug) from the market because of serious side effect reported affecting the liver. Consequently, on 21 September 2007, the European Medicine Agency (EMEA) with recommendation of the Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of nimesulide outweigh its risk, but there is a need to limit the duration of use and to restrict its use to ensure that the risk of patients developing liver problems is kept to a minimum. At present there are some countries have reconsidered and reviewed risk and benefit of nimesulide. In Thailand, we have been some reports of adverse reactions regarding liver problems associated with the use of nimesulide. An assessment of hepatic safety of this medicine would be one of a tool to reach conclusion on risk management and regulatory actions regarding hepatic safety of nimesulide use in Thailand.
Objectives: To review all serious and non-serious reactions reported to Health Product Vigilance Center associated with the use of nimesulide and to describe and characterize those reactions reported regarding to hepatic adverse reactions.
Methods: We reviewed all cases of adverse reaction reported to the Health Product Vigilance Center database (Thai-vigibase) associated with the use of nimesulide from year 2004–2008. Descriptive statistic was used for data analyses. Case definition of hepatic adverse reactions was defined from medical literatures.
Results: During year 2004–2008,Thai-vigibase has been 897 reports of adverse reactions associated with the use of nimesulide. There were 107 reports with serious reactions. Most reports came from general hospitals (29.98%). Of 897 reports, 74.77% were female. The median age of reported cases was 44 years of age. 1.11% were reported hepatic disorders reactions which were flatulence, hepatic function abnormal, hepatitis, hepatitis cholestatic and jaundice. Serious skin reactions like angioedema, Stevens-Johnson Syndrome and urticaria were also found.
Conclusions: Serious hepatic reactions were found from spontaneous reporting system. Though under-reporting, physician should be aware of the possibility of those reactions, especially idiosyncratic hepato-toxicity events when prescribing nimesulide. Carefully monitoring hepatic function is the best way to detect earliest possible signs or symptoms.
The authors would like to express the background safety of nimesulide regarding to hepatic adverse reactions in Thai patients. Other regulatory actions of this drug in country are not directly related to this research.

177. Antibody-Mediated Pure Red Cell Aplasia (PRCA) in Thailand

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In 2002, Thai National Center received the first report of suspected PRCA associated with the use of erythropoiesis stimulating agent (ESA) in chronic kidney disease patients. Up to April 10, 2009, 56 cases of Ab-mediated PRCA have been reported to the center. All of these cases were confirmed by bone-marrow aspirate and anti-EPO antibody test.
Thirty-eight of the fifty-six reports (67.86%) were male. An average age of the patients were 64.96 ± 17.03 years of age (range 16–91). Eighteen of twenty-six had HLA DRB1* 09 genotype.
Forty-two of these reports used ESA by subcutaneous route, one cases mixed between subcutaneous and intravenous and the others were not stated.
All but 8 patients of these patients (85.71%) received epoetin alfa (Eprex = 30, Biosimilar = 10 and Eprex with Biosimilar = 8). The other received epoetin beta (n = 6) and epoetin alfa in combination with epoetin beta (n = 2). An average of time to onset of PRCA occurring was 10.97 ± 8.32 months (range 0–37.5).
Although the characteristics of Ab-mediated PRCA have been described, the prospective of ESA monitoring should be further developed in order to determine incidence and risk factors for this serious event. As a result, the collaboration among Thai FDA, Nephrology Society of Thailand, Thai Society of Hematology, and the Association of Hospital Pharmacy (Thailand) developed the three year monitoring project i.e. ''A Prospective, Immunogenicity Surveillance Registry of ESA with Subcutaneous Exposure in Thailand'' which data collection has been started since Jul 28 2008.

178. ADR of Oral Antidiabetic

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Introduction: Diabetes mellitus type 2 or type 2 diabetes is a disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.While it is often initially managed by increasing exercise and dietary modification, medications are typically needed as the disease progresses.
A systematic review of randomized controlled trials found that metformin and second-generation sulfonylureas are the preferred choices for most with type 2 diabetes, especially those early in the course of the disease.
The objective of work: To determine the frequency of hypoglycaemias under sulfonylureas, and to detect their supporting factors.
Material and Methods: It is an exploratory study which was led to the service of Endocrinology and Metabolic Maladies of the CHU Hassan II of Fès. prospectif study was carried out in the unit of endocrinology and metabolic disease of university hospital in fez including diabetics adult patient with Diabetes mellitus type 2 with antidiabetic oral Treatment.

Results: 60 patients was included, 2% presented a hypoglycemia with Sulfonylureas. Serious hypoglycemias were found only in 0.5% of the cases. The two supporting independent factors are the Dietary management and association with the metformine.
Conclusion: The use of the oral antidiabetic is often associated with serious adverse reaction. Serious hypoglycemias observed were avoidable if the patients had a good therapeutic education.

179. Reappraisal of Acute Toxicity of Local Anaesthetics: Could Pharmacokinetics Prevent It?

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Aim: Local anaesthetics (LA) for regional anaesthesia were growing and improve the prognostic of numerous surgical processes dispatched from pregnant women to orthopaedic surgery in elderly. Bupivacaine [BPV] (and its L-isomer Levobupivacaine [LBV]) and Ropivacaine [RPV] are the most used.
Patients and methods: We observed few cases of severe side effects documented with high LA levels. Among them: (i) comas and convulsions (n = 1 adult and 2 neonates), confusions (n = 3), and a failure of cardiac resuscitation (n = 1). Toxic concentrations are >1000 μg/L.
Results: The adult case of convulsions had a rapid improvement after a lipid emulsion (LE) perfusion. A sample obtained during resuscitation. displayed high concentrations: RPV: 1.45 mg/L and Mepivacaine: 4.8 mg/L. (ii) Two neonatal cases after pudendal block during delivery. Lidocaine concentration confirmed intoxication (0.37 mg/L at H17 and 4.3 mg/L at H7, respectively); (iii) Three confusion syndromes in elderly after a lower limb surgery, during a Pharmacokinetics (PK) study (9 patients aged 57–76; 56–70 kg) during (200 mg RPV+4 ml/h of 0.2% RPV to extend analgesia to a 36–48 h time). The apparent T1/2 were measured during the operative period and were predictive of acute toxicity during post-operative analgesia; and (iv) A 58 y.o. woman died of a massive pulmonary embolism 3 days after a shoulder surgery with a LBV perfusion for early rehabilitation. Despite an immediate resuscitation attempt heart remained ineffective. The LBV assay was 960 μg/L at the beginning of the resuscitation.
Discussion: BPV, LBV and RPV are more and more used in vulnerable populations. These drugs display concentration dependent acute toxicity. They are bound to plasma proteins (>95%) and accumulated and/or released in sensitive tissues (CNS, heart,..). An 'antidote' consists in a perfusion of lipid emulsion to prevent or compensate dose-dependent toxicity. It reduces mortality in experimental and clinical conditions.[1] Its effect seems linked to drug uptake and to ionotropic channels responses.[2]
Conclusion: To prevent acute cardiac or neurological toxicity it could be recommended

1. to limit the duration of post-operative infusion in absence of PK monitoring
2. to assay local anaesthetics in emergency with development of the free fraction concentration because during per and post-operative times numerous drugs modify protein binding (antibiotics, NSAID, …) and tissue perfusion
3. in case of cardiac shock or convulsions to use lipid emulsion by IV route.

References

1. Weinberg GL, Di Gregorio G, Ripper R, et al. Resuscitation with lipid versus epinephrine in a rat model of bupivacaine overdose. Anesthesiology 2008; 108 (5): 907-13

2. Kawano T, Oshita S, Takahashi A, et al. Molecular mechanisms of the inhibitory effects of bupivacaine, levobupivacaine, and ropivacaine on sarcolemmal adenosine triposphate-sensitive potassium chjannels in the cardiovascular system. Anesthsiology 2004; 101 (2): 390-8

180. A Comparison of Methods for Signal Detection on Adverse Drug Reaction Spontaneous Reporting Database of the Thai FDA

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Introduction: Several statistical methods have been applied to detect signals in spontaneous reporting databases.[1-4] The Thailand Food and Drug Administration (Thai FDA) uses the reporting odds ratio (ROR) method for signal detection because of its ease of implementation and interpretation. The performance of different methods needs to be explored to determine need for modifications to the Thai FDA signal detection system.
Aim: To compare performance between the ROR and the Bayesian Confidence Propagation Neural Network (BCPNN) methods in identifying adverse drug reaction (ADR) signals using the Thai FDA database.
Methods: The two methods were retrospectively applied to identify two serious ADRs (lactic acidosis and hepatitis) reported with antiretroviral (ARV) drugs using the dataset between 1990 and 2006. The criteria of lower limit of 95% confidence interval (CI) of ROR greater than 1 with at least 3 case reports;[5] and the BCPNN information component (IC)–2 standard deviations greater than zero,[3] were used to identify possible signals for ROR and BCPNN, respectively. We plotted the ROR and the IC against time to compare the differential timing of signal detection and the pattern of signaling over time between these methods.
Results: The ROR and the BCPNN methods identified the associations between lactic acidosis and stavudine; and hepatitis and nevirapine at the same time. However, the patterns of signal development appeared relatively different with each method.
Conclusion: ROR and BCPNN are comparable in identify signals of potentially serious ADRs. Comparisons using other drug classes will provide additional insight into the performance of these two methods.

References

1. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001; 10 (6): 483-6

2. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 2002; 25 (6): 381-92

3. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54 (4): 315-21

4. van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Saf 2003; 26 (5): 293-301

5. Faculty of Pharmaceutical science Chulalongkorn University. Development of signal detection and assessment tool for the Thai FDA spontaneous reporting database. Bangkok 2005

181. Severe Apnoea in an Infant Exposed to Lamotrigine in Breast Milk

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Case summary: A 16 days old infant developed several mild episodes of apnea that culminated in a severe cyanotic episode requiring resuscitation. A thorough examination at the hospital gave no evidence of underlying diseases that could explain the reaction. The mother had used lamotrigine in increasing doses throughout pregnancy, and at the time of the apneic episodes she used 850 mg/d. The infant was fully breastfed, and the neonatal lamotrigine serum concentration was 4.87 μg/mL at the time of admission. Breastfeeding was terminated, and the infant fully recovered.

Discussion: Although there are several reports on extensive passage of lamotrigine into breast milk,[1-4] this is the first published report of a serious adverse reaction in a breastfed infant. Lamotrigine clearance increases throughout pregnancy, and maternal dose increases are often necessary to maintain therapeutic effect. After delivery the clearance rapidly returns to preconception levels, enhancing the risk of adverse reactions in both mothers and breastfed infants if the dose is not sufficiently reduced.[4,5] In our case the dose was slowly reduced after delivery, and the maternal lamotrigine serum concentration more than doubled the last week before the neonatal apneic episodes. High lamotrigine concentration was detected in the breast milk, and the neonatal lamotrigine serum concentration was in the upper therapeutic range. The neonatal lamotrigine elimination half-life was approximately twice that seen in adults. The Naranjo probability scale indicates a probable relationship between the apnea and the exposure to lamotrigine through breastfeeding.

Conclusion: Breastfed infants can be exposed to clinically relevant doses of lamotrigine through breastfeeding. Individual risk/benefit assessment is important, and close monitoring of both mother and child is advisable, especially the first three weeks postpartum.

References

1. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia 2000; 41: 709-13

2. Rambeck B, Kurlemann G, Stodieck SRG, et al. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. Eur J Clin Pharmacol 1997; 51: 481-4

3. Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. Pediatrics 2008; 122: e223-31. Epub 30 Jun 2008

4. Fotopoulou C, Kretz R, Bauer S, et al. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. Epilepsy Res. Epub 2009 Mar 7

5. Pennell PB, Newport DJ, Stowe ZN, et al. The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology 2004; 62: 292-5

182. Prokinetic Drugs in Children: Drug Utilization and Safety

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Background: Prokinetic drugs are widely prescribed to children. Their use is controversial due to serious adverse drug reactions (ADRs) like extrapyramidal disorders (EPD) and QT prolongation.

Objectives: To calculate reporting odds ratios (RORs) of ADRs related to prokinetics in children using WHO Individual Case Safety Reports.Describe time and age-dependent prescription patterns of prokinetics in children in the Netherlands (NL) and Italy (IT).

Methods: All paediatric non vaccine related spontaneous reports (N = 812 526) received by the WHO Uppsala Monitoring Centre until 2006 were analyzed. RORs were calculated stratified for age.

A retrospective population-based study was conducted to describe drug use using data from 2 primary care databases in NL (IPCI) and IT (Pedianet).

The study period ran from 1995 to 2006 for NL and from 2001 to Jun 2008 for IT. Annual prevalence of use was calculated (users/1000 PY) and stratified by age and gender.

Results: RORs for EPD and QT prolongation are highest in children <2 yr (284 [95% CI 223, 361]; 25 [95% CI 15, 40]). EPD was mainly reported for metoclopramide (ROR 171 [95% CI 161, 181]) and QT prolongation for cisapride (ROR 35 [95% CI 29, 43]).

During the study period, prescribing of prokinetics more than halved both in NL (27-13/1000 PY) and IT (43-12/1000 PY). This was mainly due to a drop in domperidone prescriptions. Cisapride prescriptions decreased to nil from 2000 on. Prokinetics are mainly prescribed to the youngest except for metoclopramide in NL (>12 yr). Gender difference could only be observed after puberty where prescription of prokinetic drugs is 3 times higher in girls compared to boys (25 vs. 8/1000 PY).

Conclusions: Prescription of prokinetics decreased dramatically, probably due to raised safety concerns. EPD and QT prolongation are associated with high RORs in children <2 yr.

In line with a recent FDA boxed warning EPD is mainly seen in metoclopramide.

Since RORs are hypothesis generating reporting bias could influence the estimates.

Disclosure: The study was funded by the European Community's 6th Framework Programme, project No LSHB-CT-2005-005216: TEDDY: Task force in Europe for Drug Development for the Young. Data from the WHO Collaborating Centre for International Drug Monitoring was used. The information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The information does not represent the opinion of the WHO.

183. Characteristics of Adverse Drug Reactions Reported by Patients: Which Differences with Doctor's Reports?

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Background: Paient reporting of suspected Adverse Drug Reactions has the potential to increase knowledge about the possible harm of medicines. Several data suggest the interest of patient's reporting.[1] Regulatory medicines agency also have publish results of patient ADRs reporting.[2]
Aim: The aim of our study was to assess the characteristics of ADRs (type, frequency,…) reported by patients and to compare to those reported by doctors.
Methods: The target population consisted of outpatients who attended the Internal Medicine at the University Hospital of toulouse-Lagrave from 1st February to 12th June 2009. Outpatients were asked with a formulary by a resident in pharmacology including different data: gender, age, knowledge of their drug(s), frequency and severity (degree of discomfort) of ADRs. After rach consultation, medical reports was assessed in order to verify if ADRs were signaled by internists (to GPs or other specialists).
Results: A total of 91 ADRs were repôrted by 66 patients (77% of women, mean age = 55.6 17.5 years, extremes = 19–87). ADRs were classified according to organ-class as follows: digestive (25.3%), neuropsychiatric (19.8%), general (14.3%), cutaneo-mucosal (9.9%), muculoskeletal or ocular (6;6%), respiratory (5.5%) and metabolic (2.2%) ADRs. Patients complained from discomfort related to ADRs in 70% of cases which was intolerable in 30% and tolerable but requiring a symptomatic treatment in 24% of cases. Around 67% of patients red the drug notice and 10.6% heard about Pharmaovigilance Center. The frequency of ADRs were reported as daily occurring for 41%, at the begining of treatment for 15%, after each drug intake for 16.7% and sometimes for 1.5%. Patients reported ADRs to internists in 86% of cases. Drugs mainly involved were: corticosteroids (22%), analgesics (16%), psychotropic (19.3%) and ophtalmological (6.3%) drugs. ADRs were found in medical reports in 42% of cases. For internists, 12% of ADRs should considered as ''intolerable'' and 1.5% were significant for reporting to Pharmacovigilance Center.
Conclusion: Our data showed the qualitative and quantitative difference of ADRs reporting between doctors and patients. Patient ADRs reporting should be considered in order to improve the overall knowledge about drugs.

References

1. Blenkinsopp A, et al. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol 2006; 63: 148-56

2. www.mhra.gov.uk/mhra/drugsafetyupdate. Patient reporting 2009; 2 (10): 5

184. Early-Onset Severe Isoniazid-Induced Motor Neuropathy

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Introduction: Peripheral neuropathy is a rare adverse effect associated with isoniazid, and it occurs after the prolonged use of this drug. This usually presents with paresthesias which can be accompanied by muscle aches, occasionally muscular weakness, and can progress to more severe symptoms such as ataxia.[1,2]
Aim: Here we report a case of acute isoniazid-induced peripheral neuropathy with predominant motor functional impairment associated with tetraplegia and in the absence of predisposition.
Case: A 30-year old man with a history of 3 months of cough, fever and sweats. Sequential investigation of sputum samples confirmed bacteriologically the diagnostic of pulmonary tuberculosis. For the first two months isoniazid, rifampicin, ethambutol and piazoline were initiated. Two weeks later, the patient complaints with difficulty to remain standing and rising from a chair. Neurological examination revealed 1/5 distal weakness of the lower extremities. Bilateral ankle and patellar tendon reflexes were absent. Despite her symptoms, the objective sensory findings were unremarkable. EMG demonstrated impairment of bilateral peroneal nerve function: evoked amplitude were markedly reduced, with slight slowing of nerve conduction velocities. The results of median sensory-motor, sural sensory, and post-tibial motor nerve conduction studies were normal. Cerebrospinal fluid examination was negative. Magnetic resonance imaging of the toraco-lumbar spine did not reveal cord compression. Cerebral TDM was normal. The dosage of isoniazid after 3 hours of 300 mg of isoniazid dose test was 1.2 mg/L which evocate a rapid acetylator status. Peripheral neuropathy due to isoniazid was suspected and the offending drug was stopped. Pyridoxine at dose of 50 mg and a physiotherapy was initiated.
Discussion: Isoniazid-induced neuropathy is dose-related. The time onset of symptoms after the initiation of the isoniazid therapy in patients receiving conventional doses symptoms usually do not appear until six months. There has been no report to our knowledge of a patient, who developed severe peripheral neuropathy just two weeks after the initial administration of conventional doses of isoniazid and in the absence of factors of predisposition. Moreover, our patient developed essentially a motor dominant neuropathy with tetraplegia and without sensory features, in contrast to typical peripheral neuropathy related to isoniazid.
Conclusion: Clinicians should be aware of the rapid occurrence of this side effect. A preventive treatment by pyridoxine is currently reserved for patients with risk factors of peripheral neuropathy. However, even in the absence of predisposition, the administration of pyridoxine in association of isoniazid therapy should be considered.

References

1. Siskind MS, Thienemann D, Kirlin L. Isoniazid-induced neurotoxicity in chronic dialysis patients: report of three cases and a review of the literature. Nephron 1993; 64: 303-6

2. Steichen O, Martinez-Almoyna L, De Broucker T. Isoniazid induced neuropathy: consider prevention. Rev Mal Respir 2006; 23: 157-60

185. Challenges with Continuity of Pharmacovigilance Systems During Transfer of Marketing Authorizations and Company Mergers and Buy-Outs

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Recent changes in the current economic situation have seen many companies re-evaluate their product portfolio, pipeline and business strategy. Others have experienced flagging sales and seen venture capital drain away. The lucky ones will be purchased by companies in a stronger financial position. While licences are changing hands, there are a number of important considerations to bear in mind, primarily continuity of the product PV system.

While ultimate responsibility for PV obligations transfers to the new Marketing Authorisation Holder (MAH) on the date a product license transfer is approved by the relevant regulatory authorities, it may be practical to put in place in advance an interim agreement under which the original MAH will continue to take responsibility for some PV tasks such as collecting, databasing and reporting ADRs, and carrying out literature searching.

Product licenses usually come along with significant quantities of product safety data. It is important to ensure that a robust safety data exchange agreement is in place, to include the type and format of data to be transferred (safety database, case files, processes and procedures).

Safety database migration is of particular importance. The 'new' MAH will require a complete dataset of all spontaneous and all serious related cases from clinical trials and this data needs to be available at least at one point within the EU. Clear exchange arrangements regarding validation, QC and support for queries are vital to this process.

In addition, there are a number of important PV responsibilities which have a 'subjective' aspect to them and which will need to be reviewed in detail prior to handing over responsibilities. These include signal detection methodologies, biomedical literature search strategies, serious classification and causality assessments. Significantly changing the signal detection tools, thresholds and evaluation processes and the search terms used to search the biomedical databases could unnecessarily present an 'altered' safety profile of the medical product(s).

On the other hand, a company taken over by another may retain its status as Marketing Authorisation Holder as well as its safety database and PV system which presents the situation in which two EU QPPVs are in existence, at least for a while.

By appreciating the potentials challenges associated with inherently complex PV systems, and by striving towards open and clear communication as far in advance as possible, MAHs can smooth the path to successful license transfer without compromising the quality and compliance of the PV system.

186. Phototoxicity and Squamous Cell Cancer with Voriconazole in Immunocompromised Patients: Review of the Cases from the French Pharmacovigilance Database

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Background: Voriconazole is a broad spectrum triazole antifungal agent used for curative and prophylactic treatment of invasive aspergillosis, resistant candidosis and infections caused by *Fusarium* and *Scedosporium*. Voriconazole-induced phototoxicity was described. Furthermore, three cases of squamous cell carcinoma (SCC) occurring after photoreaction during a long term treatment with voriconazole were published[1-3] and recently, one abstract suggests an increase of skin cancer in lung transplant recipients treated with voriconazole.[4]

Aim: To reassess spontaneous case reports of photosensitivity with voriconazole and their potential complications recorded in the French pharmacovigilance database.

Methods: All spontaneous adverse drug reaction (ADR) with voriconazole as suspected drug, notified to the regional centres from January 1, 2002 (launch of voriconazole in France) to June 11, 2009 and registered in the System Organ Class "*skin and subcutaneous tissue disorders*" and "*neoplasms benign, malignant and unspecified (incl cysts and polyps)*"were analysed.

Results: 46 cases of photoreaction with voriconazole were recorded, make up 50% of the cutaneous ADR and 11% of all ADR involving voriconazole as suspected drug. The phototoxic disorders were erythema or exaggerated sunburn limited to exposed skin areas, with cheilitis (5), keratitis (1) or residual hyperpigmentation (5). Blisters were reported in 9 cases ; porphyria cutanea tarda was excluded in 3 cases. Photosensitivity occurred from 15 days to 9 months after the beginning of voriconazole, especially during sunny season (65% of cases), but in some cases after a weak sun exposition. Phototoxicity was followed by development of SCC in 6 cases (13%). One case was published (4). All patients were immunocompromised : lung transplantation for cystic fibrosis (2) or emphysema (1), rheumatoid arthritis (1), HIV infection (2). Voriconazole was continued after onset of photosensitivity and duration of treatment reached several years (2 to 5 years). These SCC are particularly aggressive and tend to relapse and spread despite adequate surgical care.

Discussion/Conclusion: Spontaneous data confirmed the occurrence of recurrent, multifocal and invasive SCCs after photoreaction to voriconazole, prescribed for long term duration in immunocompromised patients. The incidence of non melanoma skin cancers is increased in immunosuppressed patients, as HIV infected[5] or organ transplant recipients.[6] However, a prolonged course with a phototoxic drug could promote this malignancy. Photoprotection and sun eviction must be strictly applied in these patients. In case of phototoxicity with voriconazole, physicians should follow up the occurrence of SCC, and if available an alternative antifungal agent should be considered.

References

1. McCarthy KL, Playford EG, Looke DF, et al. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. Clin Infect Dis 2007 Mar 1; 44 (5): e55-6

2. Vanacker A, Fabré G, Van Dorpe J, et al. Aggressive cutaneous squamous cell carcinoma associated with prolonged voriconazole therapy in a renal transplant patient. Am J Transplant 2008 Apr; 8 (4): 877-80

3. Brunel AS, Fraisse T, Lechiche C, et al. Multifocal squamous cell carcinomas in an HIV-infected patient with a long-term voriconazole therapy. AIDS 2008 Apr 23; 22 (7): 905-6

4. Feist AA, Osborne SL, Thistletwhaite PA, et al. Voriconazole use increases the incidence of skin cancer in lung transplant recipients. Abstract 507. J Heart and Lung Transplant 2009; S242

5. Wilkins K, Turner R, Dolev JC, et al. Cutaneous malignancy and human immunodeficiency virus disease. J Am Acad Dermatol 2006 Feb; 54 (2): 189-206

6. Ulrich C, Kanitakis J, Stockfleth E, et al. Skin cancer in organ transplant recipients where do we stand today? Am J Transplant 2008 Nov; 8 (11): 2192-8

187. Facticious Hypoglycemia: Interest of Sulfonylureas Identification in Human Plasma

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Introduction: Hypoglycemia with unknown origin can be reported with factitious sulfonylurea ingestion which has been described as Munch-

ausen syndrome. It is essential to distinguish from insulin-secreting tumor and facticiuos hypoglycemia diagnostic, which consist on identification of sulfonylureas in human plasma. Different analytical techniques have been reported and most methods are based on HPLC (high performance liquid chromatography[1]). Therapeutic levels vary between 30 and 350 ng/mL.[2] In this study we report seven cases of hypoglycemia with negative investigation and plasmatic dosage of sulfonylurea was essential to define their origin.

Case report: this study interest three men and four women with hypoglycemia (unknown origin). Their age varied from 20 to 66 years. Two patients were health professionals. All the patients had no history of diabetes and presented hypoglycemia crisis (with recurrence in two cases). Identification of sulfonylurea in plasma was positive in two cases with the presence of glibenclamid at 150 ng/mL and 494 ng/mL. Blood samples were made at the moment of the hypoglycemic crisis. In these two cases, investigations were negative. For the other patients, blood samples were made far from the moment of the hypoglycemia and sulfonylurea plasmatic dosage was negative. Among these patients, insulinemia blood level was high in one case.

Discussion: Insulin-secreting tumor is the major cause of hypoglycemia with high levels of insulin and peptide C.

It is essential to eliminate by simple means the other etiologies. Sulfonylurea intoxication is one of these causes. Trenque,[3] in a prospective study detected plasmatic sulfonylurea in 7 cases among 56 cases of unexplained hypoglycemia.

In this study, sulfonylureas were detected at the moment of the hypoglycemic crisis in two cases confirming the hypothesis of facticious hypoglycemia induced by glibenclamide. For the other cases, plasmatic dosage of sulfonylurea was negative. It is recommended to made the dosage of sulfonylurea at the moment of hypoglycemia because of their short half-life.

Conclusion: Plasmatic dosage of sulfonylurea at the moment of the hypoglycemic crisis is simple and non invasive test for the etiologic diagnosis of hypoglycemia with unknown origin.

References

1. Bardin C, Tafzi N. Difficulties in toxicologic interpretation: Identification of sulfonylureas in human plasma and unexplained hypoglycemia. Revue Francophone des Laboratoires 2008; 2008: 39-42

2. Hoizey G. Identification and quantification of 8 sufonylureas with clinical toxicology interest by liquid chromatogrphy-Ion-trap tandem mass spectrometry and library searching. Clinical chemistry 2005; 50 (9): 1666-72

3. Trenque. Prevalence of facticious hypoglycaemia associated with sulfonylurea drugs in France in the year 2000. Br J Clinical Pharmacol 2002; (54): 548-52

188. Antispasmodics in Pregnancy: A Study in EFEMERIS Database

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Antispasmodics are used to prevent gastric, intestine or urinary spasms. In France, many pregnant women are exposed to these drugs mainly to phloroglucinol for which no data are available about its use in pregnancy. The present study investigates potential teratogenic risk of antispasmodics in pregnancy.

The EFEMERIS database, a regional database including prescribed and delivered drugs during pregnancy and outcomes was used for this study. EFEMERIS concerns 10 008 women and 10 174 outcomes i.e. live-born infants or elective pregnancy terminations included from July 1st 2004 to June 30th 2005 in Haute-Garonne. In EFEMERIS, we extracted: prescribed and delivered antispasmodics (A03A to A03E ATC classes) during pregnancy (data from French Health Insurance); others prescribed and delivered drugs during pregnancy; newborn health (data from Maternal and Infant Protection Service data) and medical pregnancy interruptions (data from Antenatal diagnostic Centre data).

4119 (40.5%) of women had a prescription for at least one antispasmodic during pregnancy. Phloroglucinol, trimebutine and simeticone were the most prescribed antispasmodics concerning respectively 36.9%, 6.7% and 1.4% of pregnant women. The mean number of different drugs prescribed during pregnancy per woman was higher in women exposed to antispasmodics than in non-exposed women (15.3 ± 8.6 versus 8.6 ± 6.7, $p < 10^{-4}$). A higher number of pregnant women was exposed to one prescription of antispasmodics on the first and the second trimesters of pregnancy than on the third trimester (19.5%, 19.4% and 14.4%, $p < 10^{-4}$). We compared the 1414 newborns whose mother had a prescription of antispasmodic during organogenesis period (0–56 days) with 8760 non exposed women. 37 newborns (2.6%) had a malformation versus 191 (2.2%) in control newborns ($p = 0.3$). In the group of newborns whose mother had a prescription of phloroglucinol during organogenesis, 2.4% had a malformation versus 2.3% in the control group ($p = 0.8$).

The present study was powered to find a 1.6 fold increase in the overall rate of major anomalies. It does not support evidence of a teratogenic risk for phloroglucinol in humans.

189. Oral Anticoagulants During Pregnancy

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Oral anticoagulants are known to have teratogenic effects. Regional Centres of Pharmacovigilance (CRPV) receive requests from health professionals about women exposed to oral anticoagulants. These requests and outcomes of pregnancy are registered in a national database (TERAPPEL).

We analyzed oral anticoagulants exposed pregnancies registered in the TERAPPEL database between January 1985 and December 2007.

A total of 217 women exposed to oral anticoagulants during pregnancy were identified. In 88.5% of cases, women were exposed during the first trimester of pregnancy.

Pregnancy outcomes were known in 154 cases. These pregnancies led to 103 live-births (66.9%), 32 voluntary terminations (20.8%), 13 spontaneous abortions (8.5%), 3 stillbirths (1.9%) and 3 medical terminations (1.9%). Prematurity was more frequent (16%) than in general population. As observed in the literature, the rate of malformations was to 6.8% (7 newborns). 14 neonates (9.1%) had a neonatal pathology with mainly hypotrophy. One case of intracranial hemorrhage was identified.

In women exposed to oral anticoagulants during pregnancy, we observed high rates of voluntary termination, prematurity and malformation. A majority of women were exposed in the first trimester of pregnancy when pregnancy was unknown. Due to long half-life of oral anticoagulants, women were often exposed during the sensitive period. Women were mainly exposed to oral anticoagulants for phlebitis prevention. Some of these pregnancy exposures could have been avoided. Health professionals could be more cautious when prescribing oral anticoagulants in fertile women.

190. Cutaneous Drug Reactions: Data from an Italian Spontaneous Reporting Database

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Background: Cutaneous system is often involved in adverse drug reactions. Drug-induced skin reactions are often mild but they also include severe, even if rare, diseases with different clinical patterns. The knowledge of the cutaneous toxicity profile of the drugs is very important since the early recognition of drug aetiology in serious cutaneous diseases like Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is of high importance, leading to the withdrawal of the suspected drug.[1]

Aim: Aim of this study is to analyse cutaneous drug reactions in an italian spontaneous reporting database, with particular reference to serious and unknown reactions.

Methods: The Interregional Group of Pharmacovigilance (GIF) database is a subset (80%) of the national spontaneous reporting database collecting data from 8 Italian regions. Since 2007 all Italian reports are present in the GIF database.

Results: Up to December 2008 22 766 reports with cutaneous reactions are present in the database (34% of total reports), and 18% of them are related to vaccines. Contrast media and antibacterials are the ATC drug classes with the highest proportion of skin reactions (62.2% and 57.5% respectively). Thirty-five percent of the reports were serious and 64 fatal cases were present. The most frequent reported serious cutaneous reactions (according to the WHO Critical Term List) were angioedema (1303 reports), multiforme erythema (369), SJS (236), photosensitivity reactions (199), exfoliative dermatitis (193) and TEN (122). The drugs most frequently associated to serious skin reactions were amoxicillin (alone or combined with clavulanic acid) (248 reports), acetilsalicilic acid (164), paracetamol (109), nimesulide (107), ketoprofen (101) and allopurinol (79).

Data-mining of GIF database identified some relevant issues: (i) higher frequency of SJS and TEN associated to the combination amoxicillin-clavulanic acid (20) in comparison to amoxicillin alone (9) considering a similar pattern and frequency of use; (ii) the highest number of TEN and/or SJS associated to allopurinol (56 reports, with 9 fatal outcomes), drug often related to a non-rational use; (iii) 18 SJS and 3 TEN associated to nimesulide (the highest numbers among NSAIDs, also considering its large use in Italy); (iv) increased frequency of photosensitivity reactions by ketoprofen, (36 reports, 9 reports in the last 2 years), mostly related to topical formulations; and (v) alopecia by Ace-inhibitors (9 reports) or by coxibs (3 reports).

Conclusion: Spontaneous reporting databases can be a useful source of information on drug cutaneous reactions particularly for serious, rare or unexpected reactions.

Reference

1. Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. Drug Safety 2007; 30 (11): 1011-30

191. Antipsychotics and Metabolic Syndrome

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Introduction: Antipsychotics are, classically, used to treat the symptoms of schizophrenia. Weight gain, diabetes mellitus, hyperlipidemia adverse drug reactions (ADR) are associated with antipsychotic treatment. These metabolic disturbances are biomarkers for metabolic syndrome. Two-major definitions for metabolic syndrome are used. They are very similar, and include obesity, hypertriglyceridemia, hyperlipidemia.

Objectives: To investigate the association between exposure to antipsychotics and metabolism syndrome in the French Pharmacovigilance System Database.

Methods: Within the French Pharmacovigilance System Database, the case/non-case method was used to measure the combination between antipsychotic and weight gain, hyperglycemia or hyperlipidemia adverse event. Cases are defined as those reports corresponding to the ADR of interest and non-case are all reports of ADR other than that being studied. The study period was from 1st January 1985 to 31 December 2008. We calculated the Odds Ratio (OR) as the ratio of the odds of the association of adverse report with antipsychotic treatment.

Results: Among the total of spontaneous reports (n = 344 700), weight gain, hyperglycemia and hyperlipemia were reported in 837, 1091 and 1149 cases, respectively. 225 metabolic disturbances with antipsychotics were identified are notified. Olanzapine and risperidone were suspected in the majority of the cases (33.8% and 14.9%, respectively). For more than one ADR, the association was statistically significant for clozapine, olanzapine and risperidone. Weight gain was the most often reported (n = 155 cases), hyperglycemia in 63 cases and hyperlipidemia in 29 cases. The association with weight gain was statistically significant for all antipsychotics. Olanzapine, amisulpride, risperidone were associated with a weight gain (OR = 25.02 [19.74–26.48]), (OR = 9.9 [5.8–16.89]) and (OR = 8.1 [5.46–12.01]) respectively. Olanzapine was associated with the higher risk for hyperglycemia (OR = 12.73 [8.94–18.12]). In the second generation antipsychotic group, risperidone is associated with the smallest elevation in triglyceride and glycemia levels.

Conclusion: The prevalence of overweight and obesity is higher in people with mental illness. In particular, second generation antipsychotic increase metabolic syndromes. Metabolic syndrome increase the risk of developing cardiovascular disorder and diabetes. The psychiatrics needs to be aware of the potential metabolic side effects of antipsychotic medication. Metabolic monitoring is needed for patients taking antipsychotics.

192. Annual Report of Suspected Adverse Drug Reactions Received by the DCGMA

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Introduction: In Germany spontaneous adverse drug reporting has a dual approach. German doctors are requested by their code of conduct to report adverse drug reactions (ADRs) to the DCGMA. In parallel, pharmaceutical manufacturers are requested by the German Drug Act to report ADRs which came to their knowledge to the regulatory authorities. Pharmaceutical representatives are obliged to ask when visiting doctors whether ADRs have been observed. About 10% of the reports of ADRs by German doctors are received initially by the DCGMA while most cases are sent to the regulatory authorities by the pharmaceutical manufacturers.

Aim: An annual summary of the received reports is developed in order to inform doctors and to encourage them to report ADRs to the DCGMA.
Methods: The ADR database system was used to assess single reports. The analysis included expert opinions and expert deliberations on ADR meetings. The aim of the assessment is to detect signals.
Results: In 2008 the DCGMA received 2568 reports of suspected ADRs. 1016 (39.6%) reports were sent by hospital doctors, 1438 (56%) by doctors in outpatient care, 61 (2.4%) by pharmacists and 35 (1.4%) by patients. 1756 (68.4%) reports concerned small molecular drugs, 524 (20.4%) vaccines, 183 (7.1%) blood products and 75 (2.9%) monoclonal antibodies. 1097 (42.7%) of the reported ADRs were classified "serious", 84 fatal outcomes were reported.
89 of 2568 (3.5%) reports concerned drugs newly approved in 2007 or 2008. The most frequently suspected new drugs were Aliskiren (17), Sitagliptin (15), Varenicline (15) and Exenatide (13).
After consulting with the scientific board about 43 cases eight reports triggered a publication as possible signals: Sitagliptin/hepatitis, Sorafenib/oesophageal rupture, Piroxicam/multiple organ failure, Rotavirus vaccine/Kawasaki's disease, Mitoxantrone/acute myeloid leukaemia, Levodropropizine/depression, Fumaric acid/ Kaposi's sarcoma, HPV vaccine/brachial plexus neuritis.
In 2008 the HPV vaccine Gardasil® was the drug most frequently reported as possibly causative for adverse reactions (127 reports). After a statement about possible safety problems with Gardasil® in the German television an increase of reports of suspected adverse reactions of the vaccine was observed.
Conclusions: In the system of DCGMA important signals were detected and communicated to healthcare professionals. Information in the public media about ADRs has an influence on reporting rates.

193. Non-Cardiovascular Drugs that Inhibit hERG-Encoded Potassium Channels and Risk of Sudden Cardiac Death

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Background: Virtually all QTc prolonging drugs act by blocking the hERG (human ether a go-go related gene) encoded potassium channels, whereas not all QTc prolonging drugs are associated with an increased risk of serious cardiac arrhythmias. We studied whether non-cardiovascular drugs which inhibit hERG-encoded potassium channels are associated with an increased risk of sudden cardiac death and whether the margin between potassium channel binding capacity and free plasma concentration is an indicator of the risk of sudden cardiac death.
Methods: We studied the risk of sudden cardiac death associated with use of non-cardiovascular hERG-encoded potassium channels inhibiting drugs in the Integrated Primary Care Information (IPCI) project, a longitudinal general practice research database. We performed a population-based case-control study, matched for age, gender, GP practice and calendar time. We calculated odds ratios with conditional logistic regression analysis, multivariably adjusted. Furthermore, we compared hERG-encoded potassium channels inhibiting capacity of the different drugs, defined as the effective free therapeutic plasma concentration ($ETCP_{unbound}$) divided by the concentration which inhibits 50% of the potassium channels (IC50), with the risk of sudden cardiac death.
Results: We identified 1424 cases of sudden cardiac death and 14 443 controls. Current use of non-cardiovascular hERG-encoded potassium channels inhibiting drugs was associated with an increased risk of sudden cardiac death (adj.OR 1.4 [95%CI 1.0, 1.9]). The risk of sudden cardiac death was significantly increased in users of antipsychotics (adj.OR 3.9 [2.1–7.4]). Anti- hERG-encoded potassium channels activity ($ETCP_{unbound}$/ IC50) tended to be associated with the risk of sudden cardiac death (Spearman's correlation coefficient 0.464; p-value 0.075).
Conclusion: We demonstrated that current use of non-cardiovascular hERG-encoded potassium channels inhibiting drugs in the general population, as well as hERG-encoded potassium channels inhibiting capacity were associated with an increased risk of sudden cardiac death.

194. Population-Based Studies of Anti-thyroid Drugs and Sudden Cardiac Death

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Background: Thyroid free T4 is associated with QTc-interval prolongation which is a risk factor for sudden cardiac death (SCD). Hyperthyroidism has been associated with SCD in case reports but there are no population-based studies confirming this.
Aim: To investigate whether use of antithyroid drugs (as a direct cause or as an indicator of poorly controlled hyperthyroidism) is associated with an increased risk of SCD.
Methods: We studied the occurrence of SCD in a two-step procedure in two different Dutch populations. First, the prospective population-based Rotterdam Study including 7898 participants >55 yr). Second, we used the Integrated Primary Care Information (IPCI) database which is a longitudinal general practice research database to see whether we could replicate results from the first study. Drug use at the index date was assessed with prescription information from automated pharmacies (Rotterdam Study) or drug prescriptions from general practices (IPCI). We used a Cox proportional hazards model in a cohort analysis, adjusted for age, gender and use of QTc prolonging drugs (Rotterdam Study) and conditional logistic regression analysis in a case-control analysis, matched for age, gender, practice and calendar time and adjusted for arrhythmia and cerebrovascular ischaemia (IPCI).
Results: In the Rotterdam Study, 375 participants developed SCD during follow-up. Current use of antithyroid drugs was associated with SCD (adj.HR 3.9; 95%CI 1.7, 8.7). IPCI included 1424 cases with SCD and 14,443 controls. Also in IPCI, current use of antithyroid drugs was associated with SCD (adj.OR 2.9; 95%CI 1.1, 7.4).
Conclusion: Use of antithyroid drugs was associated with a threefold increased risk of SCD. Although this might be directly caused by

antithyroid drug use, it might be more readily explained by underlying poorly controlled hyperthyroidism, since treated patients who developed SCD still had low TSH levels shortly before death.

195. Recent Use of Bisphosphonates Associated with Atrial Fibrillation

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Background: In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial in postmenopausal women with osteoporosis, serious atrial fibrillation (AF) was reported more often among patients in the zoledronic acid group than in the placebo group.

Aim: Since there is still uncertainty about the association between bisphosphonates and AF, we investigated in a population-based cohort study whether use of bisphosphonates is associated with an increased risk of AF.

Methods: We studied the occurrence of AF in the prospective population-based Rotterdam Study including 7532 participants (>55 yr), after exclusion of participants with prevalent AF. Use of bisphosphonates at the index date was assessed with prescription information from automated pharmacies. We used a Cox proportional hazards model, adjusted for age, gender and use of corticosteroids.

Results: Overall, 683 participants developed AF during follow-up. Current use of bisphosphonates was not associated with AF after adjustment (HR 1.3 [95% CI 0.7, 2.2]). However, the risk of AF was significantly increased in recent starters (first prescription) of bisphosphonates (HR 3.9 [95% CI 1.2, 12.1]) but not in those who had used bisphosphonates for a longer period (HR 1.1 [95% CI 0.6, 2.0]).

Conclusion: We demonstrated that recent use of bisphosphonates is associated with an increased risk of AF.

196. Metformin-Induced Acute Painful Myopathy

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Introduction: Merformin is a biguanide that is widely used in the treatment of type II diabetes mellitus. Its most common adverse effects are gastrointestinal discomfort. Myotoxicity has not been reported.

We report one case of acute painful myopathy induced by metformin with positive rechallenge. This case was notified to the Tunisian National Centre of Pharmacovigilance on April 2009 and analyzed with Begaud and al. Method.[1]

Case report: A-59-old woman, with a mother history of inclusion body myositis, had started metformin (Glucophage® 850) on July 2008 for type II diabetes mellitus at one tablet in the morning. Two months later, she experienced muscle pain, tenderness and weakness of proximal limb. These symptoms were at their maximum in the morning and decreased in the evening. Patient stopped metformin with remission in three days. At April 2009, she took again metformin with reappearance one day after of muscle pain, tenderness and weakness of proximal limb and axial muscles. Reflex and sensory examination was normal. Creatine kinase level, renal and hepatic tests were normal. Patient refused to perform others investigations. She was switched with glipiride (Amarel®) with no recurrence of the event.

Discussion: The responsibility of metformin was retained in front of: compatible delay, rapid resolution of myopathy symptoms after drug withdrawal, lack of another cause accounting for myopathy and essentially positive rechallenge. Genetic predisposition factor for occurring of myopathy have been reported with statins.[2]

Numerous drugs have been reported to possess myotoxic activity such as lipid-lowering agents, antiretroviral drugs, steroid, quinolones.[3] Drug-induced myotoxicity may appear, usually as a consequence of high plasma drug concentration and their direct toxic effect on skeletal muscles.[4] In our case, muscles painful were at their maximum at the morning when drug plasma concentration was higher.

Conclusion: We report the first case of Metformin-induced acute painful myopathy in a patient with a mother history of myopathy.

References

1. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des medicaments. Thérapie 1985; 40: 111-8

2. Vladutin GD. Genetic predisposition to statin myopathy. Curr Opin Rheumatol 2008; 20: 648-55

3. Klopstock T. Drug-induced myopathies. Curr Opin Neurol 2008; 21: 590-5

4. Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies: an overview of the possible mechanisms. Pharmacological Reports 2005; 57: 23-34

197. Rationale and Design of a Semantic Portal for Analysis and Documentation of Spontaneous Reports

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Introduction: Medical terminologies such as MedDRA for adverse drug reactions or ATC for drugs are used to code information about case reports in spontaneous report systems. Unlike statistical learning that was developed ten years ago for automated signal detection, other branches of artificial intelligence were not explored in the field of pharmacovigilance. For example knowledge engineering improved creation and evaluation of new knowledge in the field of bioinformatics thanks to an active community of research. Our objective is to propose novel methods for the detection, analysis and documentation of adverse drug reactions through the development of a semantic portal to improve retrieval and aggregation of case reports coded with similar medical terms.

Methods: The French VigiTerms project started in January 2008 and consists of six academic teams, one pharmacovigilance regional centre, and two companies. Each partner contributed to the project by providing methods or software developed previously for pharmacovigilance, or generic problem solving tools to customize for adverse drug reactions. Each tool, method or software has already been evaluated and presented elsewhere in scientific conferences or journals. The interfaces are currently developed between the different pieces of software to provide an integrated platform for the end user.

Results: The softwares developed for pharmacovigilance consist of the PharmaMiner tool specialized in automated signal detection, and the

PharmARTS tool for improving access to pharmacovigilance databases, both relying on knowledge representation of adverse drug reactions; a web service dedicated to knowledge extraction about adverse drug reactions from Medline; Signal generation for drug drug interactions and syndromes based on formal concept analysis. A new conceptual model is proposed for the representation of adverse drug reaction and drug information. A skill cartridge has been developed in Luxid especially for pharmacovigilance to recognize and annotate important medical entities such as drugs, adverse drug reactions or patients' findings within texts. Additionally we provide multilingual functionalities for French, English and Japanese. All tools are currently integrated on the Intelligent Topic Manager in order to build the semantic portal.
Conclusion: The implementation of novel knowledge engineering techniques should improve the efficiency of pharmacovigilance end users for the detection, analysis and documentation of adverse drug reactions, especially for knowledge extraction from Medline that is currently the most developed result in the VigiTermes project. More evaluation is required when the integrated platform is available at the end of 2009, in order to compare these new methods with traditional methods for signal detection and verification.

198. Safety Documentation Audit: An Innovative Approach

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Introduction: Pharmacovigilance regulatory obligations are laid down in numerous regulatory documents around the world. In order to adhere to the regulations, Marketing Authorization Holders (MAHs) must continuously monitor the safety profile of medicinal products and notify competent authorities/health professionals of benefit risk modifications. As MAHs are responsible for a large number of safety-related reports and documents that require regular updates, ability to maintain quality and consistency within and across documents has become increasingly an inter-departmental effort within pharmaceutical companies.
Aim: Routine product specific Safety Documentation Audits (SDAs) were implemented to assure that rights, safety and welfare of patients are properly protected; to assess compliance with applicable regulatory requirements, Good Pharmacovigilance Practices, applicable standard operating procedures and MAHs commitments; and to provide an independent analysis of overall quality and systems.
Methods: For each SDA, a product is selected and an audit plan is developed, which includes a focus upon aggregated safety documents (i.e. Investigator Brochure, CCDS, SPCs, RMP, Study Protocols, PASS, Informed Consent, PSUR, PADER), company SOPs, MAH commitments, patient exposure figures and any other relevant supportive information. Content completeness, accuracy, relevance and consistency are reviewed across documents and document creation process. Outputs are compared with company SOPs and applicable regulatory requirements. Main audit activities include: opening discussion, documentation review, interviews with personnel and closing discussion. An audit report is distributed and an action plan, including corrective and preventive actions is created and implemented by document/process owners. Observations are graded as critical, major or minor according to significance of deficiencies observed in PV systems, practices or processes or potential risk that is posed to public health and whether there is a violation of applicable legislation and guidelines.
Results: A total of 5 products were reviewed during 2008–2009. The observations were assigned to the following categories (by decreasing order of frequency): data accuracy and completeness, periodic and aggregate reporting, adherence to requirements, written procedures, organization and training, expedited reporting, data security and confidentiality. For the first three categories, documents with highest frequency of observations were PSURs, RMPs, CCDS and IBs while for written procedures, PSUR SOP was most frequently reported.
Conclusions: The implementation of product specific SDAs provides an innovative approach and critical insight into MAH's safety-related documentation. Immediate benefits of SDAs include the early identification of fields of potential discrepancies and areas of non-compliance as well as provide the support for development of corrective and preventive actions.

199. Selective Serotonin Reuptake Inhibitors (SSRIs) and Hyperprolactinemia

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Introduction: Hyperprolactinemia is a common endocrinological disorder caused by several physiological and pathological conditions. Moreover, several drugs may determine a significant increase in prolactin serum concentration (>20 ng/mL). Psychiatrists usually see hyperprolactinemia in patients who are taking antipsychotics.
Aim: To investigate the risk of hyperprolactinemia associated with use of SSRIs.
Methods: This study analysis was performed using the French Pharmacovigilance Database from 1985 to Janv 2009. This database includes all adverse drug reactions (ADRs) reported since 1985 by French practitioners. All ADRs of hyperprolactinemia, prolactin increased and/or gynecomasty, according to the MedDRA dictionary with SSRIs antidepressants (fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, fluvoxamine, sertraline and milnacipran), as suspected drug, were investigated. The odds ratio (95% CI) was calculated by Woolf's method.
Results: 173 mentioned hyperprolactinemia or gynecomasty associated with galactorrhea. The sexe ratio was 0.38. The mean age was 40 years (range 15–84 years) were notified. SSRIs are the only drug in 55 cases. The patients recovered generally. Hyperprolactinemia is associated with the use of SSRIs antidepressant (OR: 3.28, 95% CI: 2.8, 3.84), especially: fluvoxamine (OR: 4.7, 95% CI: 2.94, 7.52), citalopram (OR: 3.92, 95% CI: 2.59, 5.94), fluoxetine (OR: 3.57, 95% CI: 2.72, 4.68), paroxetine (OR: 3.18, 95% CI: 2.37, 4.26), escitalopram (OR: 2.39, 95% CI: 0.89, 6.42), ventafaxine (OR: 2.24, 95% CI: 1.37, 3.68), sertraline (OR: 1.69, 95% CI: 0.84, 3.4) and milnacipran (OR: 1.18, 95% CI: 0.29, 4.74).
Conclusion: Few data concerning the effect of antidepressants drugs on prolactin are available. All the SSRIs are clearly associated with an increase risk of hyperprolactinemia sometimes associated with clinical signs. Among these, fluvoxamine and citalopram appear to be the most frequent cause of drug-induced hyperprolactinemia.

200. Cutaneous Drug Reactions in Elderly Patients

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Introduction: Cutaneous drug reactions (CDR) are habitually reported with many drugs and all ages. But only few studies analyzed CDR occurring in elderly patients.
The aim of our study was to determine the nature of CDR notified in elderly patients, the drugs incriminated and the seriousness of attempts.

Material and methods: We conducted a sixteen-year retrospective study at the Tunisian National Centre of Pharmacovigilance (1990-2006) where we listed all cases (486) of CDR occurring in the elderly (age ≥65 years). Imputability was established according to Begaud's method[1] and seriousness according to OMS's criteria.

Results: Patients were 265 women and 221 men (sex-ratio W/M: 1.2). Median age was 70 years (65-92 years). Polypathology and atopy were noted in respectively 23 and 2% of all the patients.

CDR were: maculopapular eruptions (MPE: 26%), pruritus (16%), urticaria (11.5%), photosensitivity (9.9%), vesiculobullous and pustular eruptions (VBPE: 9%), fixed drug eruption (8.4%), purpuric eruptions (7.4%), erythroderma (4.1%) and others (8.9%).

Imputation intrinsic score varied from doubtful (82%) to very likely (2%).

Drugs administered per patient were comprised from one to 12 with polypharmacy in 30% of elderly patients. Drugs incriminated were: antibiotics (33%), cardio-vascular (26%), drugs of metabolism and nutrition (12.5%), analgesics and non steroidal anti-inflammatory (NSAI) (8.3%), rheumatologic (8.3%: mainly allopurinol), psycho-neurological (5.4%: mainly antiepileptics) and others (6.5%). CDR were serious in 13% and inducing drugs were antibiotics (36%), allopurinol (25%), cardiovascular (14%), analgesics, NSAI (14%) and antiepileptics (11%).

One case of fatal phenobarbital toxic epidermal necrolysis was noted.

Discussion: In our study, women were predominantly attempted. This may be due to pharmacokinetic and pharmacodynamic differences and higher drug consumption in women.[2]

Polypathology was noted in 23% and atopy in 2%. Polypathology increases occurrence of adverse drug reactions without consideration of age.[2] Atopy may influence the CDR seriousness.[3]

Among CDR, MPE represented 26% and urticaria 11.5%. In a meta-analyzis, CDR were MPE (95%) and urticaria (5%) in patients of all ages.[4]

In our study, polypharmacy was noted in 30%. In literature, a linear correlation exists between the occurence of adverse drug reactions and the number of drugs administered.[5] Drugs incriminated were essentially antibiotics (33%) and cardio-vascular (26%). In literature, drugs incriminated were mainly antibiotics, analgesics and NSAI.[4]

There was serious CDR in 13%, inducing drugs were mainly antibiotics (36%) and allopurinol (25%). In literature seriousness of CDR varied from 2 to 34% in patients of all ages.[6]

References

1. Begaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

2. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol 2008; 83: 1-10

3. Doucet J, Capet C, Jégo A, et al. Les effets indésirables des médicaments chez le sujet âgé : épidémiologie et prévention. Presse Med 1999; 28: 1789-93

4. Haddi E, Charpin D, Tafforeau M, et al. Atopy and systemic reactions to drugs. Allergy 1990; 45: 236-9

5. Collège des Enseignants de *Gériatrie*. Corpus de Gériatrie: 121-9. http://www.corpusgeriatrie.org (Consulted on May 24 2009)

6. Wolf R, Orion E, Marcos B, et al. Life-threatening acute adverse cutaneous drug reactions. Clinics in Dermatology 2005; 23: 171-81

201. Hepatic Drug Reactions in Elderly Patients

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Introduction: The liver is central to the metabolic disposition of virtually many drugs. Drug induced hepatic injury is a potential complication of nearly every medication especially in elderly patients.[1] About 2–5% of hepatitis is drug induced in all age groups as compared to 20% in the elderly.[2]

The aim of our study was to identify in elderly patients the nature and the seriousness of hepatic drug reactions (HDR) and incriminated drugs.

Material and methods: We listed all cases (74) of HDR occurring in elderly patients (age ≥65 years) notified at the Tunisian National Centre of Pharmacovigilance. Imputability was established according to Begaud's method[3] and seriousness according to Zimmerman.[4]

Results: Patients were 47 women and 27 men (sex-ratio W/M = 1.74). Median age was 70 years (65–90 years). Polypathology was noted in 17.6% and polypharmacy in 32%.

HDR consisted on hepatitis (75%), cirrhosis (7%) and benign disturbances in hepatic tests (18%). Hepatitis were: hepatocellular (34%), cholestatic (31%) and mixed (11%). ALAT varied from 3.1 to 100 N in 12.5%.

Serious HDR constituted 13.5%. Death occurred in one case of hepatocellular hepatitis induced by amiodarone (ALAT: 100 N and prothrombin level: 20%).

Drugs incriminated were: cardio-vascular (31%), antibiotics (30%), analgesics and non steroidal anti-inflammatory (NSAI) (15%), antidiabetics (9%), fibrates, allopurinol and halothane (1% each one) and others (6%). In hepatocellular hepatitis, drugs incriminated were mainly: methyldopa, nifedipine and anti-tuberculous drugs in 2 cases each one, allopurinol, amiodarone, halothane and glibenclamide in one case each one. In cholestatic hepatitis, incriminated drugs were mainly: analgesics and NSAI, cardio-vascular and isoniazid and in mixed acute injury: isoniazid and oxacilline.

Discussion: In our study, sex-ratio W/M was 1.74. For unclear reasons, women predominate in HDR. In a recent study, women accounted for 79% of acetaminophen HDR and 73% of idiosyncratic HDR.[5,6]

In our study, hepatitis counted for 75% and was mainly hepatocellular or cholestatic. In patients of all ages, the presentation of HDR is often asymptomatic with raised liver enzymes.[2]

There were serious HDR in 13.5% and death occurred in one case. In literature, death is not uncommon in HDR. Elderly persons seem to be at particular risk, but specific data supporting this pattern are sparse.[5]

Drugs incriminated were essentially: cardio-vascular drugs, antibiotics, analgesics and NSAI.

In literature, there was no study detailing HDR and drugs incriminated in elderly patients.

References

1. Hartleb M, Biernat L, Kochel A. Drug-induced liver damage- a three-year study of patients from one gastroenterological department. Med Sci Monit 2002; 8: 292-6

2. Chandy GM, Chandy RG. Drug Induced Liver Diseases in the Elderly. Journal of the Indian Academy of Geriatrics 2008; 4: 68-71

3. Begaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

4. Zimmerman HJ. Hepatotoxicity the adverse effects of drugs and other chemicals on the liver. 2nd Edition. Baltimore, MD: Lippincott, 1999

5. William M, Lee MD. N Drug-Induced Hepatotoxicity. N Engl J Med 2003; 349: 475-85

6. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137: 947-54

202. Anaphylactic Drug Reactions in Elderly Patients

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Introduction: Anaphylactic reaction is a generalized hypersensitivity reaction involving multiple mediators using several different pathways for the development of a systemic response. It can occur immediately after drug administration leading to an anaphylactic drug reaction (ANDR).

In elderly patients having ANDR, outcome may be influenced by a higher risk of co morbidity and polypharmacy.[1]

The aim of our study was to evaluate the nature of ANDR, drugs incriminated in their genesis and their seriousness in elderly patients.

Material and methods: We conducted a retrospective study at the Tunisian National Centre of Pharmacovigilance (December 1990–2006) where we listed all cases (65) of ANDR occurring in the elderly (age ≥65 years). Imputability was established according to Begaud's method.[2]

Results: Patients were 32 women and 33 men (sex-ratio W/M: 0.97). Median age was 71 years (65–87 years). Chronic diseases were noted in 64% with polypathology in 27% and atopy in 6%.

ANDR were: angioedema (68%), anaphylactic shock (26%), loss of consciousness (4.6%) and generalized erythema with convulsion (1.4%).

The average of drugs administered was 2.8 (1–9 drugs). Polypharmacy was noted in 27%. Among drugs incriminated, we cite: antibiotics (40%), analgesics and non steroidal anti-inflammatory (NSAI) (30%), contrast media (CM: 7%), cardio-vascular (6%) and hypolipidemic drugs (4%). Antibiotics were represented by betalactamins (16 on 23 cases) and quinolones (2 on 23 cases. Among NSAI, salicylic acid induced 8 ANDR on 14.

ANDR were serious in 96% and inducing drugs were mainly antibiotics (33%), analgesics and NSAI (31%), cardio-vascular and CM (8% each one) and fibrates (4%). Two fatal anaphylactic shocks induced by noramidopyrine and CM were noted.

Discussion: In our study, sex-ratio W/M was 0.97. Atopy was noted in 6%, polypathology in 27% and polypharmacy in 27%. ANDR were mainly angioedema and anaphylactic shock. Drugs incriminated were essentially: antibiotics (betalactamins mainly), NSAI and CM. In literature, betalactamins are the most frequent cause of drug allergy representing 0.7–10% of all hypersensitivity reactions.[3] NSAI act in a non immuno-allergic mechanism by inducing a histamine-liberation. ANDR occur in 10–25% in atopic patients and in 1% in healthy patients.[4] ANDR induced by CM are rare.[5]

Serious ANDR occurred in 96%, inducing drugs were mainly antibiotics, NSAI, cardio-vascular and CM. Age and renal deficiency seem to be risk factors of serious adverse reactions induced by NSAI drugs.[6] Fatalities were noted in 2 anaphylactic shocks induced by noramidopyrine and a CM.

References

1. Khan BQ, Lieberman P. Anaphylaxis in the elderly. Aging Health 2008; 4: 377-387

2. Begaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des médicaments. Thérapie 1985; 40: 111-8

3. Demoly P. Identifier et comprendre les allergies médicamenteuses. http://www.erudit.org/ (Consulted on May 24 2009)

4. Hardman JG, Limbird LE, Gilman AG. Goodman & Gilman's: the Pharmacologic Basis of Therapeutics. 9th Edition. London: Mc Graw Hill, 1996

5. Sweetman SC. Martindale: the complete drug reference. 34th ed. London Chicago: Pharmaceutical Press, 2005: 412-4

6. Buffum M, Buffum JC. Nonsteroidal anti-inflammatory drugs in the elderly. Pain management nursing 2000; 1 (2): 40-50

203. Hydroxyurea-Induced Lupus Erythematosus

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Introduction: Lupus erythematosus is an autoimmune disease of the connective tissue, whose specific causes are still unknown. Many drugs and other chemical agents have been reported to cause a syndrome similar to systemic lupus erythematosus (LE).[1] We present a case of hydroxyurea-induced lupus and review the features of this entity.

Observation: A 73-year-old woman with a medical history of hypertension, diabetes, and essential thrombocytaemia treated with hyroxyurea for 2 years, has developed a facial erythema and labial erosions within 8 months. Anamnesis has noted a photosensitivity and inflammatory polyarthritis. Physical examination has objected erythematous and pigmented facial plaques without atrophy mainly located on cheeks. A squamous cheilitis scattered with multiple erosions of the upper lip and an effluvium telogene were also noted. Histological examination and direct immunofluorescence have showed typical aspects of lupus erythematosus. Biological investigations revealed an inflammatory anaemia, positive antinuclear antibodies (ANA) at 1/3200 and positive anticardiolipid antibodies. Pharmacovigilance enquiry concluded to a probable responsibility of hyroxyurea in lupus induction. After withdrawal of the causative drug, cutaneous and mucosal symptoms have regressed within 1 week.

Discussion: Drugs responsible for the development of LE can be divided into three groups. The first includes drugs for which there are well-controlled studies and their role for inducing LE has been documented. To this group belong such drugs as hydralazine, procainamide, isoniazid, methyldopa, chlorpromazine, and quinidine. To the second group belong drugs very possibly related to DILE such as anticonvulsant agents, antithyroid drugs, penicillamine, sulfasalazine, beta-blockers, and lithium. The third group comprises drugs suggested as causes for LE but lacking well-controlled studies because of rarity of reported cases. To this group belong hydroxyurea. Induced LE is recognized to be a mild SLE without severe systemic involvement. Symptoms and signs usually resolve in weeks. The ANA level typically remains elevated after symptoms have resolved on an average of 4 months.

Reference

1. Kyrill D. Pramatarov: drug-Induced Lupus Erythematosus. Clinics in Dermatology 1998; 16: 367-77

204. Furosemide-Induced Toxic Epidermal Necrolysis

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Introduction: Toxic epidermal necrolysis are rare and severe, life-threatening, drug-induced cutaneous reactions. Furosemide (Lasilix®) is a hypokaliemic diuretic sulfonamide, widely used to treat hypertension and oedema of various origins (renal, hepatic or cardiac). Toxic epidermal necrolysis (TEN) has been exceptionally reported with furosémide. We describe a case of TEN in a young woman having systemic lupus erythematosus, and using multiple medications, and discuss drug of different drugs mainly furosémide.

Case report: A 24 year old female, with a medical history of systemic lupus erythematosus with 8 ARA criteria (skin lesions, photo-

sensitivity, buccal ulcerations, blood and renal involvements, pleurisy, anti-nuclear antibodies et anti native DNA), was referred in nephrology for treatment of lupic glomérulonephritis. She received prednisone (1 mg/kg/day), and furosemid (20 mg/day). Three weeks later, the patient presented a maculo-papular diffuse eruption of the trunk, limbs and face associated with buccal and genital ulcerations. Rapidly, she developed flaccid confluent bullous lesions with detachment of dorsal skin. Histology showed keratinocytic necrosis with mononuclear perivascular infiltrate. Direct immunofluorescence was negative. Pharmacovigilance enquiry concluded to a very probable imputability of furosemid. Favourable evolution was observed after withdrawal of the causative drug.

Discussion: Toxic drug eruptions to furosemid are rares. They include mainly photosensitivity, vascularitis and cutaneous pseudoporhyria. Toxic epidermal necrolysis has been exceptionally reported with furosémide. Kennedy and Lyell[1] reported 7 cases of patients with severe renal failure, receiving furosémide at the doses of 0.5 to 2 mg/day for several months, who developed TEN.

Severe toxic drug eruptions to furosemid should be well known to assure an early and adequate treatment and avoid fatal issue.

Reference

1. Kennedy AC, Lyell A. Acquired epidermolysis bullosa due to high-dose frusemide. Br Med J 1976 Jun 19; 1 (6024): 1509-10

205. Epidemiology of Isotretinoin Exposure During Pregnancy

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Background: Exposure to isotretinoin during pregnancy is associated with a high risk of major fetal malformations. In three previous studies we have shown that pregnant women are still being exposed to isotretinoin. The relaxation of recommendations, together with the release of generic drugs, led us to carry out a fourth study.

Aim: Our purpose was to determine the incidence of isotretinoin exposure during pregnancy since the previous study and the reasons for in utero exposure to isotretinoin.

Methods: We analysed all spontaneous reports of exposure to isotretinoin in pregnant women to the French Regional Pharmacovigilance Centres (RPVC), to the manufacturers or to the Reference Centre for Teratogenic Agent (CRAT) between January 2003 and December 2006.

Results: During this 4 years, 147 cases of pregnant women exposed to isotretinoin during the period of teratogenic risk have been reported. Timing of conception in relation to initiation of therapy with isotretinoin was known for 147 women. Of these, 24 (16%) were already pregnant when they started isotretinoin, 89 (61%) became pregnant during isotretinoin treatment and 34 (23%) became pregnant less than a month after stopping isotretinoin. Pregnancy was due to failure of contraception (48%), to the incorrect use of contraception (17%), to the stop of contraception (3%) or to the absence of contraception (32%). The method of contraception did not comply with recommendations in 23% of women. Pregnancy outcomes were known for 103 pregnancies (70%): 73 (71%) ended in elective abortion, 7 (6%) in spontaneous abortion and 23 (23%) give birth. Two babies (4.5%) had malformations (cerebellar vermis agenesis) in accordance with isotretinoin exposure. Based on the dose regimen used of isotretinoin, incidence of pregnancy exposed to isotretinoin can be estimated between 0.41 [0.34–0.49] and 1.24 [1.05–1.46] per 1000 women in child-bearing age.

Conclusion: Since the previous study, the incidence of pregnancy exposed to isotretinoin has increased by 30%. The high proportion of pregnancy occurring during isotretinoin treatment illustrates the importance of a better explanation of reliable contraceptive methods for women and prescribers. A negative pregnancy test before initiation of isotretinoin therapy and a monthly pregnancy test during the treatment are mandatory. Soon it will be given a booklet to every French woman to be treated with isotretinoin, where the prescriber will record the type of contraception used, all pregnancy tests,... so that the pharmacist can checked everything before isotretinoin delivery.

206. Hydroxyurea-Induced DRESS Syndrome

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Background: Drug-induced hypersensitivity syndrome also called DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a new entity described by Bocquet and Callot in 1996. It is a severe hypersensitivity drug reaction with mortality estimated at about 10%. DRESS syndrome has been frequently reported with aromatic anticonvulsant drugs, allopurinol and minocycline.[1] To our knowledge, hypersensitivity syndrome to hydroxyurea (Hydrea®) has not been reported before. We describe a case of DRESS syndrome in a 32-year-old woman following treatment of thrombocythaemia of Vaquez with hydroxyurea.

Case report: A 32-year-old woman was referred in June 2008 with a pruritic diffuse erythemato-papular eruption affecting face, trunk and extremities. The patient had an 8-mounth-history of essential thrombocythaemia and had been treated with hydroxyurea for 4 months. On clinical examination, she had an erythroderma with facial oedema associated with fever at 385°C and inguinal and cervical lymphadenopathy. Laboratory investigations showed eosinophilia (2120/μL) without atypical lymphocytosis. Biology showed an increased gamma GT (2 folds). Viral tests (HHV6, HHV7) were not available. A DRESS syndrome was suspected and hydroxyurea was discontinued. The patient was treated with oral corticosteroids (0.5 mg/kg daily) during 2 weeks with rapid clinical and biological improvement within 1 week.

Conclusions: Cutaneous side-effects with hydroxyurea occur in 10–35% of cases and include diffuse hyperpigmentation, photosensitivity, oral and leg ulceration, alopecia, nail changes, fixed drug eruptions and cutaneous vasculitis. Hydroxyurea dermopathy has also been described as a poikilodermatous skin eruption with atrophy, erythema and scaling. To our knowledge, DRESS syndrome has never been reported with hydroxyurea (Hydrea®). In our patient, pharmacovigilance enquiry concluded to a responsibility of hydroxyurea (score I2B3 according to Begaud score).

Reference

1. Kardaun SH, et al. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007; 156: 609-11

207. Tranexamic Acid and Retinal Vein Occlusion

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Background: Tranexamic acid is an antifibrinolytic drug used to prevent bleeding, in particular in menorrhagia, for which indication it

is prescribed primarily in Primary Care. A signal was raised for an association between retinal vein occlusion and tranexamic acid in the MHRA spontaneous reporting database.

Aim: Although the SPC states that there have been rare reports of thromboembolic events associated with the use of tranexamic acid, it was considered that it would be useful to try to estimate the incidence of such events in females receiving tranexamic acid for menorrhagia.

Methods: Annual incidences of thrombotic events were calculated for 11 cohorts of patients in the Full Feature General Practice Research Database (FF- GPRD). There was one cohort for each year between 1996 and 2006, consisting of female patients aged between 18 and 50 prescribed tranexamic acid between the beginning and end of the relevant year. The incidences were compared to those in age-matched cohorts of female patients who were in active practices in the relevant year and had never been prescribed tranexamic acid.

Results: The rate of thromboembolic events is raised in some of the exposed cohorts compared to the unexposed cohorts, although not always significantly. There are some raised rates across the three exposure groups, currently exposed, recently exposed and past exposure. However there are more raised rates in the past exposure group than in the currently exposed or the recently exposed group.

Attributable risks were calculated across all exposure groups, current past and recent, compared to women with no exposure. The risk attributable to tranexamic acid is negative for all years. Across all years from 1996 to 2006 the excess risk of thromboembolic events attributable to tranexamic acid exposure is -1.67 per 1000 patients exposed.

Conclusion: The numbers of thromboembolic events in patients exposed to tranexamic acid in this study was very low, and the study lacked power to detect an effect. It is also possible that due to the SPC wording regarding thromboembolic events, patients with other risk factors for thromboembolic events are not prescribed tranexamic acid, contributing to the low event rate seen.

Discussion: The results of the study were inconclusive. However the signal in the spontaneous reporting database was fairly strong and there is biological plausibility for the reaction. This signal will be kept under review.

208. Fixed Drug Eruption Due to Mefenamic Acid with Positive Patch Test

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Introduction: Mefenamic acid is a non-steroidal anti inflammatory drug with analgesic properties. Generally, mefenamic acid is well tolerated. Cutaneous adverse reactions attributed to this drug are very rare and include rash, erythema multiforme, photosensitivity, Urticaria, fixed drug eruption and toxic epidermal necrolysis.

Aim: We report a case of fixed drug eruption with positive patch test associated with mefenamic acid.

Case: A 48-year old woman presented to the outpatient dermatology clinic with a pruritic, well-circumscribed and hyperpigmented patches located on the trunk, face and arms. The current rash appeared 24 hours after the consumption of mefenamic acid, paracetamol and dextropropoxyphene for dysmenorrhoea. The examination of her skin revealed multiple, well-limited, non-confluent, purplish-livid and ovalar patches spread diffusely over her arms, trunk and face. A skin biopsy was carried out from a lesion affecting her forearm. Histological examination revealed orthokeratosis, spongiosis and a slight inflammatory perivascular infiltrate of lymphocytes and plasmocytes. Patch tests were performed two weeks later. Mefenamic acid and vaseline were applied on the left arm in a lesion of fixed drug eruption. The result was a positive skin reaction (++) after the application. Occlusive patch performed in the same arm with vaseline, paracetamol and dextropropoxyphene was negative. The temporal correlation between the drug introduction and the rash appearance, previous history of recurrent reaction in the same sites and skin biopsy findings were consistent with the diagnosis of fixed drug eruption induced by mefenamic acid.

Discussion: Fixed drug eruption induced by mefenamic acid is not a frequent adverse reaction in spite of the widespread use of the drug.[1,2] Although, mefenamic acid has been associated with fixed drug eruption in a very few reports, no cases of with a positive patch test have previously been reported. After intake of the offending agent, fixed drug eruption appears within minutes up to several hours (about 30 minutes to 8 hours). Several non-steroidal anti-inflammatory drugs have been reported as incriminated in the genesis of this adverse reaction such as phenylbutazone, oxyphenbutazone, and ibuprofen. The pathogenesis of fixed drug eruption is still unclear. According to the new sub-classification of delayed type IV immune reactions, fixed drug eruption is a type IVc reaction in which cytotoxic T cells may play an important role. Our patient was firmly instructed to avoid mefenamic acid therapy.

Conclusion: Clinicians should be aware of the ability of mefenamic acid to induce fixed drug eruption.

References

1. Long CC, Finlay AY, Marks R. Fixed drug eruption to mefenamic acid: a report of three cases. Br J Dermatol 1992; 126: 409-11

2. Rallis E, Rigopoulos D, Anyfantakis V, et al. Dalmatian dog'-like skin eruption (two cases of multifocal fixed drug eruption induced by mefenamic acid). J Eur Acad Dermatol Venereol 2005; 19: 753-5

209. Evaluating the Attitude of Doctors towards Reporting Adverse Drug Reactions in Turkey

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Background: In Turkey, the Local Pharmacovigilance Regulation was issued in March 2005. As per that date, Pharmacovigilance in Turkey has become legally based on sound scientific principles. Accordingly, all healthcare professionals are responsible of reporting Adverse Drug Reactions (ADRs) within specific time frames to the Health Authority. However, underreporting is still a major issue in Turkey and apparently, there is a real challenge to enforce pharmacovigilance activities in hospitals where traditionally doctors or other health professionals never spared enough time to detect or report ADRs.

Objective: The purpose of this study was to analyze the attitude of doctors towards reporting ADRs and their adoption of the new reporting processes in Turkey. Moreover, the study aimed to assess the effectiveness of educational sessions on the general pharmacovigilance perception of doctors. For this purpose, ''Focus Group'' as a qualitative method, survey analysis and educational sessions were used. The sessions were conducted in three types of hospitals in Turkey and particularly in Istanbul: State, University and Private. The target was to conduct these sessions with doctors of different specialities and hospitals to have a general overview and capture the different obstacles that prevent health professionals from reporting.

Results: 168 doctors participated in this study. Accordingly, 84% of the doctors stated that they have never reported an adverse event before while 16% stated that they usually reported adverse events to pharmaceutical companies when they wanted to seek medical or scientific support. The discussions of the focus groups revealed that most doctors could not define the meaning of Pharmacovigilance properly nor were they aware of the local Pharmacovigilance Regulation's requirements. Moreover, the common obstacles that prevented doctors from reporting ADRs were as follows: lack of knowledge in terms of what to report, how and where, lack of time, and the fear of being legally or professionally misjudged. As for the pharmacovigilance educational sessions, according to the survey results; 94% of the doctors found those sessions to be beneficial and 64% of them expressed that they would like to receive further information regarding Pharmacovigilance and reporting processes.
Conclusion: Perception of doctors' attitude through interactive focus groups towards pharmacovigilance activities is crucial in understanding the general drug safety environment in Turkey. The other essential point is to clarify why doctors do not report ADRs on a routine base. Thus, addressing these obstacles and increasing the awareness level of doctors through educational sessions would lead to an improvement in spontaneous reporting. Consequently, the national pharmacovigilance system would function more efficiently to protect public health.

210. Addictive Substances: Moroccan National Poison Control and Pharmacovigilance Center Retrospective Study

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Introduction: In Morocco, the use of addictive substances is on rise. These drugs can be the object of an abusive, festive, problematic consumption or for the purpose of doping or involved in criminal activities. Disastrous consequences on health and life conditions are observed in addictive substances users.
Aim: To elaborate a prevent strategy to stop the spread of addictive substance consumption.
Methods: We performed a retrospective study from Moroccan National Poison Control and Pharmacovigilance center database. The study has covered the period from 1989 to 2007 and has evaluated cases of abuse and drug dependence including medicines as well as all other psychoactive substances containing one or more active ingredients. Two inclusion factors were used: type of product (= addictive substances) and circumstance of adverse reactions (= pharmacodependence). Descriptive statistics and logistic regression are undertaken.
Results: A total of 1843 cases were concerned by the study. The other results are under assessment and will be presented in the ISoP 2009 annual meeting.
Conclusion: Results of this study will be used for development of national prevent strategy.

211. A Prospective Study of the PSUR Work Sharing Procedure: A Tool for Harmonization of the Safety Information of Active Substances?

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Background: Since 2007, an initiative has been taken in Europe to avoid duplication of work and where possible to harmonise safety information of active substances (AS) in a Core Safety Profile (CSP), through the PSUR Work Sharing Procedure (PWSP). A PSUR Reference Member State (P-RMS) is in charge of making the PSUR Assessment Report (PAR) which is commented by Member states (MS), in order to adopt a Final Assessment Report (FAR) and a CSP.
Objective: To assess the feasibility of the harmonisation of safety information in Europe.
Methods: We performed a prospective study of active substances included in the PWSP for a-6-month-period from November 2008 to April 2009. At the end, the impact of Member States' comments on the evaluation of the benefit/risk of AS, was analysed within procedures which have led to a Final AR.
Results: During the period, within 38 active substances included in the PWSP, 10 resulted in a Final AR (26%).

Table I. Number of comments on PAR from MS within the 10 Final AR

Active substance	Number of comments from MS
Barnidipine[a], Indobufene[a]	0
Ketobemidone[a], Ornidazole, Everolimus	1
Simvastatine, Levobunolol	3
Pimecrolimus, Risedronate	4
Tamsulosine	6

a No marketing authorization in France.

For each AS, less than 6 MS have sent comments on PAR (table I). Comments from MS did not modify the Preliminary AR for 4 AS (pimecrolimus, ornidazole, risedronate, everolimus). In 4 other cases (simvastatine, tamsulosine, levobunolol, and ketobemidone), comments were raised in the light of comparison between national Summary Product Characteristics and proposed CSP, and/or of the assessment of national PSURs.
Discussion: Participation from MS seems to be limited. However, AS don't have a Marketing Authorization in all MS. Most of products assessed under the PWSP are not innovative. The majority of comments consists in including national specificities in the CSP but few new safety information from national PSURs were raised. Thus, P-RMS plays a prominent part in selecting safety information to be included in the CSP.
Conclusion: This is a learning period for both MS and MAHs where a clear definition of CSP will simplify the Work Sharing and could be used as a tool for safety information harmonisation.

212. A Case-Control Study to Investigate the Association Between Finasteride and Male Breast Cancer Using the GPRD

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Introduction: Finasteride is a type II 5α-reductase inhibitor indicated for the treatment of benign prostatic hyperplasia at a 5 mg dose and at a lower 1 mg dose for male pattern baldness. A signal was detected in the Yellow Card spontaneous adverse drug event database for 5 mg finasteride associated with breast cancer. The mechanism of action of finasteride reduces the levels of the circulating androgen dihydrotestosterone. Since androgen deficiency due to testicular disease has been linked to an increased risk of male breast cancer[1] it is biologically plausible that finasteride may also increase the risk. Additionally, gynaecomastia is a known side-effect of finasteride therapy.

Aim: To further investigate the signal of breast cancer associated with finasteride.
Methods: A retrospective matched case control study was conducted using the General Practice Research Database. Cases were defined as adult male patients with a medical code for breast cancer between 1997 and 2007 and no prior history of breast cancer. Controls were matched to the cases on age and practice. Odds ratios of breast cancer for male patients exposed to finasteride compared to unexposed male patients were calculated using conditional logistic regression adjusting for smoking status, BMI and alcohol use.
Results: A total of 180 male patients with an incident medical code for breast cancer between 1997 and 2007 were identified. The adjusted odds ratio for the risk of male breast cancer associated with finasteride exposure was increased at 1.29 but not statistically significant and had a wide 95% confidence interval (0.44–3.75). When the data were stratified according to duration of therapy a non-significant trend for a higher risk of male breast cancer was observed with a longer duration of more than 2 years (<2 years duration adjusted OR 0.52 (0.06–4.24), >2 years duration adjusted OR 2.04 (0.59–7.10)).
Conclusion: The results of this study are inconclusive regarding a causal association between exposure to 5 mg finasteride and the risk of male breast cancer. Due to the rarity of male breast cancer, only a small number of cases were identified in the GPRD and with a relatively low finasteride exposure rate of approximately 3.5% the study lacked sufficient power to detect or refute a causal relationship. A study using a much larger database than GPRD would be required in order to provide a more conclusive result.

Reference

1. Contractor KB, Kaur K, Rodrigues GS, et al. Male breast cancer: is the scenario changing? World J Surg Onc 2008; 6: 58

213. Induction of Violence by Psychotropic Drugs: Signal Detection

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Introduction: Violence which presents as a public problem is often inadequately managed, particularly for those with mental disorders who are prescribed psychotropic medications. We discuss what needs to be done.
Methods: We reviewed the institutional frameworks relevant to responding to and managing violence by people prescribed psychotropics.[1]
Results: Violence is typically investigated and dealt with by the police and criminal justice systems. These agencies are accustomed to handling violence caused by alcohol, and by abuse or illegal misuse of drugs, but are still largely unaware of the effects of prescribed psychotropic medicines. National drug regulatory agencies collect and analyse reports of adverse effects of medicines (ADRs). They need to recognise and investigate signals of potentially important adverse effects so that these can be investigated or minimised, and people can be warned about them. However, profesionals and patients or their carers tend not to report violence as a suspected ADR; the police never do-they don't know when it is appropriate to suspect medicines, and hardly ever obtain an offender's medication history.
Conclusions: Violence as a potential ADR is grossly under-reported to regulators, and there is an associated lack of understanding in the criminal justice system, and among health professionals and the public. New arrangements are needed for reporting, collection, investigation and analysis of these incidents. This will require alerting of professionals, training in the police and criminal justice services, and the establishment of prompt and reliable communication between these and medicines regulatory agencies.

Reference

1. Healy D, Herxheimer A, Menkes D. Antidepressants and violence: problems at the interface of medicine and law. PLoS Medicine 2006; 3 (9): e372

214. Critical Analysis of the Risk/Benefit Ratio of First-Line Antibiotics Included in Guidelines for the Treatment of Community-Acquired Pneumonia

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Background: Resistance of the target organism(s) is a potential cause of treatment failure in antimicrobial therapy and should, therefore, be included, together with other, conventional adverse drug reactions (ADRs), in the analysis of the risk/benefit ratio of anti-infective drugs.[1] Although this is implicitly taken into account in the setting of national or regional guidelines, the ever changing pattern of resistance may make them rapidly less effective than expected.
Objective: To assess to what extent most recent guidelines for the treatment of community-acquired pneumonia (CAP) in Europe and North America are safe and well-balanced with respect to the risk of bacterial resistance and other ADRs.
Methods: Guidelines published or updated in or after 2004 from European (ERS/ESCMID), national (DE, FR, GB, ES, NL, BE, SE, AU, CH, and NO) and North-American (ATS) organizations were retrieved. The frequent conventional ADR's of the recommended antibiotics were compiled from the corresponding official labeling. In parallel, resistance data for *S. pneumoniae* (most critical organism in CAP) were obtained from systematic literature analysis (2007-2008, incl. abstracts to main congresses) and from the main surveillance networks (TRUST, GLOBAL, PROTEKT, EARSS).
Results: 12 guidelines for adults and 3 for children were reviewed. Most European guidelines for patients without co-morbidities presented beta-lactams or macrolides as first-line therapy, with fluoroquinolones as alternatives. Yet, current resistance patterns of *S. pneumoniae* for beta-lactams and macrolides are often high (typical examples: France [recommending beta-lactams or macrolides] where reduced susceptibility to penicillins [requiring high doses] is >25% and full resistance to macrolides is >30%; North-America [recommending macrolides] where full resistance is >30%). Most frequent conventional ADRs were allergy for beta-lactams (with hepatotoxicity if addition of clavulanic acid), impairment of hepatic metabolism of co-administered drugs for macrolides (with cardiac toxicity for IV forms). In contrast, resistance of *S. pneumoniae* to "respiratory" fluoroquinolones remains low in all countries. Yet, fluoroquinolones are not registered for children and expose to the risk of tendonitis (esp. in elderly and patients receiving corticoids).
Conclusion: Two antibiotic classes commonly recommended (beta-lactams, macrolides): (i) may constitute rational choices for CAP in regions with low resistance rates but carry significant risk of conventional ADRs; (ii) expose patients to risk of treatment failure in many other regions. While other classes of antibiotics have also their own conventional ADRs, integration of resistance pattern data, and continuous readjustment of guidelines based on a more global assessment of risk/benefit ratio may be necessary.

Reference

1. Aronson JK. Drug therapy. In: Haslett C, Chilvers ER, Boon NA, Colledge NR, Hunter JAA, editors. Davidson's principles and practice of medicine 19th ed. Edinburgh: Elsevier Science, 2002: 147-63

215. The Knowledge, Perceptions and Practice of Pharmacovigilance Among Community Pharmacists in Lagos State, Southwest Nigeria

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Background: Adverse drug reactions (ADRs) are significant causes of morbidity and mortality. ADRs may cause many hospitalizations and lead to large economic burdens to patients and to society.[1]

Spontaneous reporting of ADRs remains the cornerstone of pharmacovigilance and is important in maintaining patient safety. However, the success of this activity is dependent on the frequency of reporting by the health care professionals, under-reporting being the main disadvantage.[2]

In order to boost the performance of our pharmacovigilance system, it is necessary to assess the practice of pharmacovigilance, and identify reasons for under-reporting amongst healthcare professionals.

Aim: This study aims to investigate the knowledge, perceptions and practice of Pharmacovigilance amongst community pharmacists in Lagos State, South West Nigeria Also, their attitude towards adverse drug reactions reporting was investigated.

Methods: Lagos, one of Nigeria's largest metropolitan city, has the highest number of pharmacies in the country.

A face-to-face questionnaire was used to conduct the study. The questionnaire consisted of questions about the socio-demographic characteristics of the pharmacists, their post graduate qualification, knowledge, perceptions and practice of pharmacovigilance as well as their attitudes towards ADR reporting.

Results: A total of 400 out of the over 500 registered pharmacies in Lagos were visited. All the pharmacists visited consented to participate in the study. Most of the community pharmacists visited (376, 90%) were on duty while the remaining participated during subsequent visits. Only 18% of respondents had a good knowledge of 'Pharmacovigilance'. Forty percent of the pharmacists stated that patients reported ADRs to them on a monthly basis, and 20% of pharmacists reported to the relevant authorities. However only 3% of the above respondents actually reported an ADR to the National Pharmacovigilance Centre. Meanwhile, 90% of the pharmacists believed that the role of the pharmacist in ADR reporting was essential. Factors responsible for these seemingly discrepant findings are also explored

Discussion: One important reason for poor reporting is inaccessibility to the ADR forms, as 88% of respondents claimed that they did not have access to the forms. Some studies have given various reasons for poor reporting including ignorance, lack of time, complacency and uncertainty about the drug causing the adverse reaction.[3]

Conclusion: Community pharmacists in Lagos had poor knowledge about Pharmacovigilance. Reporting rate was also poor despite a positive disposition to reporting. There is an urgent need for educational programs to train them about pharmacovigilance.

References

1. Lundkvist J, Jonsson B. Pharmacoeconomics of adverse drug reactions. Fundam Clin Pharmacol 2004; 18 (3): 275-80

2. Wiholm BE, Olsson S, Moore N, et al. Spontaneous reporting systems outside the United States. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons Ltd, 1994: 139-55

3. Hale ZT, Meral KU. The knowledge and attitude of Turkish community pharmacists towards pharmacovigilance in the Kadikoy district of Istanbul. 2008; 30 (5): 556-62

216. Novel Biomarkers of Drug Safety Related to Drug-Induced Neuropsychiatric Adverse Events Including Drug-Induced Suicidality

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Introduction: Serious drug-induced neuropsychiatric adverse reactions have been reported for many pharmacological agents. Serious concerns were recently raised over drug-induced suicidality respectively to antidepressant or anti-obesity agents. Contrary to renal or hepatic drug-induced toxicicity, those adverse drug reactions cannot be predicted by drug screening or monitored by laboratory testing. This raises a specific concern from an evidence-based pharmacovigilance point of view, respectively to adverse reaction documentation and imputability.

Neuropsychiatric drug safety biomarkers: We are currently validating functional biomarkers of neuropsychiatric diseases whose clinical utility may encompass predictive neuropsychiatric toxicology and monitoring thereof. Those biomarkers could be used complementarily to genetic testing. Our biomarkers are derived from receptor editing, a mechanism of growing interest in neurosciences.

Scientific rationale: Serotonin 5HT2C receptors, as other pharmacologically relevant receptors such as Glutamate AMPA receptors, undergo a post-transcriptional modification known as RNA editing, whose alteration of has been evidenced in several studies,[1-4] respectively to various neuropsychiatric conditions, including suicide. We eventually developed an in vitro and ex vivo drug screening assay and found correlations, among 65 screened compounds, between certain drug-induced editing profile and known occurrence of neuropsychiatric adverse events. Additionaly, we identified 5HT2C receptor editing-related biomarkers that are testable by blood sampling and initiated a clinical trial in interferon a treated patients.

Opened perspective for neuropsychiatric drug safety assessment: Utility of our biomarkers is twofold. Early in the discovery and preclinical phase, our biomarkers could be use to prioritize candidate drugs according to their receptor editing-related profiles. The closer the profile of the candidate drug will be to those of drugs for which neuropsychiatric adverse events (e.g. suicidality) were reported, the lower the priority for further development or the higher the safety surveillance to put the candidate drug under. This approach will allow a very early identification of risks and thus an better assessment of the benefit risk ratio. On the other hand, our biomarkers could monitor and/or evidence alteration of receptor editing in treated patients during clinical development or as part as a post marketing pharmacovigilance. In this case, risks factors and groups at risk will be identified and assessed, leading either to preventive/minimizing action or to changes in the clinical development plan. In both cases, our biomarkers could contribute to the adverse events imputability. Our approach is similar to the systematic cardiac safety assessment in clinical trials and is aimed at providing an effective tool for neuropsychiatric safety assessment of drugs.

References

1. Niswender CM, Herrick-Davis K, Dilley GE, et al. RNA editing of the human serotonin 5-HT2C receptor. Alterations in suicide and implications for serotonergic pharmacotherapy. Neuropsychopharmacology 2001; 24: 478-91

2. Gurevich I, Tamir H, Arango V, et al. Altered editing of serotonin 2c receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. NeuronApril 2002; 25: 349-5

3. Dracheva S, Patel N, Woo DA, et al. Increased serotonin 2C receptor mRNA editing: a possible risk factor for suicide. Mol Psychiatry 2008; 13 (11): 1001-10

4. Weidong Yanga, Qingde Wanga, Stephen J. Kanesb, et al. Altered RNA editing of serotonin 5-HT2C receptor induced by interferon: implications for depression associated with cytokine therapy. Molecular Brain Research 124 (2004) 70-8

217. Premature Closure of the Ductus Arteriosus after Exposition, During the Second Trimester of Pregnancy, to Indomethacin

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Nonsteroidal antiinflammatory drugs (NSAIDs) are the most widely used agents in medicine. They are frequently used in prevention in the preterm labor. The risk associated with NSAIDs use late in pregnancy is well known: oligohydramnios and intrauterine closure of the ductus arteriosus to persistent pulmonary hypertension and fetal death. Adverse neonatal outcomes associated with maternal NSAIDs use include respiratory distress syndrome, renal failure, intraventricular hemorrhage, bronchopulmonary dysplasia and necrotising enterocolitis.[1]

Indomethacin is known to cross the human placenta freely, independent of gestational age, it inhibits prostaglandin synthesis in the developing fetus.[2] Some authors showed that the human fetal ductus arteriosus is sensitive to the constrictive effects of indomethacin as early as the late second trimester.[3]

We report one case of constriction of ductus arteriosus at 19 weeks of amenorrhea (SA). It is a monochorial biamniotic twin pregnancy; at 17 SA and 4 days, the fetal echography showed a growth anomaly out of one fetus, with pathologic umbilical Doppler, without sign of twin-twin transfusion syndrome. A selective feticide by percutaneous cord interstitial laser coagulation is selected. Two hours before the intervention the mother had received a tocolytic medication by indomethacine (suppository of 100 mg), this therapy for tocolysis is re-elected six hours after the cord coagulation at the same posology. The following day, a fetal echocardiography showed a right cardiac hypokinesis with a pleural effusion of the twin remaining alive. These abnormalities are in keeping with a constriction of ductus arteriosus.

A 24 hours medical supervision showed improvement of cardiac function and contractility of the right ventricle and the ductus arteriosus became permeable.The pregnancy was later complicated by premature rupture of membranes at 26 SA. A boy of 1640 grams is born at 30 SA by caesarean. Apart from respiratory distress quickly resolved, the evolution has been good.

Although most authors agree that a use of the NSAIDs before 24 SA is possible,[4] this observation shows that whatever the term of pregnancy is, it would always made with caution.

References

1. Koren G, Florescu A, Costeri AM, et al. Nonsteroidal ntiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. Ann Pharmacother 2006; 40: 824-9

2. Loudon JAZ, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labor. Best Pract Res Clin Obstet Gynaecol 2003; 17: 731-44

3. Vermillon ST, Scardo JA, Lashus AG, et al. The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. Am J Obstet Gynecol 1997; 177: 256-61

4. AFSSAPS. Rappel sur la contre-indication des AINS à partir du 6ième mois de la grossesse, quelle que soit la voie d'administration (Lettre aux professionnels de santé).27/02/2009

218. Unraveling the Safety Profile of Biologicals Using Postmarketing Safety Data

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Background: Biologicals carry specific risks, e.g. infections and immunogenicity.[1,2] Additional knowledge of the safety profile and risk factors for occurrence of these adverse events may lead to a more targeted pharmacovigilance.

Objective: To further unravel the post-marketing safety profiles of biologicals and identify characteristics that influence the safety profile.

Methods: Data was obtained from the International Drug Monitoring Program of the WHO (Vigibase). Case reports for biologicals approved in EU and US between January 1995 and December 2008 were selected. Biologicals were classified in mechanistic classes (e.g. antibodies, hormones, interferons, receptors) and within the mechanistic classes additional characteristics of the biological and treatment was studied, e.g. route of administration. Adverse events (AEs) were classified as infections, neoplasms (benign, malignant, and unspecified), immunological events, general disorders and administration site conditions, nervous system disorders, and others.

Results: A total of 584,157 AEs were reported between January 1995 and December 2008.

Infections represented 3.2% of the total number of AEs reported for hormones, compared to 6.7% for interferons, 10.8% for antibodies, and 12.4% for receptors. Neoplasms involved 1.2% of AEs for hormones, 2.7% for interferons, 3.0% for antibodies, and 2.2% for receptors. Immunological events involved 5.2% of AEs for interferons up to 14.6% for receptors. Nervous system disorders involved about 7% of AEs for antibodies and receptors compared to 10% and 15.3% for hormones and interferons, respectively.

For antibodies, infections were reported less frequently for subcutaneous administered antibodies (10.7%) than for intramuscular administered antibodies (31.7%). For subcutaneous administered antibodies, a higher percentage of adverse events was reported in the classes immunological events (15.2% vs. 6.7%) and general disorders and administration site conditions (20.3% vs. 11.3%).

Differences in the safety profile for the different routes of administration was also seen for the other mechanistic class, e.g. nervous system disorders occurred less frequently for subcutaneous administered interferons (10.7%) compared to intramuscular administered interferons (17.2%).

Discussion and conclusion: Although limitations exist, e.g. underreporting and causality assessment, collection of spontaneously reported adverse events is an important tool for further unravelling

the benefit-risk profile of drugs.[3,4] This study showed that differences exist in the safety profile of different mechanistic classes of biologicals, e.g. 12.4% of the AEs reported for receptors concerned infections compared to 3.2% for hormones, and within these mechanistic classes the classification of the AEs differs, e.g. infections involved a higher percentage of AEs reported for intramuscular administered antibodies compared to subcutaneous administered antibodies.

References

1. Kessler M, Goldsmith D, Schellekens H. Immunogenicity of biopharmaceuticals. Nephrol Dial Transplant 2006; 21 Suppl 5: v9-12

2. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, et al. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA 2008; 300: 1887-96

3. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006; 29: 385-96

4. Meyboom RH, Hekster YA, Egberts AC, et al. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997; 17: 374-89

219. Effect of Iron Pills on The Upper Gastrointestinal Tract Mucosa

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Introduction: Oral iron therapy is a widely used treatment of iron-deficiency anemia. Although it is generally well tolerated in healthy young volunteers (mean age : 29.1 years).[1] Recent studies have shown that iron pills taken on standard dosage could cause upper digestive tract damage such as erosion or ulcers.[2-4] These adverse drug reactions are not mentioned in french Summary Product Characteristics (SPC). Only one case of iron-induced ulcer have been reported to our Pharmacovigilance regional center.

Methods: The pathology archives of the Reims Robert Debré CHU were searched from 1989 to 2009 for upper digestive tract biopsy looking for the keywords ''iron'' or ''hemosiderin'' in the conclusion. Haematoxylin and eosin, and Perl's Prussian blue-stained slides were reviewed. Endoscopic description and patients treatment were searched.

Results: Fifteen biopsy contained iron, but only three were iron pill specific attested by the presence of brawn cristalline material stained by Perl's Prussian blue. Each of those patients had taken iron pills. The endoscopic examination was normal in one case. It showed fundic diffuse erosion in one other case. The last case concerned a 75 year old man who had been treated with oral iron for 17 days before the endoscopic examination. This exam was practiced because of microcytic-anemia. It showed oesophageal candidosic erosion and fundic ulcer with black crater. In this case a pharmacovigilance report was made. Oral iron therapy was not discontinued. Hemoglobin level remained stable with a proton pomp inhibitor therapy.

Discussion: Our study shows that iron taken at therapeutic doses can cause gastric erosion or ulcer. The literature confirm this adverse event. In the literature cases occur in elderly (mean age : 71.5 years) with polymedication. Very few cases were included in our study probably because sparsely reported by pathologists.

Conclusion: Physicians should be aware of this potential adverse reaction when prescribing iron, especially in old patient with multiple medication. Pathologists should alert clinicians of this side effect to adapt therapeutic. Gastric erosion or ulcer should be mentioned as an iron-induced adverse reaction in every SPC.

References

1. Laine LA, Bentley E, Chandrasoma P. Effet of oral iron therapy on the upper gastrointestinal tract: a prospective Evaluation. Dig Dis Sci 1988; 33: 172-7

2. Kaye P, Abdulla K, Wood J, et al. Iron-induced mucosal pathology of the upper gastrointestinal tract: a common finding in patients on oral iron therapy. Histopathology 2008; 53: 311-7

3. Haig A, Driman DK. Iron-induced mucosal injury to the upper gatrointestinal tract. Histopathology 2006; 46: 808-12

4. Abraham SC, Yardley JH, Wu TT. Erosive injury to the upper gastrointestinal tract in patients receiving iron medication: an underrrecognized entity. Am J Surg Pathol 1999; 23: 1241-7

220. Withdrawal Symptoms Following the Onset of a Naltrexone Treatment for Ethanol Dependence During Opioid Addiction Substitution

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Introduction: Naltrexone (a synthetic opioid antagonist) is used to treat alcohol dependence. Buprenorphine is similarly used to treat opioid dependence. These two addictions can be encountered simultaneously, which can lead to the association of various weaning drugs that may induce potentially harmful interactions. In the case reported herein, naltrexone was added to an unknown treatment with buprenorphine ; as a result, withdrawal symptoms occurred.

Case: A 38 year-old man, who was dependent on opioids, was being treated by a general practitioner with buprenorphine (8 mg per day). His condition had stabilized.

Seven months after starting buprenorphine an ethanol dependence treatment was initiated. The patient was therefore referred to an alcohol rehabilitation centre where a clinician, unaware of the previous and current treatment with buprenorphine, prescribed naltrexone 50 mg per day. About four hours after the first administration of naltrexone, the patient displayed the same symptoms he had previously experienced when inadvertently reducing or stopping drug consumption. He was therefore taken to a hospital emergency unit where he was treated with clorazepate.

After having left the hospital, he robbed a gardening tool in a supermarket.

Discussion: Buprenorphine is a partial opioid agonist with both agonist and antagonist properties which binds to opioid receptors and is associated with a low risk of overdose and abuse.

Naltrexone is a long-acting synthetic opioid receptor antagonist. While the precise mechanism of action for naltrexone effect is unknown, reports from successfully treated patients suggest that it blocks the opioid receptors involved in the alcohol addictive effects.

Several similar cases have been reported in the French pharmacovigilance national data base. The interaction between naltrexone and buprenorphine is widely established and probably the consequence of a competition due to an affinity for the same opioid receptors. However this could be misleading as these two drugs are given as treatment in very different situations. So when prescribing one of these drugs to alleviate craving, the prescriber has to enquire whether a previous other weaning drug is still being given to treat a different dependence. Furthermore, in our case, the benzodiazepine administered to alleviate the opioid withdrawal symptoms induced an episode of anterograde amnesia leading to an abnormal behaviour.

Conclusion: Treatment of alcohol addiction with naltrexone is not always associated by prescribers with opioid receptor antagonism. As a dependence with various other drugs is commonly associated, one always has to enquire about the treatments already given to the patients.

221. The Yellow Card Scheme: Experience of Patient Reporting of Adverse Drug Reaction Since Nationwide Launch

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Background: Until 2005 only healthcare professionals were asked to contribute to the UK spontaneous adverse drug reaction (ADR) reporting scheme, the Yellow Card Scheme (YCS). Following an independent review of access to the scheme[1] direct patient reporting of suspected ADRs was introduced in January 2005. Patients were encouraged to report suspected ADRs they or someone they care for experienced; a child, partner or family member. As a result of a positive evaluation of the pilot,[2] UK patient reporting was formally established in February 2008. Simultaneously the MHRA launched a six-week campaign encouraging community pharmacists to mention the YCS when talking to patients about their medicines. All UK pharmacies were sent an information pack containing patient Yellow Cards, information leaflets and a poster. Patient Yellow Cards were also distributed to GP surgeries, pharmacies, hospitals, National Health Service Primary Care Trusts and various other patient organisations throughout the UK. The Yellow Card reporting website which had been redeveloped was also re-launched.

Method: Patient Yellow Card data from received in 2008 were compared to 2007, in terms of reporting method, reporter type and region and patient demographics. Details of the ADRs reported were analysed to show most commonly reported drugs, vaccines and reactions, and to compare proportions of those considered serious.

Results: In 2008, 2482 patient Yellow Cards were received, an increase of 50% from 2007. Numbers of Yellow Cards received each month showed a significant rise during the promotional campaign, but this increase was not sustained by the year end. Proportions of reports which were serious or had fatal outcomes were similar between years. Although electronic reports were increased to 34% from 1% in 2007, proportions of total reports received from patients, parents and carers were similar. Demographics of patients experiencing the ADRs were similar with approximately 5% for children, and 60% for females. For both years most reports were for established medicines of which simvastatin was the most commonly reported.

Conclusion: Patients want to contribute to the YCS and increased numbers of Yellow Cards received coinciding with the promotional campaign and electronic Yellow Card launch suggests these efforts had a positive impact. The sources, type and content of reports received are largely similar for both years despite the increased volumes. Efforts must continue to promote reporting to the YCS to members of the public and trends and the impact of patient reporting must be kept under close review.

References

1. Report of an independent review of access to the Yellow Card scheme. The Stationary Office. 2004

2. Ekins-Daukes S. The Yellow Card Scheme: evaluation of patient reporting of suspected adverse drug reactions. Pharmacoepidemiology & Drug Safety 2006; 15: 105

222. Signal Detection at the MHRA

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Background: The identification of possible new Adverse Drug Reactions (ADRs) or a change in frequency or characteristics of an ADR from spontaneous reports is known as signal detection. Automated signal detection tools are frequently used to enable fast and efficient identification of signals of potential interest and further assessment is required to establish whether event(s) are causally related to the drug. The MHRA reviews all drug-reaction combinations received for medicines that are new to the market (black triangle ▼drugs), while quantitative methods are used to identify drug-reaction combinations of interest in established medicines. The Bayesian Multi-item Gamma Poisson Shrinker method of disproportionality has been used since May 2006, with a signal selection threshold of at least 3 reports of the drug-ADR combination with 1 report received in the previous week, Empirical Bayes Geometric Mean (EBGM)≥2.5 and EB05≥ 1.8. Additionally, all fatal, child, parent-child, drug interactions and alert terms (internal list of serious ADRs potentially due to medication) are highlighted.

Cases highlighted for review are assessed by scientific or medically qualified members of the team who determine whether ADRs are adequately listed in the Summary of Product Characteristics and Patient Information Leaflets, and if not will assess the event for causality and confounding factors. Where the signal selection threshold is met or there are underlying concerns, the ADR is discussed at a signal detection meeting attended by assessors and medics. At this stage a statistical tool called Impact Analysis[1] may be used to aid the meetings' decision as to whether further evaluation is required or if more evidence is needed. Where the meeting agrees that further evaluation of signals are required, Signal Assessment Case Folders (SACFs) are created, where all signal details and correspondence are recorded.

Results: Each week, all SACFs created in the previous week are reviewed in the Signal Management Review Meeting, comprising unit and group managers from across the division, and assessment expertise from the rest of the division. Timelines within which regulatory action is required are decided with the aid of another mathematical tool known as RPPS (Regulatory Pharmacovigilance Prioritisation System). Advice from various Expert Advisory Groups/Committee on Human Medicines or Europe is sought if necessary. In 2008, 162 SACFs were opened and investigated.

Conclusion: This process enables the MHRA to identify and prioritise potential safely issues effectively, ensuring expert advice is sought at each step of the process.

Reference

1. Waller P, Heeley E, Moseley J. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data. Drug Safety 2005; 28 (10): 843-50

223. Trends in Spontaneous Adverse Drug Reactions Reported to the UK Medicines and Healthcare Products Regulatory Agency 2007 to 2008

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Introduction: The Yellow Card Scheme is one of the most recognized and emulated spontaneous adverse drug reaction (ADR) reporting

schemes worldwide. Spontaneous reporting levels are known to fluctuate over time due to media influence and publicity, and the need to strengthen ADR reporting in the UK was highlighted in an Independent Review on Access to the Yellow Card Scheme.[1] Subsequently, the MHRA developed a strategic approach to strengthen the Scheme – the Yellow Card Strategy. Part of this strategy; analysis of trends in ADR reporting, is a useful method for illustrating the type of ADR data collected by the Scheme. In addition, in February 2008, the MHRA launched an enhanced version of the electronic Yellow Card, to facilitate easier ADR reporting for patients and healthcare professionals.

Aim: To identify areas of potential interest on which to focus the Yellow Card strategy to strengthen spontaneous ADR reporting in the UK over the next year.

Methods: We performed an in depth analysis of spontaneous ADR reports received by the MHRA for the period from January 2007 to December 2008. All drugs were analysed by active substance using the MHRA's drug dictionary; suspected ADRs were classified according to the Medical Dictionary for Regulatory affairs (MedDRA).

Results: In 2008, there was a 17% increase in the overall number of ADR reports received compared to 2007, with a 66% increase in electronic ADR reporting. Just 40 (3.1%) of the 1300 suspected drugs reported on in 2008 accounted for approximately 50% of all reports received. In 2008, the number of Yellow Card reports received from patients increased substantially (50%); the largest proportions of reports received from healthcare professionals were from GPs and nurses (29.0%, 16.8% respectively); however the number of reports from GPs decreased compared to 2007 (7.2% decrease).

Conclusions: The increases in electronic ADR reporting and patient reporting indicate the importance of both regular targeted promotional activities to raise awareness of the Yellow Card Scheme, and making ADR reporting as quick, easy and accessible as possible. However, it is also important to provide regular feedback to reporters on the meaning and importance of the ADR data collected. Focusing the MHRA's Strategy on these areas will ensure the continued success of the Yellow Card Scheme.

Reference

1. Report of an independent review of access to the Yellow Card scheme. The Stationary Office. 2004

224. Automatic Signal Generation from Relevant Criteria of Spontaneous Reports of Pharmacovigilance

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Background: All adverse drug reactions (ADRs) based on the spontaneous reporting have to be registered in the French Pharmacovigilance Database (FPD). Four minimum criteria as reporter, patient, drug and ADRs are necessary for initial registering and for generating signals via a Proportional Reporting Ratio.[1,2] Four facultative criteria as onset of treatment, index date of ADR, indication and dosage are relevant and could be used for generating new automated signals in France and in Europe.

Primary aim: Assess and compare, in addition of four minimum criteria, information of four facultative criteria (onset of treatment, index date of ADRs, indication and dosage) on national and regional spontaneous reports registered in the FPD.

Method: All spontaneous reports of ADRs recorded in the FPD from 1st January 2003 to 31st December 2008 were retrospectively analysed. We define two major criteria as onset of treatment and index date of ADRs and two referral criteria as indication and dosage.Information of major and referral criteria relating to regional and national reports were assessed and compared using the Chi2 test.

Results: Onset of treatment and index date of ADRs were respectively informed in 80% for regional reports versus 70% for national reports and in 91% for the two groups. Dosage and indication criteria were respectively informed in 60% of regional reports versus 53% of national reports and in 13% versus 22%.The fineness rate, compared between these two groups by chi2 test, showed the difference was significant for onset of treatment and dosage in favour of regional reports and for indication in favour of non regional reports. The difference between these 2 groups was not significant ($p < 0.01$) for index date of ADRs.

Discussion/Conclusion: This study aimed to assess the percentage of information of four facultative criteria in the FPD. It shows that national and regional spontaneous reports are well enough informed for the two major criteria unlike the two referral criteria. Average information of dosage on spontaneous reports decreased since 2003 and reached its lowest level in 2007-2008. A possible explanation is the transition, on June 2007, to a new FPD.

Average information of indication has increased since 2004 but remains the last informed criteria among the fours. An explanation of this percent increase could be the harmonization of coding through the MedDRA dictionary. Based on spontaneous reports, these 4 facultative but relevant criteria have to be more informed for generating new automatic signals via European database.[3]

References

1. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001 Oct-Nov; 10 (6): 483-6

2. Bousquet C, Sadakhom C, Le Beller C, et al. A review of potential signals generated by an automated method on 3324 pharmacovigilance case reports. Therapie 2006 Jan-Feb; 61 (1): 39-47

3. Thiessard F, Roux E, Miremont-Salamé G, et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986-2001). Drug Saf 2005; 28 (8): 731-40

225. Continuation of Pregnancy After First-Trimester Exposure to Mifepristone: Is There a risk?

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Background: Mifepristone is commonly used for the early termination of intra-uterine pregnancy in combination with a prostaglandin analog (misoprostol or gemeprost) or alone for softening and dilating the cervix prior to mechanical cervical dilatation. In case of failure or protocol interruption, some women may decide to continue their pregnancy. Few data is available on the outcome of such pregnancies.

Aim: To report the prospective follow-up of pregnancies exposed to mifepristone during the first trimester of pregnancy. The main outcome was the rate of congenital malformations.

Methods: Prospective data collected by the 16 participating centers was analyzed when the request related to mifepristone exposure during the first trimester of pregnancy was received before 22 weeks after the last menstrual period (LMP). Data on the maternal history and drug

exposures were collected during the first contact, and pregnancy outcomes were documented at follow-up.
Results: Data were obtained on 108 pregnancies after exclusion of cases with unknown outcome (61 cases) and termination of pregnancies without pathological examination of the fetus (41 cases). The mean age of the patients was 28.8 years and the mean gestational age at the time of request was 14.1 weeks after LMP. Fifty-six patients were exposed to mifepristone only, and 52 were also exposed to misoprostol. There were 96 live births (88.9%), 11 spontaneous abortions (10.2%) and 1 termination of pregnancy after subsequent diagnosis of Down syndrome. After exclusion of this last case, 6 birth defects were observed (4 major and 2 minor defects). The resulting rate of major congenital malformations was 4.2% [95% CI = 1.1%, 10.3%] with 2 cases among 46 live births in the mifepristone-only exposed patients (Claude Bernard Horner syndrome with stridor and possible periconceptional cytomegalovirus infection; major hydrocephaly) and 2 cases among 50 live births in the combined mifepristone-misoprostol exposed patients (Moebius syndrome; one infant with retrognathism, slight cleft palate, trismus, major swallowing disorders, club foot with four toes, incomplete genital development and mild hypoplasia of the cerebellar vermis).
Conclusion: This prospective study suggests that first-trimester exposure to mifepristone is not associated with an increased risk of major malformations. Interestingly, the two cases of major malformation in the mifepristone-misopostol exposed group were consistent with the spectrum of malformations described after exposure to misoprostol alone. Despite limitations due to the sample size, such findings provide reassuring data for risk evaluation in case of pregnancy continuation after mifepristone exposure.

226. Risk Management Plans In The Argentinian Regulatory Administration: Current Situation

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Introduction: In Argentina, an ANMAT regulatory Act of 2000[1] suggests to the MAH to send ADRs to the Pharmacovigilance Department (PhD). In 2008 an update of that Act[2] was released, and included an item referred to Risk Management Plans (RMP). That article recommends to the MAH that all RMPs should be submitted to the PhD for approval.
Aim: To describe the current situation for risk management plans submission in Argentina.Materials and Methods: The PhD receives and assesses the RMPs from the MAHs. A list of all RMPs is created. The rationale of this assessment are the ICH E2E guidelines and the Volume 9A of EMEA. An excel file is developed, and includes Name of the drug, MAH, date of approval, date of submission, consistency with recommendations according to guidelines, improvement requirements and outcome of this requirements.
Results: Since the 2008 update we received 10 RMPs from three different MAHs, one of them from a national MAH. 9 of them were consistent with the recommendations. Only the lenalidomide RMP needed an improvement requirement that was fulfilled in a late submission. That RMP was the only one submitted prior to the launch.
Discussion: Almost all of the received RMPs were from drugs that were previously on the market. Only lenalidomidés was sent before launch as a requirement due to the chemical similarities to thalidomide. Since the 2008 update wasńt mandatory the amount of RMPs submitted was small.
Conclusion: We believed a mandatory act must be implemented in order to achieve the ultimate goal that all drugs must have an RMP before launch. That act will be presented for discusion within this year.

References

1. Disp. ANMAT 2438/00: http://www.anmat.gov.ar/normativa/Normativa/Medicamentos/Disposicion_2438-2000.pdf

2. Recordatorio Disp. ANMAT 2438/00: http://www.anmat.gov.ar/farmaco/Disposicion_2438-Informe_FVG.pdf

227. Patient Reporting of Adverse Drug Reactions in the UK: A Comparison of Potential Signals Generated by Patients and Healthcare Professionals.

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Background: Patient reporting of adverse drug reactions (ADRs) to the Yellow Card Scheme (YCS) commenced in 2005. Here, we present results from an ongoing project evaluating the potential pharmacovigilance impact of patient reporting.
Aim: To compare signals of disproportionate reporting (SDRs) of ADRs generated by patient versus healthcare professional reports.
Methods: Data were analysed for patient and healthcare professional (HCP) reports received in the YCS between Oct 2005 and Sept 2007, excluding pharmaceutical industry reports. Suspect drugs were classified using the Anatomical Therapeutic Chemical (ATC) system. Reaction terms were grouped by 'preferred term' within the Medical Dictionary for Regulatory Affairs (MedDRA). A database of drug-reaction pairs for each reporter group was created. The Proportional Reporting Ratio (PRR) method[1] was used to generate SDRs defined by the following arbitrary thresholds: PRR ≥2, the lower 95% confidence interval of the PRR ≥1 and the number of reports for a particular drug-reaction pair ≥3. The number and type of SDRs generated by each reporter group at the end of the two year period were compared as was the average time taken to generate these SDRs.
Results: Data were received for 5180 patient and 20 949 HCP reports, comprising respectively, 16 566 and 28 775 drug-reaction pairs. Only 4340 (10.6%) of all drug-reaction pairs were common to both reporter groups suggesting that the suspect drugs and/or reaction terms used to code patient reports may be very different from HCP reports. A higher proportion of SDRs* were generated by HCP reports compared to patient reports: 2203 (7.7% of pairs) compared to 784 (4.7% of pairs). Only 167 SDRs were generated by both reporter groups (21.3% of patient SDRs; 7.6% of HCP SDRs). The HCP reports also generated a higher proportion of SDRs than patient reports* for serious ADRs: 1029 (46.7% of HCP SDRs) compared to 214 (27.3% of patient SDRs) and for reactions involving black triangle drugs: 674 (30.6% of HCP SDRs) compared to 90 (11.5% of patient SDRs). The average time (median; IQR) to generate SDRs was similar for both patient and HCP reports (6; 3-11 months). * $p < 0.001$, Chi^2.
Conclusions: Patient reports appear to generate quite different SDRs to that of HCP reports but further work is required to determine whether this is a true difference or whether this is due to the coding terminologies used. Furthermore, qualitative analysis is planned to investigate the clinical importance of the SDRs generated and determine whether patient reports add value to pharmacovigilance and public health.

Reference

1. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001; 10: 483-6

228. Patient Reporting of ADRs in the UK: How Do Patient Reports Affect Potential Signals Generated By Healthcare Professionals?

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Background: Patient reporting to the Yellow Card Scheme (YCS) was launched in 2005. Here, we investigate its potential impact on quantitative signal detection.

Aim: To examine how pooling data from patient and HCP reports affects the generation of signals of disproportionate reporting (SDRs).

Methods: Data were analysed for patient and healthcare professional (HCP) reports received in the YCS between Oct 2005 and Sept 2007, excluding pharmaceutical industry reports. The Anatomical Therapeutic Chemical (ATC) system was used to classify suspect drugs. Reactions were grouped by 'preferred term' within the Medical Dictionary for Regulatory Affairs (MedDRA). A database of drug-reaction pairs for HCP reports was created. The Proportional Reporting Ratio (PRR) method[1] was used to generate SDRs using arbitrary thresholds: PRR ≥2, lower 95% confidence interval of the PRR ≥1 and number of reports for a particular drug-reaction pair ≥3. The number of SDRs generated by HCP reports at the end of the study period and the time taken to detect these SDRs were compared before and after pooling with patient reports.

Results: Data were received for 20 949 HCP and 5180 patient reports (Table I). The pooled data comprised 41 001 drug-reaction pairs. Only 4340 (10.6%) of pairs were present in both patient and HCP reports suggesting significant heterogeneity of pairs in the pooled dataset. Although the majority (1994, 90.5%) of the 2203 SDRs generated by HCP reports remained SDRs in the pooled dataset, 209 (9.5%) became non-SDRs including 58 (27.8%) potentially serious reactions and 71 (34.0%) reactions involving black triangle drugs. Of the remaining 1994 SDRs, the time to detection was unchanged in 1559 (78.2%), faster in 290 (14.5%) and delayed in 145 (7.3%). The pooled data generated an additional 1135 SDRs that had either not been present (287) or had not reached SDR thresholds (848) in the HCP dataset.

Conclusions: Pooling data from patient and HCP reports appears to generate more potential signals overall with a relative minority being 'diluted out' or delayed. However, qualitative evaluation is required to assess the clinical significance of these 'statistical signals' to ensure they are not 'false positives' impacting on the pharmacovigilance workload and, further, to ensure important signals are not missed. It remains unclear as to how the heterogeneity of the pooled data affects the usefulness of quantitative signal detection methods. Additional analysis is planned including the use of shrinkage methods and, also, stratification by reporter type.

Reference

1. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001; 10: 483-6

229. Serious Adverse Effects Associated with the Off-Label Use of Sodium Oxybate

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Introduction: Coffin-Lowry syndrome is a well-defined clinical entity classically associated with disability and delayed development, distinctive facial features, skeletal abnormalities and tapering fingers. About 10% of patients can experience brief episodes of atonic collapse (hyperekplexia) when excited or startled by a loud noise. Several symptomatic treatments, with variable improvements, exist for hyperekplexia. Sodium oxybate is indicated in the treatment of narcolepsy with cataplexy. It has been successfully used, off-label, in a young adult with Coffin-Lowry syndrome.

Aim: To report on the occurrence of respiratory depression and non-epileptic tonic status in an adult with Coffin-Lowry syndrome with off-label use of sodium oxybate.

Methods: A 20 year-old man with Coffin-Lowry syndrome (mutation of RSK2 gene) with hyperekplexia was put on sodium oxybate after several unsuccessful treatments in controlling hyperekplexia. He also suffered from mild sleep apneas syndrome stabilized after surgery procedures. Sodium oxybate was gradually introduced from 2.25 mg twice a day (10 pm and 2 am) on November 2008 under polysomnographic control on the night of the first administration. During this first night no adverse effect appeared. In December 2008, the patient was hospitalised for a new polysomnography in order to increase the dose to 3 mg twice a day. After the first dose of 3 mg (10 pm), apneas and arterial desaturation appeared. Continuous positive airway pressure was then used. After the second dose during the night, an epileptic-like seizure appeared, characterized by generalized tonic contractions and tremor without loss of consciousness. As it seemed to be an epileptic seizure, the patient received clonazepam (1 mg). Respiratory then cardiac arrest occurred soon after resulting in cerebral anoxia, despite rapid resuscitation. The patient recovered with sequelae.

Discussion: Sodium oxybate is also known as gamma-hydroxybutyrate. It is a $GABA_B$ receptor agonist but the exact mechanism responsible for its effects on narcolepsy with cataplexy is unknown. In this patient, the use of sodium oxybate had no therapeutic effect on atonic collapse.

Sodium oxybate can be responsible for apnea, respiratory depression, abnormal muscle movements, muscle cramps and tremor. The patient did not take other drugs. Electroencephalography performed during the night excluded any epileptic activity.

Conclusion: According to the Naranjo scale, the increased dose of sodium oxybate was probably responsible for aggravation of apneas and prolonged non-epileptic tonic status. In our experience, sodium oxybate had no therapeutic effect on stimulus induced collapse, but was responsible of serious adverse effects, in a patient with a genetically proved Coffin-Lowry syndrome.

230. Knowledge, Attitude and Practice of Nurses in Lagos University Teaching Hospital towards Self Medication

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Background: Self medication has been documented to be one of the major causes of adverse drug reactions and the practice of self medication is known to be alarming in developing countries.[1-4]

Aim: This study intends to assess the knowledge, attitude and practice of nurses in Lagos University Teaching Hospital towards self medication as they form an important group of Health workers that ought to counsel people on the implication of self medication.

Methodology: The study was carried out using a descriptive cross sectional method with a well structured questionnaire to assess the knowledge, attitude and practice of 150 nurses towards self medication.

Results: The results showed that 6 (4%) of the respondents were males and 144 (96%) were females. Most of the respondents' age ranged from

31–40 (32.7%). Though self medication was practiced by 81.0% of the respondents, majority of them (79.0%) think self medication results in adverse drug effects. 93.3% of the respondents agreed that medical doctors should prescribe drugs while 16.7% think the nurses could also prescribe. Analgesic and antipyretic 118 (79.7%) were the most common drugs used for self medication. Some of the respondents found self medication to be time saving (30.4%), economical (36.5%) and allowed quick relief of common illnesses. Thus, 41.3% of the respondents use old prescriptions and 50% think they could take care of themselves.

Conclusion: These findings have shown that self medication is practiced among the health personnel (nurses) despite their knowledge. Therefore, there may be need for urgent and massive awareness campaign against self medication so as to reduce the occurrence of adverse drug reaction.

References

1. Calva J, Bojalil R. Antibiotic use in a periurban community in Mexico: a household and drugstore survey. Soc Sci Med 1996; 48 (8): 1121-8

2. Geissler PW, Nokes K, Prince RJ, Achieng RO, et al. Children and medicines: self-treatment of common illness among Luo school children in Western Kenya. Soc Sci Med 2000; 50: 1771-83

3. Habeeb GE, Gear hart JG. Common patient symptoms: Patterns of self treatment and prevention. J Miss State Med Assoc 1993; 34 (6): 179-81

4. Scalfer J, Slamet LS, de Visscher G. Appropriateness of self-medication: method development and testing in urban Indonesian. J Clin Pharm Ther 1997; 22 (4): 261-72

231. Study of Adverse Drug Reactions in Hospitalized Patients in Angers University College Hospital

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Introduction: Nowadays, iatrogenic pathology remains a non negligible reason for hospitalization or extension of hospitalization and should be an important health concern.

Aim: Recording and analysing adverse drug reactions (ADRs) as causes of hospitalization or occurring during hospitalization in a department of internal medicine and geriatrics.

Method: The study was performed from December 2008 until May 2009 in two medical units of the internal medicine department. Demographic data, full treatment at admission, reason and length of hospitalization have been recorded for every hospitalized patient. In case of serious or medically significant ADRs, a pharmacovigilance file has been set up and recorded in the national pharmacovigilance database. Data have been analysed by means of EXCEL software.

Results: Four hundred and seven patients (average age 74 years) have been enrolled in the study (sex ratio = 1). The average number of drugs taken at admission was 6 (range 0 to 15). Twenty eight ADRs have been observed in 22 patients. In 19 cases, ADRs were the reason for hospitalization (incidence 4.7% IC 95% [2.8-7.3]), in 7 cases, the ADRs occurred during the hospitalization (incidence 1.7% IC95% [0.7-3.5]) and in 2 cases, the ADRs were already observed at the time of admission but were not the reason for hospitalization. The average age was not significantly different between patients presenting ADRs and the other hospitalized patients in the department.

In 20 cases, the ADRs could be explained by the pharmacological properties of the treatment and, in the majority of cases, ADRs were mentioned on the SPC of the incriminated drugs. The most frequent ADRs were neurological (7 cases) or ionic imbalance such as hyponatremia or hypokalemia (5 cases). Three cases of hematoma following antithrombotic treatment have been recorded.

Discussion: The incidence of ADRs responsible for hospitalization is comparable to that reported in the EMIR study for included patients with the same age. In most cases, the observed ADRs are well-known and expected, if we consider the pharmacological properties of the treatment. An analysis of the occurrence of these ADRs is currently realized in order to determine if they can be avoided.

Conclusion: This study confirms at the local level the importance of the ADRs as a reason for hospitalization of elderly patients and the necessity of higher prevention procedures in order to reduce the risk of iatrogenic complication in this population.

232. Disulfiram (Antabuse)-Ethanol Reaction: Review of Cases from French North-East Poison Centers.

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Introduction: Disulfiram is prescribed since the years 1960 s as a deterrent to ethanol abuse. Disulfiram toxicity and first cases of disulfiram-ethanol reaction (DER) have been published by French toxicologists in 1967.

Aims: As Toxicovigilance Center, we have notified to Reims Pharmacovigilance (PV) Center, a severe Disulfiram ethanol reaction in a 54 years-old women, with blood ethanol level of 1.01 g/L, needing noradrenaline; 4 MP was not prescribed infortunatly. North East French Poison Centers (PC) receive calls for poisoning cases with many xenobiotics. Adverse Drug Effects notifications by Health professionnals to Pharmacovilance Centers are poor. Could PC be a new data source for FV?

Discussion: Disulfiram is well prescribed in France by alcohologists, despite doubts for the benefit and risk for using this drug. To quantify the adverse effects and DER, we asked the French North East Poison Centers (PC) Reims (data base Arsenic), Lille (data base Arsenic-Cigue), Nancy and Strasbourg (data base SICAP). Global datas; 1991-1999 y. for Reims, and up to 2008 y. for the others PC; exhibited 169 expositions-poisonings to disulfiram with 61 DER (37 PSS1, 16 PSS2 and 8 PSS3). None fatality was found. PSS is Poison Severity Score. PSS1 is defined by nausea, vomiting, flush; PSS2: moderate blood hypotension , rush, tachycardia; PSS3: neurologic signs, coma, severe hypotension, abnormalities of ECG. Only few ethanol dosages were known except those from the 8 PSS3 from 0,3 g/L to 5,3 g/L (0.30, 1.01, 1.20, 1.35, 3.0, 3.55, 5.0 et 5.30 g/L). Two PSS2 cases were found: one with a small alcohol amount in a cake, the second was a DER 7 days after stop of treatement. A PSS2 case (Reims) did a rechallenge a few days later and turned in PSS3 case (see table I).

Table I data reporting

Poison Center (data ys)	Cases report	DER	PSS1	PSS2	PSS3
Reims (1991-1999)	9	7	3	1	3
Lille (1991-2008)	127	41	28	8	5
Nancy (2002-2008)	26	9	5	4	0
Strasbourg (2002-2008)	7	4	1	3	0

Few rare PSS3 were registered by PC of North East of France. All of them had no relapse despite life threatening symptoms. We think that disulfiram cases report of poisoning and DER are under-valuated. Yet, in reference to a new law (HSPT 2009), health professionals will have the duty to notify to PC the cases of voluntary or accidental poisoning. All xenobiotics will be examined and evaluated in the next years for the benefit of our word wide long-during best life.

Conclusion: We have the responsibility to warn again the prescribers for disulfiram toxicity and DER which have to be notified to PC and also to PV.

233. Depressive Episodes Reported during a Modified Prescription Event Monitoring Study for Rimonabant

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Introduction: Rimonabant was launched in the UK in June 2006. At the time of approval, psychiatric side effects, particularly depression, were identified as the main safety concerns. In July 2007, contra-indication in patients with major depression or those being treated with antidepressants was recommended by the European Medicines Agency. In October 2008, the marketing authorisation was suspended because the available data indicated that in clinical practice the effectiveness is more limited than was expected on the basis of clinical trials and the psychiatric side effects could not be addressed by further risk minimisation.

Objective: To compare the number of major and minor depressive episodes reported in the 6 months before starting to those in the 6 months after starting treatment with rimonabant.

Methodology: A post-marketing surveillance study was conducted using the observational cohort technique of Modified Prescription Event Monitoring. Patients were identified from dispensed prescriptions issued by primary care physicians June 2006–October 2008. Demographic and event data were requested 6+ months after date of 1st prescription for each patient. Data collected included whether patients had major or minor depressive episodes in the 6 months before starting and in the 6 months after starting treatment with rimonabant. Risk ratios were calculated comparing before and after events using a matched analysis (no adjustment for confounders is necessary as patients are their own controls).

Results: The cohort comprised 10011 patients. Numbers of reports (for all patients) 6 months before and 6 months after starting rimonabant were: major depressive episodes (n = 147 & n = 168; RR 1.1, 95% CI:0.9, 1.4) and minor depressive episodes (n = 825 & n = 829; RR 1.0, 95% CI:0.9, 1.1). For patients with a previous history of psychiatric illness (n = 1132), the numbers of reports 6 months before and 6 months after starting rimonabant were: major depressive episodes (n = 91 & n = 73; RR 0.80, 95% CI:0.62, 1.03), minor depressive episodes (n = 367 & n = 220; RR 0.60, 95% CI:0.53, 0.68). For patients without a previous history of psychiatric illness (n = 8879), the numbers were: major depressive episodes (n = 56 & n = 95; RR 1.7, 95% CI:1.2, 2.3), minor depressive episodes (n = 458 & n = 609; RR 1.3, 95% CI:1.2-1.5).

Conclusion: When considering all patients in the cohort, there was no significant difference in the number of depressions in the 6 months before and 6 after. However, in patients without a previous history of psychiatric illness, there were more reports of depressive episodes in the 6 months after starting than in the 6 months before starting rimonabant.

234. Characteristics of Patients Prescribed Rimonabant in England: Data from a Modified Prescription Event Monitoring Study

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Introduction: Rimonabant, launched in the UK in June 2006, was licensed as an adjunct to diet and exercise for the treatment of obese (BMI ≥30 Kg/m^2) and overweight patients (BMI > 27 Kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia. In October 2008, the marketing authorisation was suspended because the available data indicated that in clinical practice the effectiveness is more limited than was expected on the basis of clinical trials and the psychiatric side effects could not be addressed by further risk minimisation. At the time of marketing, the efficacy and safety of rimonabant had not been established in patients <18 and over 75 years. Rimonabant was also contraindicated in patients who had a previous history of psychiatric illness.

Objectives: To describe the characteristics of patients prescribed rimonabant in primary care in England between June 2006 and October 2008.

Methodology: A post-marketing surveillance study was conducted using the observational cohort technique of Modified Prescription Event Monitoring. Patient characteristics, including age, sex, BMI, previous use of anti-obesity medications, smoking status, previous history of psychiatric illness, type 2 diabetes and dyslipidaemia and indication for prescribing, were requested 6+ months after the date of 1st prescription for each patient. Data were summarised using descriptive statistics.

Results: The cohort comprised 10011 patients (median age 51 yrs; range: 15-90); 67% female (6743/10009). There were 11 patients aged <18 yrs (0.1% of cohort), all female; and 142 aged >75 yrs (1.4% of cohort), 68% of whom were female. Median BMI 38.7 (range: 20.8-116); 67% of patients (6306/9466) had previously used anti-obesity medications; 15% were current smokers (1334/9138); 41% had previous history of type 2 diabetes (3922/9638); 40% had previous history of dyslipidaemia (3603/9025) and 13% had previous history of psychiatric illness (1132/8687). Off-label indications included type 2 diabetes mellitus (n = 30) and smoking cessation (n = 3).

Conclusion: The majority of patients were prescribed rimonabant within the terms of the license. Results of this study should be taken into account together with other clinical and pharmacoepidemiological studies in assessing the risk-benefit of this product.

235. Pharmacoepidemiology, Drug Safety and Drug Abuse Evaluation in France: Experience of the Networks of Pharmacovigilance and Addictovigilance Centres and Pharmacoepidemiology

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Background: Pharmacoepidemiology was first mentioned in the early 1980s, as the application of epidemiological methods to the study of

the effects of drugs in the society. Pharmacoepidemiology aims to complete the evaluation made before approval, by providing reliable information concerning effectiveness, safety and utilization of medicines in realistic conditions. The relationship between drug safety evaluation (pharmacovigilance and addictovigilance) and pharmacoepidemiology is ambiguous: for some, pharmacoepidemiology encompasses both pharmacovigilance (PV) and epidemiological studies. For others, PV includes all contributive methods, including spontaneous reporting and epidemiological methods. In France, and more generally in Europe, the second definition appears to be more appropriate.

Aim: The aim of this presentation is to summarize the different pharmacoepidemiological approaches developed by the French networks of Regional Pharmacovigilance Centers (CRPV) and of Drug Abuse Evaluation Centers (CEIP) during the last years.

Results: The first experience was performed in 1997 by the French network of CRPV to investigate the frequency of drug-related hospitalizations and their preventability,[1] and repeated in 2007. Several methods have also been implemented before to better investigate some drug risks, for example by using the French pharmacovigilance database, applying the case-non case methodology or investigating the potential of signal generation.[2] Case-control or cohort study's designs have also been applied to improve knowledge about drug safety. In the context of drug abuse evaluation, the French network of CEIP had created original tools such as OPPIDUM or OSIAP to better appreciate the magnitude of medication abuse.[3-5] During the recent years, even if the availability of database on drug exposure remains scarce, several studies were performed: record-linkage databases allowing investigation between drug exposure and cancer,[6] use of health insurance system databases to investigate appropriate use of drugs, drug diversion,[5] or drug utilization, use of hospital medical databases or data coming from epidemiological studies.

Conclusion: A recent query about research publications in the field of pharmacoepidemiology coming from these 2 networks underline that the pharmacoepidemiological approach is now clearly widely used in France. More recently, a new group of experts in the field of pharmacoepidemiology, epidemiology and public health has been created at the Afssaps in order to give a pharmacoepidemiological insight to future actions concerning the rational use of drugs and their safety. This underlines the needs for the development of specific pharmacoepidemiological competencies and networking in France that led us to launch the French Network for Pharmacoepidemiology.

References

1. Pouyanne P, Haramburu F, Imbs JL, et al. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres BMJ 2000 Apr 15; 320 (7241): 1036

2. Ahmed I, Haramburu F, Fourrier-Réglat A, et al. Bayesian pharmacovigilance signal detection methods revisited in a multiple comparison setting. Stat Med 2009 Jun 15; 28 (13): 1774-92

3. Barrau K, Thirion X, Micallef J, et al. Comparison of methadone and high dosage buprenorphine users in French care centres. Addiction 2001 Oct; 96 (10): 1433-41

4. Boeuf O, Lapeyre-Mestre M, French Network of Centers for Evaluation and Information Pharmacodependence (CEIP). Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. Drug Saf 2007; 30 (3): 265-76

5. Pradel V, Frauger E, Thirion X, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. Pharmacoepidemiology and Drug safety 2009 Jan; 18 (1): 36-43

6. Chaplain G, Milan C, Sgro C, et al. Increased risk of acute leukemia after adjuvant chemotherapy for breast cancer: a population-based study. J Clin Oncol 2000 Aug; 18 (15): 2836-42

236. Aseptic Meningitis Associated with Sulphasalazine

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Introduction: Aseptic meningitis is an illness characterized by serious inflammation of the linings of the brain. It is usually induced by septic, malignant or autoimmune causes. Iatrogenic aseptic meningitis has been described with many drugs: non-steroid anti inflammatory drugs, rarely with leflunomide, methotrexate, infliximab, or salazopyrine. We report a case of aseptic meningitis associated with sulphasalazine (Salazopirine®) with positive rechallenge.

Case report: A 34-old-woman, with no medical history, was treated on October 2002 by sulphasalazine at the starting dose of 2 g daily. Two weeks later, she suffered from fever, violent headache, vomiting and neck stiffness. Hospitalization was decided and clinical examination found a meningeal syndrome with high grade fever at 41°C. Lumbar puncture found clear fluid with 102 cells/mm^3 with lymphocytes predominance (normal < 5 leucocytes/mm^3), protein estimated at 0.77 g/L (normal 0.28 and 0.52), glucose estimated at 0.55 g/L (normal glycoraquia = 60% of glucose plasma level and plasma glucose level was 1.87 g/L). Direct bacteriological examination and cultures of cerebrospinal fluid (CSF) were negative. An acetylation test with 100 mg of isoniazid, found slow acetylator phenotype. The rest of biological investigations were normal. On the first day of hospitalization, sulphasalazine was discontinuated. Rapid spontaneous improvement was noted and symptoms diappeared within 2 days. On the third dayof admission, sulphasalazine was restarted at the same initial dose. Few hours later; fever(41°C) and headache reappeared inciting to withdrawal immediately sulphasalazine with rapid resolution within 24 hours. The score of imputation was likly (I_3).

Discussion: Diagnosis of aseptic meningitis was retained in front of meningeal syndrome, cerebrospinal fluid results and negative investigations.

Sulphasalazine responsibility was retained in front of: a compatible delay of 2 weeks, rapid resolution after drug withdrawal, absence of infectious cause and essentially positive rechallenge.

In literature, sulphasalazine-induced meningitis is exceptional. After Pub med and Science direct internet search using ''sulphasalazine'' and ''aseptic meningitis'' as key words, six cases of aseptic meningitis associated with sulphasalazine were found. The indication was arthritis in all cases. The dose varied between 1000 mg and 1500 mg daily. The delay varied between 2 weeks and few months. Complete resolution was obtained within 48 hours to 2 weeks after sulphasalazine withdrawal. In three cases, reintroduction of sulphasalazine was not attempted. In one case, positive rechallenge was noted few hours after sulphasalazine reintroduction.

Conclusion: Two proposed mechanisms have been suggested for drug induced aseptic meningitis: a delayed hypersensitivity type reaction and direct meningeal irritation due to cytokine release.

237. Descriptive Study of Pregnant Women Exposed to Oestroprogestogenic Hormones

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Introduction: Since the beginning of teratovigilance activity in the Tunisian National Centre of Pharmacovigilance in 1995, notifications number doesn't stop increasing every year. Therefore, it is interesting to computerize available data. The aim of this study is to describe the main characteristics of pregnant women that had been

Table I. Distribution according to the exposition period to drugs[a]

Exposition period	Number	Percentage
First trimester		
Before conception	5	6.1
Periimplantation period	14	17.2
Organogenesis period	49	60.5
Second trimester	12	14.8
Not specified	1	1.2
Total	81*	100

a Some pregnant women took oestroprogestogenic hormones during more than one period.

exposed to oestroprogestogenic drugs and to establish a database for these cases.

Methods: We performed a retrospective study implying all the notifications of pregnant women having taken drugs during pregnancy notified to the Tunisian National Centre of Pharmacovigilance during the year 2006. We chose oestroprogestogenic hormones as example to test database implementation. Data was collected from the medical file and transcribed in fact sheet including the following parameters:

- Parturient: age, identity, date of last menstrual period, parity, antecedents (fetal malformations, fetal or infant death, spontaneous or voluntary abortion), profession, address, telephone number, conjoint identity and profession.
- Medication: number of drugs, international common denomination of drugs and the period of exposition.
- Notification origin: hospital, physician identity, speciality, grade and address.
- Notification: number and date.

Data was input by Access program to form database of pregnant women exposed to oestroprogestogenic hormones for the year 2006.

Results: There were 63 women exposed to oestroprogestogenic contraceptives. The median age of the pregnant women was 31 years (min/max 21/47 years). Period of exposition to drugs is presented in table I. The public sector was the origin of 52.3% of notifications. The gynecologue physicians participate in 96.8% of notifications. In 18 cases (28.5%), oestroprogestogenic hormones were used on monotherapy. In 4 cases (6.3%), parturents used association of 2 different, oestroprogestogenic hormones. In 41 cases (65%), they were associated to others drugs. Different pharmaceutical classes of oestroprogestogenic hormones were used. The most common drug used was levonorgestrel. It was followed by cyproterone, ethylestradiol and normogestrel at the same rate.

We create data design model using analyzes data-processing method (MERISE) provided by Microsoft access. Thus, all data described above was input by Access program

Conclusion: Access teratovigilance database ensure easy data access. It is a necessary method to follow pregnancy issue and control teratogenic risk of pharmaceutical class in our country.

238. Neurological Disorders due to Cefepime: Three Cases

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Introduction: Neurological disorders are well-known adverse side effects of cephalosporin antibiotic treatments. Only few cases are described with cefepime. These side effects are described more often in patients with kidney failure treated by high dosages. We report 3 cases of neurological disorders in which cefepime overdosage was confirmed by blood assays.

Cases report: Three cases of cefepime neurotoxicity have been notified to the Regional Center of Pharmacovigilance of Amiens. Those cases are reported in table I.

Discussion: The occurrence of central nervous system side-effects due to cefepime is around 3%.[1] Cefepime is mostly eliminated by kidneys (85%).[1] Most of the cases occur in patients with renal failure treated with high dosages but some cases have also been reported with dosages adapted to renal function.The three cases we report here concern patients with acute or chronic renal disease treated with dosages too high and/or not appropriate to the renal function. In those patients, half life of cefepime is longer due to a drug accumulation, an increase in the permeability of blood-brain barrier and a decrease in the protein bounding.[2] Cefepime half-life is 2 hours but it increases proportionally to the decrease of the renal function.[3] Concentration of cefepime in other liquids may be of clinical importance. In our 1st and 3rd cases, the ratio of blood/CSF concentrations was increased (close to 2 in the last case), as it is usually of 10.[4] Case C woman had presented several acute kidney failure bouts with previous aminosid treatments and should have been viewed as a high-risk patient.

Conclusion: Risk of cefepime neurological adverse side effects requires to adjust dosage to the renal function. But this may not be sufficient enough so checking of blood (and CSF) concentrations of cefepime, especially in patients with risk factors, seems to be necessary to prevent this effects.

References

1. Sonck J, Laureys G, Verbeelen D. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. Nephrol Dial Transplant 2008; 23: 966-70

2. Abanades S, Noolla J, Rodriguez-Campello A, et al. Reversible coma secondary to cefepime neurotoxicity. The Annals of Pharmacotherapy 2004; 38: 606-8

Table I. Report of our three cases of cefepime neurotoxicity

Patient description	Dosage of cefepime	Clinical manifestations of overdosage	Cefepime blood levels (hours after last administration)
77, female, chronic kidney disease	3 g/day for 54 hours	Clonic movements and confusion	31h: 41 μg/mL 79h: 4 μg/mL (blood) and 14 μg/mL (CSF)
82, male, oligo-anuric acute kidney disease	2 g/d for 3 days then 1 g/d for 1 day	Coma	8h: 48.1 μg/ml After 4 dialysis: 1.1 μg/mL
71, female, previous episodes of renal failure with antibiotherapy	4 g ×2/d for 3 weeks	Alteration of consciousness	20h: 160 μg/mL 32h: 29 μg/mL (blood) and 13 μg/mL (CSF) 92h: 7 μg/mL CSF: 32h:

3. Barbhaiya RH, Knupp CA, Forgue ST, et al. Pharmacokinetics of cefepime in subjects with renal insufficiency. Clin Pharmacol Ther 1990; 48 (3): 268-76

4. Chatellier D, Jourdain M, Mangalaboyi J, et al. Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. Intensive Care Med 2002; 28: 214-7

239. Characteristics of Patients Prescribed Atomoxetine in England: Data from a First Interim Modified Prescription Event Monitoring Study

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Introduction: Atomoxetine was launched in the UK in July 2004 for the treatment of Attention Deficit Hyperactivity disorder (ADHD) in children of six years and older and in adolescents as part of a comprehensive treatment programme.[1] In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood.[1]

Objectives: To describe the characteristics of patients prescribed atomoxetine in primary care in England from June 2004 onwards.

Methodology: A post-marketing surveillance study was conducted using the observational cohort technique of Modified Prescription Event Monitoring. Demographic, drug utilisation and clinical event data were collected at least 12 months after the date of the first prescription. Data were summarised using descriptive statistics.

Results: The cohort comprised 2544 patients [median age 12 years] (Interquartile range [IQR] 9–14; range 2–90 years; 85.7% [n = 2181] male). Although atomoxetine is licensed for use in children aged 6 and over, there were 30 children (1.2%) aged 5 years and less within the cohort (of note; there is no lower age limit for the diagnosis of ADHD in DSM-IV). The majority of patients were aged between 10–19 years (1698, 66.7%). There were 7 patients (0.3%) prescribed atomoxetine over 50 years, ranging from 51–90 years. The majority of patients had their treatment initiated by a hospital specialist (2459, 96.7%). Within the less than 70 kg weight range, 21 patients (0.8%) exceeded the maximum daily dose of 1.8 mg/kg/day, aged 7–18 years. Five of these stopped treatment; one patient experienced ''persistent headaches'', and one patient reported ''weight loss and abdominal pain, with daytime drowsiness''. In the over 70 kg range, 3 patients (0.1%) exceeded the recommended dose of 150 mg per day; 2 of the 3 stopped treatment, one due to ''nausea and erectile dysfunction''. GPs recorded 928 reasons for stopping (RFS) atomoxetine in 733 (28.8%) patients; the most common clinical RFS were behaviour abnormal (49, 6.7%); nausea, (21, 2.9%); vomiting (8, 1.1%); and hyperactivity (23, 3.1%). There were 55 patients who were co-prescribed Ritalin (methylphenidate); no cardiovascular events were reported for this group.

Conclusion: The results of this interim study show off label prescription of atomoxetine, with respect to both age of patient and recommended dosing regimen corresponding to the patients' weight. These results are based on an interim analysis of the data, further information or subsequent analyses may alter these results.

Reference

1. Eli Lilly and Company Limited. summary of product characteristics. 22-10-2008

240. A Study to Examine Events of Suicidal Ideation in Patients Prescribed Atomoxetine in England; Results of an Interim Modified Prescription Event Monitoring Study

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Introduction: Atomoxetine was launched in the UK in July 2004 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children of six years and older and in adolescents as part of a comprehensive treatment programme. Suicide-related behaviour (suicide attempts and suicidal ideation) have been reported in patients treated with atomoxetine. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour.[1]

Objectives: To quantify and examine reports of suicidal ideation and related events during treatment with atomoxetine.

Methodology: A post-marketing surveillance study is being conducted using the observational cohort technique of Modified Prescription Event Monitoring. Information has been obtained on events of suicidal ideation, suicide attempt, overdose, deliberate self harm (DSH), and depression during treatment with atomoxetine, and on whether the patient had a history of these events prior to starting atomoxetine. For this interim analysis event data were stratified according to prior (or no) history of these events.

Results: The cohort comprised 2544 patients [median age 12 years] (Interquartile range [IQR] 9–14; range 2–90 years; 85.7% [n = 2181] male). There were 23 patients in whom suicidal ideation was reported during treatment; 6 had no additional recorded psychiatric history i.e. these patients had no history of suicidal ideation, suicide attempt, overdose, DSH or depression prior to starting therapy (prior history 7, not specified 10); 9 cases of suicidal attempt during treatment, 1 had no additional prior psychiatric history (prior history 3, n/s 5); 8 cases of overdose were reported during treatment (prior history 5, n/s 3); 26 cases of DSH during treatment, 7 had no additional previous history (prior history 12, n/s 7). Finally 89 cases of depression were reported during treatment; 20 patients had no additional prior psychiatric history (prior history 60, n/s 9).

Conclusion: Of the cases of suicidal ideation during treatment with atomoxetine for whom prior psychiatric history was known, 46% had no psychiatric history. For the events of suicide attempt, DSH and depression, there were 25.0%, 36.8% and 25.0% of patients respectively with no prior history. This pattern is not seen for overdose, although prior history was n/s for 3 of the 8 patients. These results confirm the importance of carefully monitoring patients for the emergence/exacerbation of these symptoms, including patients that have no prior psychiatric history.

These results are based on an interim analysis of the data, further information/subsequent analyses may alter these results.

Reference

1. Eli Lilly and Company Limited. summary of product characteristics. 22-10-2008

241. A Study to Examine Cardiac Events in Patients Prescribed Atomoxetine in England: Results of an Interim Modified Prescription Event Monitoring Study

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Introduction: Atomoxetine was launched in the UK in July 2004 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in

children of six years and older and in adolescents as part of a comprehensive treatment programme. The Summary of Product Characteristics (SPC) states that there is the potential for an increased risk of QT interval prolongation when atomoxetine is administered with other QT prolonging drugs, and that many patients taking atomoxetine experience a modest increase in pulse and/or increase in blood pressure. Sudden death has been reported in children and adolescents with structural cardiac abnormalities who were taking atomoxetine at usual doses.

Objectives: To quantify and examine reports of cardiac events during treatment with atomoxetine.

Methodology: A post-marketing surveillance study is being conducted using the observational cohort technique of Modified Prescription Event Monitoring. Information has been obtained on 5 cardiovascular (CVS) events of cardiac arrest, chest pain, arrhythmia, tachycardia, and QT interval during treatment with atomoxetine, and on whether the patient had a history of these events prior to starting. Interim event data were stratified according to prior history of these cardiac events.

Results: The cohort comprised 2544 patients [median age 12 years] (Interquartile range [IQR] 9–14; range 2–90 years; 85.7% [n = 2181] male). There was a cardiac arrest in a patient aged 7. There were no cardiac events prior to starting atomoxetine in this patient (i.e. no reported chest pain, arrhythmia, tachycardia, or QT prolongation prior to starting atomoxetine). There were 14 patients (0.6%) with reported chest pain during treatment; 12 had no history of this event (1 had a prior history, 1 not specified); 7 cases (0.3%) of arrhythmia; 6 had no history of this event (1 n/s); 22 cases (0.9%) of tachycardia; 15 had no history of this event (2 previous histories, 5 n/s). Finally there were 4 cases (0.2%) of QT prolongation, two of whom had no history of this event (1 previous history, 1 n/s). Of the 2 patients who reported QT prolongation during treatment with no past history of this event, one was taking risperidone and concerta XL (methylphenidate) concomitantly.

Conclusion: These results highlight the importance of monitoring patients taking atomoxetine for possible CVS side effects, particularly patients with pre existing CVS conditions and those taking concomitant medications which may affect the QT interval. These results are based on an interim analysis of the data, further information or subsequent analyses may alter these results.

242. Adverse Drug Reactions in an Intensive Care Unit

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Introduction: Adverse drug reaction (ADR)-related hospitalizations have been widely assessed. ADRs occurring during hospitalization, especially in an intensive care unit (ICU), can contribute to patient morbidity and mortality.

Objective: To estimate frequency and severity of adverse drug reactions in a 32-bed medical ICU.

Methods: We conducted a prospective cohort study in an ICU, in a French hospital teaching hospital. All patients admitted in the ICU during a 3-week period (Jun 23–Jul 14, 2008) were included in the study. One of the intensivists, trained in pharmacovigilance, and a pharmacology resident looked for potential ADRs, daily from Monday to Friday. Potential ADR cases were centrally reviewed by an assessment committee, including one pharmacology resident, one intensivist and two clinical pharmacologists.

Results: A total of 93 patients were admitted in the ICU during the study period. They had a mean age of 52.0 years (range: 14–89) and a mean stay duration of 10 days (0–145). The male/female ratio was 1.73; 19 patients died (20%). Eighteen ADRs occurred in 17 patients (18%); these patients had a mean age of 53.8 years (21–89); the mean stay duration in the ICU was 15.6 days (2–61). Insulin-induced hypoglycemia represented one third of all ADRs. One ADR was involved in the patient death. Eight cases were assessed as possible ADRs (44%) and 10 as certain (66%). Sixteen ADRs (89%) were well-known and potentially preventable effects and 2 (11%) were unlabelled.

Conclusions: ADRs were frequent in this ICU: they have complicated the patient's care in a high-risk clinical context. As most of them were preventable by simple measures (dose adjustment, rate of infusion, etc.), a permanent alertness is needed both from intensivists and nurses.

243. Hematological Drug-Induced Effects and PMSI: a French Hospital Database

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Background: The "Programme de Médicalisation des Systèmes d' Information" (PMSI), a French national hospital database, was built to transfer to French authorities data on hospital medical activities. This hospital database has already been used in some epidemiologic studies to identify cancer or adverse drug reaction (ADR) cases.

Objective: To identify hematological drug-induced effects in PMSI database.

Methods: We conducted a cross-sectional study during the last trimester of 2008 in the Bordeaux teaching hospitals, France. All patients discharged during this period and presenting with ICD-10th codes of hematological drug-induced effects and some non-specific codes of hematological diseases were included. ADR cases were identified by ICD-10th codes of hematological drug-induced effects and by crossing between non-specific codes of hematological diseases and codes of ADR or intoxication. Case validation was based on medical records and biological data.

Results: A total of 197 patients were firstly selected with the PMSI database as potential ADR cases; after assessment of these cases, 66 ADRs were identified in 60 patients. They had a mean age of 56.1 years (range: 0.6–87) and a mean stay duration of 10 days. The male/female sex ratio was 2. Hematological drug-induced effects were as follows: 35% pancytopenia, 24% thrombocytopenia, 17% neutropenia, 15% bicytopenia and 9% anemia. Anticancer agents were involved in more than 80% of ADR cases. Pancytopenia induced by anticancer agents resulted in two patients' death.

Conclusion: To use the PMSI database as an indicator for identification of ADR needs to select specific codes and crossing codes of ADR and intoxication.

244. Prospective Cohort Study of Pregnancy Outcome Following First-Trimester Exposure to Propofol

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Background: Propofol is an intravenous anesthetic widely use either for general anesthesia or for sedation. Reproductive studies in animals did

not show any teratogenic potential. To date, no clinical data regarding the safety of propofol during first trimester is available and this is the first series related to the consequences of its use during early pregnancy.
Objective: To identify malformative risk of first trimester propofol use.
Methods: The Paris (France) Teratology Information Service-TIS (CRAT) prospectively collected pregnancy outcomes of women whose health care providers had asked for counselling about teratogenic risks from January 1987 to June 2009. The study group consisted in pregnant women exposed to propofol between gestational week 2 and 15. Control group consisted in pregnant women exposed to antihistamines during the same pregnancy period.
Results: Follow-up data were obtained for 182 exposed pregnant women and 209 controls.
The indications for anesthesia were gastroenterology (mainly coloscopy) in 23.7%, obstetrics-gynecology in 23.7%, otolaryngology (mainly rhinoplasty and teeth extraction) in 19.4% and orthopedics in 14.0%.
Maternal age did not differ significantly between exposed and control groups (29.6 ± 5.5 vs. 30.6 ± 4.8, $p = 0.71$).
One hundred forty seven (80.8%) exposed pregnancies ended with a birth (151 children, 4 sets of twins, one twin is stillborn). There were 11 (6.0%) miscarriages in the study group, ten of them before or at GW 12 and one at GW 20 (SLE diagnosed during pregnancy). Twenty four pregnancies (13.2%) resulted in a termination of pregnancy. After exclusion of chromosomal anomalies (none in propofol group, 2 in control group), there were 5 major malformations in each group. In the propofol group, 2 malformations resulted in elective terminations of pregnancy (1 spina bifida and 1 polymalformative pattern including heart defect and corpus callosum agenesia) and 3 were diagnosed in live children (1 single heart ventricle, 1 unilateral renal cyst, 1 ureteropelvic junction obstruction).
Distribution of pregnancy outcomes did not differ between the 2 groups. Major birth defects were not increased in the propofol group: 3.27% vs. 2.81%, OR = 1.17 (95% CI: 0.33, 4.1).
Conclusion: Based on our findings and on preclinical data, first trimester use of propofol is not expected to carry a significant malformative risk.

245. Ferinject® (Ferric Carboxymaltose): A Review of Adverse Reactions and Anaphylaxis in Switzerland

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Introduction: Ferinject® is a novel iron complex for intravenous application. In the published literature treatment with ferric carboxymaltose was associated with rapid and sustained increases from baseline in haemoglobin levels. Ferric carboxymaltose was considered to be as least as effective as oral ferrous sulphate[1-3] and as safe, with most drug-related adverse events considered to be mild to moderate in severity.[1-4]
Aim: To verify the safety profile of Ferinject® based on the Swiss pharmacovigilance data.
Methods: We have reviewed all spontaneous reports with Ferinject as suspect drug received at the Swiss Pharmacovigilance Centre between April 1st 2008 and June 20th 2009 with emphasis on the kind of adverse drug reaction (ADR), the seriousness and the outcome reported.
Results: Swissmedic has received 157 reports on Ferinject with 414 ADRs. Among these 157 reports, 73 (46%) concern immediate type hypersensitivity reactions (ITR). Among these we registered 7 anaphylactic shocks, 21 ITR grade 3 (with respiratory symptoms), 7 grade 2 (with angioedema or G-I symptoms) and 38 grade 1 (skin reaction). In 68 reports the outcome is stated as recovered and in 5 cases, as unknown. We had no reports with fatal outcomes. The relative reporting ratio of immediate type reactions in our database for Ferinject® is higher that with other iron products for intravenous application.
Conclusions: The international market for intravenous iron preparations has grown significantly in the past years. According to the product information leaflet Ferinject® can be administered in higher dosage (<= 1000 mg) and at a faster rate (15 minutes) than the other products available. Even though published data indicate a good safety profile,[5] the reports received at our centre suggest a considerable risk of anaphylactic/anaphylactoid reactions. Data from a spontaneous reporting system do not allow the calculation of incidence rates and therefore no direct comparison between different products, nevertheless our observations indicate the necessity to monitor the hypersensitivity potential of Ferinject closely.

References

1. Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. Drugs 2009; 69 (6): 739-56
2. Seid MH, Derman RJ, Baker JB, et al. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. Am J Obstet Gynecol 2008 Oct; 199 (4): 435
3. Van Wyck DB, Martens MG, Seid MH, et al. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. Obstet Gynecol 2007 Aug; 110 (2 Pt 1): 267-78
4. Grimmelt AC, Cohen CD, Fehr T, et al. Safety and tolerability of ferric carboxymaltose (FCM) for treatment of iron deficiency in patients with chronic kidney disease and in kidney transplant recipients. Clin Nephrol 2009 Feb; 71 (2): 125-9
5. Galenica, communiqué de presse, 11.11.2007

246. Factors Associated with the Occurrence or with the Aggravation of Anaemia in HIV-Infected Patients: a Nested Case-Control Study

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Introduction and objectives: Recent data suggest that anaemia, even mild, is associated with mortality in HIV patients.[1] The objective of the present study was to investigate factors associated with an occurrence or an aggravation of anaemia in HIV-infected patients, and in particular to study the role of drugs as well as co-infection with the hepatitis C virus (HCV) which is frequent in HIV-infected patients.
Methods: We performed a nested case-control study into a cohort of 190 HIV-infected patients followed from 2002 to 2007. The cases had an occurrence or an aggravation of anaemia during the follow-up and were matched with controls. Patients were classified as ''not exposed'', ''exposed less than 3 months'' and ''exposed more than 3 months''. Statistical analysis was performed by using multiple conditional logistic regression model.
Results: This study included 59 cases and 97 controls. Most of the patients (77%) were not anaemic on the date of their inclusion in the cohort. Among the 59 cases, the great majority (87%) presented with an anaemia during the follow-up, while an aggravation of the

anaemia was observed in the other subjects (13%). The AIDS stage, a weak number of CD4, co-infection with HCV, exposure to zidovudine and exposure of less than 3 months to ritonavir appeared as risk factors of onset or worsening of anaemia. Conversely, the exposure of more than 3 months to atazanavir was associated with a lesser risk of anaemia.
Conclusion: According to the Summary of Product Characteristics (SPC) of ritonavir, a decrease of the rate of haemoglobin is frequently found when this protease inhibitor is used in the doses necessary for its antiretroviral effect. However, this effect is not mentioned for the weaker doses of ritonavir used to boost the associated protease inhibitors. The data of the present study suggest that an exposure lower than 3 months to ritonavir used as a booster is a factor associated with the occurrence or with the aggravation of anaemia. On the contrary, exposure of more than 3 months to atazanavir seems associated with a decrease of this risk. Even if these data require to be confirmed, the observed effect of atazanavir could be explained by the lower dose of ritonavir used in association in comparison with the doses of ritonavir required to boost the other protease inhibitors.

Reference

1. Harris RJ, Sterne JA, Abgrall S, et al., Antiretroviral Therapy Cohort Collaboration. Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. Antiviral Therapy 2008; 13: 959-67

247. Contribution of Therapeutic Monitoring in the Assessment of Toxic Adverse Effects of Methotrexate

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Introduction: Methotrexate (MTX) is a competitive inhibitor of dihydrofolate reductase a key enzyme of nucleic acid biosynthesis. Thus, it can block tumoral cell growth and is widely used as a cytostatic agent. The treatment of Tunisian patients is unusually confronted to a high incidence of systemic toxicity compared with other population, especially the European patients.
Aim: The aim of this study is to correlate the toxicity of methotrexate and the concentration level.
Methods: Between January to May 2009, we have tried 126 courses of high-dose methotrexate therapy, in the treatment of 14 patients with LAL, and osteogenic sarcoma (5 g/m^2 for LAL and between 12 g/m^2 for osteosarcoma).
We measured the plasma level of methotrexate at 24, 48, 72, 96, 120 from the beginning of infusion, using fluorescence polarization immunoassay (FPIA) method. We estimated pharmacokinetic parameters, systemic clearance (CL), area under the curve (AUC), and plasma half-life ($t_{1/2}$) of methotrexate by non parametric method.
Result: Severe toxicity was observed such as oral mucositis, renal failure, and nausea. Infact the concentrations at different time were toxic. The mean plasma levels ±SD were 8.24 µmol/L ±5.102 at 24 h, 1.716 µmol/L ±3.801 at 48 h, 0.652 µmol/L ±1.163 at 72 h, 0.638 µmol/L ±0.821 at 96 h, 0.575 µmol/L ±0.677 at 120 h. The mean AUC ±SD, CL ±SD and $t_{1/2}$ ±SD were respectively 459 ± 203 µmol/lh; 47 ± 28 l/h and 4.28 ± 1.9 l/h. These toxic concentrations affect the elimination of methotrexate that's why the systemic clearance and plasma half life were very low in these patients.
The values of pharmacokinetic parameter were different from litterature. The study of Rask and al.,[1] in 1998 achieved at a pediatric population affected by LAL and treated with the same dose of MTX that our patients recovers values of AUC of 279.02 µmol/L*h and one CL of 81.28 l/. Piard et al., (2007)[2] done at a pediatric population affected by LAL returns values of CL of MTX equal to 2.11 l/h.
Conclusion: These results show that the toxicity of MTX relatively frequent in Tunisian patients is related to particular pharmacokinetic characteristics which tend to leave the longer MTX accumulate in their bodies. For this adaptation of the MTX dose and drug monitoring is essential in all patients treated with this drug.

References

1. Rask C, Albertioni F, Bentzen S, et al. Clinical and pharmacokinetic risk factors for high-dose methotrexate induced toxicity in children with acute lymphoblastic leukemia: a logistic regression analysis. Acta Oncol 1998; 37 (3): 277-84

2. Piard C, Bressolle F, May F, et al. A limited sampling strategy to estimate individual pharmacokinetic parameters of methotrexate in children with acute lymphoblastic leukaemia. Cancer Chemother Pharmacol 2007; 60: 609-20

248. Potentially Inappropriate Medications in the Elderly: Analysis of the Usual Treatment of Patients Residing in the Poitou-Charentes Region

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Introduction: Drug-related adverse effects can have profound medical and safety consequences for older adults and economic impact on the health care system.
Polypharmacy, polypathology and physiologic modifications linked to aging were factors that potentiate iatrogenic events. Their occurrence can be limited by an adapted prescription.
Aim: To evaluate inappropriate medications in the usual treatment of patients residing in Poitou-Charentes.
Methods: We collected the reports of the French Pharmacovigilance database from january 2008 to december 2008 concerning patients aged 75 or over residing in Poitou-Charentes region.
Age, sex, number and names of drugs were noted.
We identified potentially inappropriate medications (IM_S) in every usual treatment from the French consensus panel list published by Laroche et al.[1]
Results: We identified 122 reports. Older patients received on average 7.5 drugs a day, 57% of them were treated by psychotropic drugs, 43% by proton-pump inhibitors and 38% by benzodiazepine and benzodiazepine like drugs.
Forty three percent of elderly people were treated by at least one IM_S and 14% by two IM_S.
The majority of IM_S were sedative and hypnotic drugs (dose of short- or intermediate- half-life benzodiazepines > half the dose given in young subjects) and represented 34% of drugs. Thirty one percent of prescriptions were cerebral vasodilatators drugs, medications with no proven efficacy. Twenty percent were medications with anticholinergic properties and 8% of drugs were centrally acting antihypertensives and antiplatelets drugs.
Conclusion: We showed that the number of prescribed drugs is high and frequently inappropriated. More than 4 patients on 10 could see their prescription optimized according to the criteria of the French list of potential IM_S, i.e. to delete drugs the efficiency of which is not clearly demonstrated or to use better tolerated alternatives.

Reference

1. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly : a French consensus panel list. Eur J Clin Pharmacol 2007; 63: 725-31

249. Evaluation of Misuse, Non-Medical Use and Dependence on Tramadol: A Pharmacoepidemiological Study Based on Community Pharmacies in France

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Introduction: In addition to the μ opioid agonist activity of tramadol and its main metabolite O-desmethyltramadol, tramadol also acts on serotoninergic and noradrenergic neurotransmission. This difference in the mechanism of action, compared to that of other opioid analgesics, could account for differences in rates and characteristics of problematic uses of this drug, in particular pharmacodependence.

Aim: To investigate the reasons for use of tramadol others than alleviating pain, as well as the characteristics of pharmacodependence on this drug, from reports of patients via a self-administered questionnaire given in community pharmacies.

Methods: This cross-sectional study was conducted during a two month period (january-march 2008) and was based on the responses to an anonymous questionnaire by patients presenting a prescription for tramadol in community pharmacies. The recruitment of pharmacies was done by pharmacy students performing a training period in a pharmacy of the French Midi-Pyrénées area. Patients were asked to fill in the questionnaire which investigated patterns of drug use and criteria of dependence adapted from the Diagnostic and Statistical Manual IV (DSM-IV). Several questions also explored pain relief related to tramadol use.

Results: Sixty six percent (n = 61) of the solicited pharmacies (n = 92) participated in the survey. Four hundred and sixty five patients filled and returned the questionnaire. Among the 257 patients who had used tramadol in the previous month, 66% were women, and the mean age was 59 ± 17 years. Three of them (1.1%) said that they used tramadol for purposes other than pain alleviating: ''to help to cope with life'', ''to relieve tiredness'', and ''because of drug withdrawal symptoms''. Sixty five patients (25%) were classified as dependent on tramadol as they presented at least 3 out of 6 criteria adapted from the DSM-IV and exploring physical dependence and compulsive drug use. In addition, the answers of the patients suggest that, in the majority of cases, the positive answers to the questions relying on pharmacodependence are related to the persistence of pain.

Conclusion: These results suggest that tramadol prescribed to patients to relieve pain can lead to pharmacodependence. However, the persistence of pain could be also an important factor associated to the criteria of pharmacodependence evaluated in the present study.

250. Tenosynovitis, a Complication of Accidental Injection of BCG Vaccine in Health Professionals

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Background: Since 2007 Bacille Calmette-Guérin (BCG) vaccine is recommended in high risk population for tuberculosis in France, by intradermal route. BCG vaccine is an attenuated live vaccine derived from strains of *Mycobacterium bovis*. We report two cases of granulomatous flexor tenosynovitis following an accidental injection of BCG vaccine.

Observations: After an infant vaccination, two paediatricians, while hooding the syringe of the BCG vaccine, stuck accidentally themselves with the needle respectively in the pulp ring finger and in the flexor tendon of the second finger of their right hand. The needle penetrated deeply and provoked mild bleeding. Two months after, they experienced a sudden and intense nocturnal pain of their right wrist.

As carpal tunnel syndrome was suspected, they both were treated by oral corticosteroid preceded in one case by a local corticosteroid injection. The symptoms increased gradually during one month, with painful oedema of the wrist, associated with paresthesia or anaesthesia of the fingers leading to the diagnosis of tenosynovitis, confirmed by MRI or echography.

In one case, the electromyogram showed a sensitive and motor carpal tunnel syndrome with cubital neuropathy. No history of immunologic disorders or diabetes were recorded and the patients had BCG vaccination in their childhood.

Synovectomy was carried out and flexor synovial biopsies performed. Direct microbiologic assessments were negative in both cases. Culture was positive for *Mycobacterium bovis* in one patient and not yet available for the other. Histopathologic examinations disclosed epitheloid granuloma and gigantocellular granulations. Biology when recorded did not demonstrate inflammation signs. A 6-month regimen antimycobacterial therapy including isoniazide and rifampin was prescribed.

Discussion: Specific risks of accidental vaccine injection in health workers are not always well carried out. Publications on inadvertent inoculation of BCG vaccine are limited.[1] The clinical course of both cases is quite similar and closely resembles the case report already published. Our cases raise the role played by the corticosteroid in the evolution of the infectious tenosynovitis.

Conclusion: Health professionals should be warned concerning accidental inoculation of Bacille Calmette-Guérin vaccine, even if they are vaccinated. The diagnosis has to be quickly established in order to start as soon as possible an antimycobacterial treatment.

Reference

1. Pinocy J, Eingartner C, Ruck P, et al. Recurrent soft tissue infections after accidental inoculation with BCG vaccine. Unfallchirurg 1998 Aug; 101 (8): 658-60

251. Bisphosphonate-Related Osteonecrosis of the Jaw: Description of Six Cases

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Introduction: Biphosphonate-related osteonecrosis of the jaw (ONJ) is a rare but serious adverse drug reaction (ADR).[1,2] It is therefore mandatory to carefully gather and analyze any available information.

Aim: To report six cases of biphosphonate-related ONJ.

Methods: Case Reports were gathered in the Department of Orthodontics, University of Insubria, Varese, Italy.

Results: From 2003 to 2008, six patients with biphosphonate-related ONJ were observed, 3 males and 3 females, with mean (±DS) age of 70.3 (±7.6) years. Five subject had been treated for bone metastases with intravenous zolendronic acid, preceded in one case by a 26-month treatment with pamidronate, for a mean (±DS) period of 21.6 ± 14.3 months. In the sixth case, ONJ occurred 40 months after intravenous clodronate for osteoporosis. Biphosphonate treatment was withdrawn at ONJ occurrence in all the cases. A complete recovery followed curettage and antibiotics in one case only, while partial recovery or no

Table I. Relevant Features of the Cases

Sex, age (y), principal disease	Comorbidity/risk factors	Treatments	ONJ outcome
Case 1, M, 59, renal cancer	Dental implant	Zolendronic acid, radiotherapy	Recovery
Case 2, M, 75, prostate cancer	Diabetes	Zolendronic acid, enantone, ticlopidine	No recovery
Case 3, M, 74, multiple myeloma	HBV+, HCV+/prednisone, dexamethasone	Pamindronate/zolendronic acid, melphalan, prednisone, dexamethasone, thalidomide, levothyroxine	Partial recovery
Case 4, F, 65, breast cancer	Dexamethasone,	Zolendronic acid, radiotherapy, chemotherapy, tamoxifen, letrozole, dexamethasone, paracetamol	No recovery
Case 5, F, 80, breast cancer	None	Zolendronic acid, exemestane, nitroglycerin, paracetamol	No recovery
Case 6, F, 69, osteoporosis	Dental avulsion	Clodronate	Partial recovery

recovery occurred in two and in three cases, respectively. Principal disease, comorbidiy, risk factors and other treatments are shown in table I.

Conclusions: Biphosphonate are effective in the treatment of bone metastases and osteoporosis, though are burdened by the risk of ONJ. The present case series confirms previously identified risk factors and strengthens the need for biochemical and genetic markers[3,4] allowing early identification of people at risk for biphosphonate-related ONJ. In addition, educational intervention targeted at caring physicians are essential for effective prevention, since no effective therapy is currently available.

References

1. Gliklich R, Wilson J. Epidemiology of bisphosphonate-related osteonecrosis of the jaws: the utility of a national registry. J Oral Maxillofac Surg 2009; 67: 71-4

2. Saussez S, Javadian R, Hupin C, et al. Bisphosphonate-related osteonecrosis of the jaw and its associated risk factors: a Belgian case series. Laryngoscope 2009; 119: 323-9

3. Baim S, Miller PD. Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. J Bone Miner Res 2009; 24: 561-74

4. Sarasquete ME, García-Sanz R, Marín L, et al. Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. Blood 2008; 112: 2709-12

252. Falls at the Hospital: Retrospective Analysis of Drugs Using an Automatic Software System

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Introduction: Accidental falls and falls-induced injuries are a major health problem nowadays, specially in older patients. Indeed, about 30% of patients over 65 years fall at least once a year;[1] prevention includes regular exercise, vitamin D and calcium supplementation, and drug evaluation.[2] The potential association between drugs and falls has been extensively studied, specifically for psychotropic drugs[3] and cardiac and analgesics drugs.[4]

Methods: A retrospective descriptive non-interventional study was realised in our Universitary Hospital. We used a specific questionnaire available 24 hours/24 by intranet for all medical and non-medical healthcare professionals. We performed a retrospective analysis of all falls reported between January and June 2007 with a special focus on medications prescription and use.

Results: During the 6 months of the study, 236 falls were recorded concerning 178 patients. Considering hospitalisation rates in the same time-period, the incidence of falls was estimated to 1.6% of the hospitalised patients. Falls notification were mainly made by nurses (98%). Falls occurred during night (from 24 PM to 7 AM) for 40% of all cases and at evening for 9% of all cases (from 7 PM to 24 PM). After evaluation, 8 patients couldn't be correctly identified so we analysed data for 170 patients. Patients were aged 72 years [18–101], sex ratio was 1.33. For 23 patients (13.5%) no drugs were recorded.

The remaining 147 patients received an average of 5 medications [1–17]. Repartition of medications was as following:

- 125 patients (73,5%) received at least one medication that affects the central nervous system: benzodiazepines (29%), opioid analgesics (20.5%), antidepressants (19%), other anxiolytics (17%), hypnotics and sedatives (13.5%), anticonvulsivants (9.5%) antipsychotic (6%) and antiparkinsonians (3%).
- 57 patients (39%) received at least one medication classified as affecting the cardiovascular system : diuretics (19%), beta-blockers (18%), calcium-inhibitors (16.3%), anti-arythmics (8%).
- 15 patients (10.5%) received antidiabetic drugs. And 90 patients (53%) received at least two drugs such as two benzodiazepines or a benzodiazepine and an antidepressant.

Discussion and conclusion: using this software system, we found interesting information about drug use in hospitalised patients after falling. The use of medication that affects central nervous system seems high in our study and even if the fall cause is not equivocal, drug use should be routinely analysed during hospitalisation by physicians, especially after a fall and/or prospectively in older patients. This information should also be routinely added in the patient's medical care documents. These steps will be evaluated in a further prospective study.

References

1. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs Aging 1998 Jan; 12 (1): 43-53

2. Kannus P, Sievänen H, Palvanen M, et al. Prevention of falls and consequent injuries in elderly people. Lancet 2005 Nov 26; 366 (9500): 1885-93

3. Leipzig RM, et al. Drugs and falls in older people: a systematic review and meta-analysis I. Psychotropic drugs. J Am Geriatr Soc 1999; 47 (1): 30-9

4. Leipzig RM, et al. Drugs and falls in older people : a systematic review and meta-analysis II. Cardiac and analgesic drugs. J Am Geriatr Soc 1999; 47 (1): 40-50

253. Definition of Potential Interactions Between Synthetic Drugs, Herbal Drugs and Dietary Supplements During Preoperative Anaesthesiological Assessment: A Cross-Sectional Study in Tuscan County, Italy

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Background: In the last years the use of herbal drugs (HDs) and other complementary/alternative therapies (CAMs), such as homeopathy and dietary supplements (DSs) have sharply increased.

The use of certain HDs during preoperative period may cause serious clinical complications (e.g. prolonged bleeding) due to a direct pharmacological action of these products or to interactions with conventional drugs. Moreover, because of the uncommon habit of referring the use of CAM medications to physicians, patients generally miss or misclassify the products' name and/or typology.

Herein we performed a survey aimed at evaluating the predictors of potential interactions among drugs, HDs and/or other CAM medications, as well as the characteristics of patients unable to refer the type of the consumed products.

Methods: A cross-sectional study was conducted in three Tuscan hospitals (Italy). A questionnaire concerning the use of CAM medications was administered to patients during preoperative anaesthesiological visit.

Univariate analysis was performed in order to determine the predictors of potential Drug-HRs and/or DSs interactions occurrence, as well as the patients' characteristics whenever missing products typology.

Results: On the basis of 572 interviewed patients, 478 (83.5%) entered the analysis according to data quality checking. Among them 155 (32.4%) were at least exposed to one synthetic medications and HRs and/or DSs. Eighty eight patients (56.7%) were detectable for potential interactions evaluation, while 67/155 (43.2%) could not be considered because they missed the type of HR and/or DS being consumed.

Among 88 evaluable patients, 35 (39.7%) were exposed to one potential interaction; univariate models did not show any significant predictors among age, gender, level of education and operatory class of risk. The same results were obtained when patients were asked to remind the type of consumed HRs and/or DSs.

The interactions being identified by our analysis mainly comprised: furosemide with ginseng/liquorice (2 cases), aspirin with devil's claw (2 cases), and warfarin with red ginseng, blueberry (2 cases). All these products are able to potentially affect cardiovascular system during surgical procedure.

Conclusions: Among patients undergoing preoperative anaesthesiological assessment, a widespread use of HRs and DSs was found. According to our univariate models, no predictors of potential interactions between synthetic drugs and HRs/DSs were identified. Moreover, patients poorly reported the use of HRs/DSs to attending physicians.

Specific guidelines should therefore be implemented for preoperative anaesthesiological assessment. The attending physician should be specifically instructed to ask the patient regarding CAM use whose risk in surgical procedure has been already demonstrated.

254. Perianaesthetic Anaphylactic Reactions: A Review of the French Pharmacovigilance Database

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Background: Anaphylactic reactions remain a major cause of concern for anesthesiologists, and they are usually unpredictable. The incidence of allergic reactions during anesthesia is estimated to be from 1 : 3500 to 1 : 13 000 anesthesias in France.

Objective: The aim of this study is to evaluate the seriousness of peranesthetic anaphylactic reactions.

Methods: The study was performed in the French Pharmacovigilance Database from 1st January 2000 to 31th December 2005. We reviewed all cases of anaphylactic reactions and selected those occurring during a general anesthesia.

Results: From the 112 186 adverse drug reactions (ADRs) reported to the French Pharmacovigilance network (53 917 serious) between 1st Jan 2000–31th Dec 2005. We identified 1 678 anaphylactic reactions (1.49% of ADRs and 3.11% of serious ADRs). Among these anaphylactic reactions, 597 have occurred during an anesthesia, that is 0.53% of ADRs and 1.11% of serious ADRs. Female gender was predominant: 376 women (63%) and 215 men (36%). Mean age (range) was 47.75 years (7-86) for women and 49.8 years (5-85) for men. The patients generally recovered. A fatal outcome was reported in 16 of 597 peranesthetic reactions (2.68%) and in 44 of the 1081 other anaphylactic reactions (4.07%).

In 416 cases among 597, the suspect drug was a neuromuscular blocking agent: suxamethonium (43.7%), atracurium (25%), rocuronium (16.3%). Other more often suspected drugs were antibiotics, patent blue dye, latex. These findings were compared to those of the literature.

Conclusion: These data confirm the frequency and the seriousness of peranesthetic anaphylactic reactions.

255. Valproic Acid in Children: Adverse Reactions and Drug Interactions

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Introduction: The objective of this study is to assess the adverse effects (ADE) of valproic acid in epileptic children aged less than 15 years and treated with this drug. We have correlated ADE with the plasma concentrations (PC) of this drug. We have also assessed the influence of socio-economic context of the patient and his family on the occurrence of the ADE.

Material and methods: We made a prospective study between August 2008 and March 2009, we collected 191 plasmatic samples (PS) from children aged of 15 years or below and regularly treated by VA.

Results: Our group was formed of 112 males and 79 females. Median age was 5 years (8 months to 15 years). The indications of VA were essentially idiopathic seizures in 60%, hyperpyretic seizures in 34% and encephalopathy in 3.5%. The median administered dose was 26 mg/kg/day (8 to 53.9 mg/kg/day). VA was administered twice daily in 69% and 3 times a day in 31%. PL were in the therapeutic range in 63%, infra therapeutic in 30% of cases and supra therapeutic in 7%. ADE were noted in 3.1%. The associated drugs were mainly: carbamazepine in 3 cases (PL of VA was infra therapeutic in 2 cases and in the therapeutic range in the 3rd case), phenobarbital and phenaspirine in one case each where PL of VA was infra therapeutic. No correlation

is found between ADE and PC of VA. There is no influence of socio-economic factors on the occurrence of ADE.

Discussion: In our study, ADR were noted in 3.1%. The most frequent ADR reported during VA treatment appear to be dose-dependent and include gastrointestinal disturbances, somnolence, tremor and weight gain.[2-4] Gastrointestinal ADR are transient.[1] Somnolence may be present in 20–25% of patients when initiating treatment. Serious adverse ADR are pancreatitis and hepatotoxicity. Age below 2 years is a risk factor of hepatotoxicity.[1] No case of hepatitis or pancreatitis was noted in our study.

The associated drugs were mainly: carbamazepine (3 cases) with infra therapeutic PL of VA in 2 case and phenobarbital and phenaspirine in one case each with infra therapeutic PL of VA. Phenobarbital or carbamazepine coadministration leads to a higher clearance of VA with corresponding reductions in PL ranging from 30% to 40%.[1] When administered with aspirin, VA free fraction increases secondary to a decreased plasma protein binding and an inhibition of VA metabolism.[1]

References

1. DeVane L. Pharmacokinetics: drug interactions and tolerability of valproate. Psychopharmacology Bulletin 2003; 37 (2): 25-42

2. Loscher W. Basis pharmacology of valproate: a review after 35 years of use for the treatment of epilepsy. CNS Drugs 2002; 16: 669-94

3. Perucca E. Patient-tailored antiepileptic drug therapy: predicting response to antiepileptic drugs. International Congress Series 2002; 1244: 93-103

4. Product information, Depakoate®, Abbott Laboratories, Inc., Physians Desk Reference, Thomson PDR, Montvale, NJ, 2003

256. Newer Antiepileptic Drugs in Pregnancy: Study of 298 Pregnancies

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Introduction: Recently marketed antiepileptic drugs are lamotrigine, gabapentine, topiramate, levetiracetam, oxcarbazepine, vigabatrin, zonisamide and rufinamide (NAED). Their safety during pregnancy is not known but pregnant women are exposed, which may raise serious concerns for patients and physicians. We report our experience of pregnancies exposed to theses drugs.

Aim: Our purpose was to determine the frequency of congenital malformation and of neonatal outcomes.

Methods: We analysed all reports of exposure to new antiepileptic drugs (NAED) in pregnant women to French regional Pharmacovigilance Centers. Suitable cases were pregnant women exposed to NAED during the period of teratogenic risk or at the end of pregnancy, either singly or along with other antiepileptic drugs.

Results: In 8 years (2000 – October 2008), 418 pregnancies were exposed to NAED: lamotrigine 198 (47%), gabapentine 102 (24%), topiramate 70 (17%), levetiracetam 59 (14%), oxcarbazepine 46 (11%), vigabatrin 15 (4%). No cases were observed with stiripentol or zonizamide. Mean age of pregnant women was 29 years [16 y–43 y]. Of these, 193 (46%) were exposed to NAED polytherapy, 145 (35%) to NAED monotherapy and 80 (19%) to NAED monotherapy associated with others medications. Full outcome data are available on 298 (71%) pregnancies. Of these, 243 (80.5%) resulted in live birth. Forty four (15%) foetus/neonates had major congenital malformation: 26 live born (among which 8 (22%) were also exposed to valproate); 17 medical abortions (among which 8 [47%] were also exposed to valproate) and 1 death in utero secondary to cardiac malformation. There were 17 craniofacial defects, 13 central nervous system malformations, 10 cardiovascular malformations and 6 skeletal defects. For the 223 newborn exposed to NAED at the end of pregnancy, for which neonatal outcome is available, 45 (20%) had neonatal complications: the most common was respiratory distress or apnea (19) (7 also exposed to benzodiazepine) and hypotonia (15) (5 also exposed to benzodiazepine).

Conclusion: Because this study is not a prospective follow-up, data should be interpreted with caution. However, the major congenital malformation rate for polytherapy (8%) raises some concerns.

The incidence of neonatal complication seems more frequent with NAED polytherapy than with monothérapie probably because a synergy of their sedative effect.

257. Spontaneous Reporting with Methylphenidate: Insufficient Data

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Introduction: Methylphenidate is a piperidine derivative structurally and pharmacologically similar to amphetamin. Methylphenidate is usually prescribed for chidren aged over 6 years affected by ADHD (Attention Deficit Hyperactivity Disorder). In adults, its indication, except in narcolepsy, is not clearly defined. Methylphenidate received its regulatory approval fifty years ago with a first registration in Switzerland in October 1954. In France, methylphenidate was launched in 1995 with restriction conditions of prescription and delivery.

Objective: To evaluate data obtained by spontaneous reporting in patients under methylphenidate treatment.

Methods: This study analysed data from the French Pharmacovigilance Database of adverse drug reactions spontaneously reported by health professionals from 1985 until June 2009. Off-label use was evaluated with respect to age, dose, indication and frequency of administration.

Results: Methylphenidate is suspected in 95 observations. 77 children are concerned, 63 boys and 14 girls (mean age: 10 ± 3 years), and 18 adults, 11 men and 7 women. Neuropsychiatric effects (9 hallucinations, 5 seizures) were the most frequent adverse effects reported (48.42%) followed by skin effects (23.2%). Cardiac toxicity was reported in eight cases (hypertension, tachycardia, chest pain). Only 4 decreased rate growth and one suicide were notified. Off-label use was very frequently observed in adults (77.8%), also for children in 23.4% of the prescriptions.

Discussion-Conclusion: No signal neither unexpected adverse effects are detected in French Pharmacovigilance Database. Methylphenidate has been marketed for more than 50 years. However, we have no information related to long term outcome as decreased rate of growth, effect on final height, delayed sexual maturity, carcinogenicity. The pharmacovigilance based on the spontaneous adverse drug reactions reporting is not appropriated to resolve these questions. Additional long term exposures and independant clinical studies are necessary to establish the long term profile safety of methylphenidate. A national register to evaluate the safety and benefits of long-term treatments with methylphenidate should be created. ADHD diagnostic and methylphenidate indication should be more respected and guidelines prescription, handling status controlled.

258. Gabapentin and Visual Field Constriction: Case Report

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Introduction: Gabapentin is a cyclic GABAergic analog indicated in the treatment of partial seizures with and without secondary generalization. The main adverse visual side effects of gabapentin included blurred vision, diplopia and changes in visual evoked potentials.[1] Only one case of visual field impairment has been reported in a 52-year-old woman taking gabapentin.[2]

Methods: We report a case of a 37-year-old woman taking gabapentin who presented concentric visual field constriction.

Results: This patient, suffering from epilepsy, was treated with gabapentin (1800 mg/day). Her medical history reported right occipital infarct with left homonymous hemianopsy and cerebral abscess in july 2003. Since 2004, visual field constriction gradually increased and in january 2009, ophthalmologic examination showed a tubular vision in the left eye and a right visual field loss. Results of the neurological examination and magnetic resonance imaging of the brain were normal**,** except for the abscess and cerebral infarction sequelae. Gabapentin was stopped in june 2009. The evolution is unknown this day but ophtalmological examinations are planned in the months to come.

Conclusion: The French Pharmacovigilance database report 6 cases of visual field impairment during treatment with gabapentin with a doubtful imputability for the treatment. In this case, neither medical history nor all complementary investigations can explain concentric visual field constriction. In case of favorable evolution, it would be a new plausible case of visual field constriction, little described until then.

References

1. Verrotti A, Manco R, Matricardi S, et al. Antiepileptic drugs and visual function. Pediatr Neurol 2007; 36: 353-60

2. Bekkelund SI, Lilleng H, Tønseth S. Gabapentin may cause reversible visual field constriction. BMJ 2006; 332: 1193

259. Isotretinoin-PPP Compliance

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Introduction: Isotretinoin is highly effective in treating severe forms of acne, but is also a potent teratogen. The possibility of an unplanned pregnancy and the high risk of congenital defects led to the implementation of a Pregnancy Prevention Plan (PPP). The PPP was designed to ensure that Female of Childbearing Potential (FCBP) are not pregnant one month before starting treatment and do not become pregnant during or for at least one month after stopping treatment.

Aim: To evaluate the compliance with PPP recommendations.

Methods: Cross sectional study designed to collect information among Healthcare Professionals (HCP) and FCBP. The information was collected through questionaries based on the PPP and product information recommendations and targeted to dermatologists, community pharmacies and FCBP (14–49 years old). The sample included all dermatologists (330), 400 community pharmacists and all FCBP recruted by the pharmacies. A letter was sent by mail to the dermatologists with a questionnaire and another letter was sent by mail to the pharmacies with a questionnaire to be fulfilled by the pharmacist and 2 questionnaires to be fulfilled by the FCBP that agreed to participate.

Results: The response rate from dermatologists was 29%. All dermatologists were informed about teratogenic risk and 96% were aware of the PPP. 24% requested the patient to sign the informed consent. 48% gave the educational materials (EM) to the patients. 21% of dermatologists checked the pregnancy test results before and during treatment. 26% prescribed isotretinoine only for one month treatment. The response rate from community pharmacies was 13%. All Pharmacists were informed about teratogenic risk and 74% are aware of the PPP. Concerning the dispensing limitations, only 18% complied with 30 day supply and only 16% complied with 7 days prescription validity. 52 FCBP have agreed to participate in the study. The questionnaire results showed that: 17% were followed on a monthly basis. 19% had received the educational materials and 13% had signed the inform consent. 44% didn't use contraceptive methods. 86% didn't perform pregnancy tests at all.

Conclusions: HCP are informed about teratogenic risk and aware of the PPP implemented for isotretinoin but are not in compliance with the recommendations of the PPP concerning the information given to the patients and the criteria for prescription and dispense. The majority of FCBP don't receive the necessary information and when they do they don't comply with the recommendations.

260. Adverse Drug Reactions To Artemisinin Combination Therapy In General Outpatient Departments of Some Public Health Institutions In Southwest Nigeria

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Background: In many Africa countries, intensity of malaria transmission is high and antimalarial drugs are used frequently for presumptive treatment of fever, even in the absence of laboratory confirmed malaria diagnosis.[1-4]

Nigeria has successfully adopted the use of artemisinin-based combination therapy (ACT) for malaria treatment for more than three years with WHO recommended drug-combinations available in the country under different proprietary names. However, obtaining information on adverse reaction profile of ACT will be necessary in Nigeria, to ensure that the common and rare adverse drug events to ACT are documented. Although, the previous work of Adisa and Colleagues (2008) showed that the incidence of adverse drug reaction (ADR) to ACT is mild and well tolerated.

Objective: This study was designed to investigate the frequency of ADRs associated with the ACTs studied as well as determining if the adverse effects are ACTs specific.

Method: A pre-tested, semi structured questionnaires were administered to 241 respondents in sixteen public health institution in Lagos state, Southwest, Nigeria. Between August and October, 2008.

Information on demographic characteristics, nature of experienced adverse reactions and the most frequently used ACT, among other questions, were collected. EPI-INFO 2006 was used to extract information from the questionnaire while SPSS was used to analyze the information and CHI- SQUARE was used to compare the effects of demographics on adverse drug events.

Results: The study achieved a response rate of 99.2%. The results revealed that 239 (99.2%) of respondents said they had used artemisinin – based combination drug. The most common adverse drug reactions elicited are weakness 55.2%, Lethargy 48.5%, insomnia 31.5%,

depression 27.8%, restlessness 20.3%, headache 31.1%, nausea 34.0%, dizziness 38.6%, and nightmares 12.0%. The most common ADR were from the use of Artemisinin-Amodiaquine combination.

Discussion: Insomnia, depression, restlessness and nightmare are not known symptoms of malaria which strongly suggest ADR from the use of ACT. These effects is of importance in neuropsychiatry patients being treated with ACTs.

Conclusion: Despite high efficacy of ACTs their ADRs is sufficiently significant therefore their safety profile needs to be investigated on large scale.

References

1. Adisa R, Fakeye TO, Dike D. Evaluation of Adverse Drug Reactions to Artemisinin–based Combination Therapy in a Nigeria University Community. Tropical Journal of Pharmaceutical Research 2008 Jun; 7 (2): 937-44

2. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Cochrane Database syst Rev 2000; CD000256

3. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug saf 2004; 27: 25-61

4. Talisuna OA, Sarah G, D'Alessandro U. Pharmacovigilance of antimalarial treatment in Africa: is it possible. Malaria Journal 2006 Jun 16; 5 (1): 50

261. Case Report: Ventricular Tachycardia in a Patient Treated with Amiodarone, Ciprofloxacin and Clarithromycin

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Background: Agents producing a blockage of rapid potassium channels in myocyte membranes can produce a prolonged QTc interval, ventricular tachycardia, Torsades de Pointes or ventricular fibrillation. The risk of malignant arrhythmias is increased by concomitant administration of Type Ia or III anti-arrhythmic or other drugs prolonging the QTc interval or having competitive metabolism. Cytochrome P450 (CYP) 3A4 metabolizes more than 50% currently available therapeutic drugs, its inhibition can produce toxicity due to substrates' increased bioavailability.

Case report: A 71 year-old woman (weight: 65 kg) was hospitalized because of acute respiratory failure and atrial fibrillation with tachycardia. Medical history: allergy to penicillin, smoking, hysterectomy. 1st day: Atrial fibrillation was treated with amiodarone 300 mg in bolus followed by 900 mg/day infusion. Cardiac frequency normalized and ECG showed sinus rhythm with negative T-waves in anterior derivations. 2nd day: respiratory failure continued, with hypercapnia; community-adquired pneumonia was suspected and because of patient's allergy history she was treated with clarithromycin 1 g-/day and ciprofloxacin 1 g/day (instead of ceftriaxone). 3rd day: patient presented again atrial fibrillation with tachycardia and hemodynamic worsening requiring mechanic ventilation. 4th day: ECG showed sinus or nodal rhythm, 58 beats/minute, Q-T interval prolongation. Later, she presented sustained ventricular tachycardia, which was treated with amiodarone infusion. Clarithromycin and ciprofloxacin were stopped, and patient was treated with ceftriaxone (patient didn't present allergy). 5th day: probable nodal rhythm with bradycardia (50 beats/min) and Q-T interval 0.64 s. Mechanical ventilation continues. amiodarone's dose was decreased and patient presented again atrial fibrillation with tachycardia. 6th day: sinus or atrial rhythm, bradycardia (50 b/min), ventricular repolarization but Q-T interval prolongation remained (0.63 ms, Q-Tc 0.57 s.).

Discussion: The patient presented ventricular tachycardia after the administration of clarithromycin and ciprofloxacin, and this adverse effect stopped after dechallenge. Prolongation of the QT interval is an adverse effect associated with the use of fluoroquinolones; ciprofloxacin also produces some inhibition of CYP3A4 citocrome P450. Blockade of HERG may be a common feature of macrolides and may contribute to the QT prolongation observed clinically with some of these compounds. Besides, clarithromycin is a potent CYP 3A4 inhibitor. Amiodarone, which is metabolized by isoenzyme CYP3A4, prolongs Q-T interval.

Conclusion: It's important to know drugs prolonging the QT interval and thus having pro-arrhythmic effects in order to minimize the risk of ventricular arrhythmias. Their combined administration should be avoided. Drug-drug interactions due to citocrome P450 isoenzime's inhibition could increase this additive effect.

262. The Suitability of Elastic Nets for Signal Detection in Spontaneous Report Databases

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Introduction: It is frequently reported that collecting adverse drug reactions (ADR) by spontaneous reporting systems provides a very effective possibility for ADR-monitoring after drug approval. Currently the methods most commonly used for mining those databases are disproportionality measures like the 'Proportional Reporting Ratio' or regression methods in order to correct for confounding by concomitant medication.

Aim: The objective of this study is to analyzing the suitability of the elastic net method[1] for detecting signals in mining spontaneous report databases.

Methods: The database of the net of regional pharmacovigilance centers of Germany contains more than 8000 ADR reports (including the year 2007) collected since 1996 which caused hospital admissions to departments of internal medicine.[2] The data is coded with the hierarchical structure 'ATC' for drugs and 'MedDRA High Level Term' for adverse events.The elastic net method combines the Lasso[3] and Ridge[4] regression method representing a regularization technique that simultaneously performs variable selection and continuous shrinkage. The former minimizes the sum of squares of the residuals combining L1 (absolute value) and L2 (quadratic) penalty. Also the elastic net is a regression method with the capacity of selecting groups of correlated data. Coefficients greater than zero are highlighted as a signal. All calculations are made using the R-package 'penalized'.[5]

Results: 8281 reports and all drugs (suspected and concomitant) are included in the analysis. In a pilot study four MedDRA high level terms are analyzed. Table I shows the number of the coefficients greater than zero for the Lasso model and the elastic net model.

Table I. Number of the coefficients greater than zero for the Lasso model and the elastic net model

ADR (High Level Term)	Lasso ($\lambda1 = 1.4$)	Elastic Net ($\lambda1 = 1.4$, $\lambda2 = 5$)
Hypoglycaemic conditions NEC	56	62
Non-site specific gastro-intestinal haemorrhages	82	85
Rate and rhythm disorders NEC	79	84
Renal failure and impairment	65	74

The results show that the elastic net method sets fewer coefficients to zero and shrinks the other coefficients more than the Lasso regression. The additional coefficients in the elastic net model are often correlated with another coefficient. Hence potential interactions can be found using the elastic net method.

Conclusions: The elastic net model produces sparse models and can support a grouping effect in contrast to Lasso regression. This capability is particularly important as spontaneous report databases contain a lot of correlated variables with ADRs often caused by drug interactions. In the future we will use this method for all MedDRA Preferred Terms in our database.

Disclosure: This study was supported by BfArM: Fo V-5329/68605/2008-2010.

References

1. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Statistic Soc B 2005; 67: 301-20

2. Schneeweiss S, Hasford J, Göttler M, et al. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 2002; 58: 285-91

3. Tibshirani R. Regression shrinkage and selection via the lasso. J Royal Statist Soc B 1996; 58 (1): 267-88

4. Hoerl A, Kennard R. Ridge Regression. Encyclopedia of Statistical Sciences 1988; 8: 129-36

5. Goeman J. The penalized Package. Version 0.9-24 2009; URL: http://cran.r-project.org/web/ packages/penalized/

263. Preventability of Adverse Drug Reactions Leading to Hospital Admission: Assessment of Inter-Rater Variability Within the Network of Regional Pharmacovigilance Centers

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Background: Preventability of adverse drug reactions (ADRs) depends on e.g. setting and clinical relevance of ADRs and determing the fraction of preventable ADRs exactly is hampered by inter-rater variability (IRV) to a significant extent. Within the German Network of Regional Pharmacovigilance Centers (NRPC), ADRs leading to hospitalisation are collected in 4 hospitals and quality assurance (QA) is performed independently.[1] Preventability of ADRs is assessed under consideration of several aspects (e.g. drug-drug interaction, dose adjustments, contraindications) by the regional centers (RC) as well as by the QA.

Aim: We aimed to quantify IRV between RC and QA of the NRPC regarding eight statements associated with ADR preventability.

Methods: Out of all cases documented in 2008 and 2009 100 ADRs were randomly chosen. IRV were analysed for ADRs assessed as 'probable' or 'definite' by the physicians of the QA (e.g. absence of relevant admission related co-morbidity). Since there are 3 potential answers ('yes', 'no', 'not known') for assessing each topic, a 3×3-square table was used for evaluating concordance between RC's and QA's preventability assessments.

Results: Out of 100 ADRs, 80 cases were assessed as 'probable' or 'definite' ADRs and included in the final analysis. Overall, there was a good agreement between RC and QA regarding the preventability statements. Best agreement (95.0%) was observed for the statement regarding over the counter drugs and non-consideration of contraindications and warnings/precautions whereas lowest agreement (68.8%) was calculated for the statement regarding non-consideration of required dose adjustments related to age, sex and co-morbidities. In 36 cases (45%), all preventability statements were assessed in complete concordance by either RC and QA.

Conclusion: For a sample of ADRs leading to hospitalisation we found a good agreement in assessing preventability within the NRPC. Interestingly, consideration of dose adjustment seemed to be the most difficult issue in assessing preventability of ADR. We will further analyse non-agreement focussing on specific ADR characteristics (ADR-type, drugs, drug-drug-interactions, ADR affected organs organ). Furthermore, independent assessment of preventability by the QA will be continued. On this base an algorithm for assessing the overall preventability will be developed taking into account the complex benefit-risk-ratio of pharmacotherapy particularly in elderly multimorbid patients suffering from ADR. (supported by BfArM Project No.: Fo 2.1-68502-201).

Reference

1. Schneeweiss S, Hasford J, Göttler M, et al. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 2002; 58: 285-91

264. Use and Side Effects of Anticoagulant in Intensive Care: Prospective Study

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Introduction: Anticoagulants are among the drugs most implicated in the occurrence of side effects, in Morocco they are often used without any protocol and we have no idea about the importance of adverse reactions to anticoagulation in hospital.

Aim: To define the modality of use of anticoagulants in intensive care units and the adverse reactions of anticoagulation.

Methods: We performed a prospective study in different intensive care units. The study has covered the period from 1 march 2008 to 31 august 2009, we monitor all patients placed on anticoagulants therapy in units or hospitalized for an adverse reaction to anticoagulation.

Results: We collected 340 cases during the six month study with 32 adverse reactions. The other results are under assessment and will be presented in ISoP 2009 annual meeting.

Conclusion: Results of this study will be used to elaborate a protocol of use and monitoring of anticoagulation in Morocco.

265. Safety Profile of Tegaserod (Zelmac®) from a Local Adherence Program in Mexico

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Introduction: Tegaserod is an agonist drug effective for the treatment of Irritable Bowel Syndrome with chronic constipation in Mexico since 2001. On 2007, Tegaserod was temporally discontinued from the

market in the US due to an imbalance in cardiovascular events (myocardial infarction, unstable angina and cerebral vascular accidents) derived from a cumulative analysis of clinical trials (13; 0.1% vs. 1; 0.01%).[1,2] The marketing of Tegaserod remains in Mexico with additional prescribing restrictions.[3]

Aim: To describe the adverse events profile of Tegaserod reported to the local adherence program in Mexico.

Methods: Patients with prescription of Tegaserod were databased in the local adherence program through a call center. Initial and periodic calls were done to patients for drug adherence follow-ups. The adverse events were notified directly from the consumers. The AEs were processed according internal procedures and national regulatory requirements. The period of studied time was from Jan-2007 to Dec-2008.

Results: A total of 241 (2.7%) reports of 8821 patients taking Tegaserod notified AEs in a period of 2 years. These reports represent 394 AEs which 117 (30%) were SAEs and 277 (70%) were non serious AEs. The most common non serious AEs were related with gastrointestinal symptoms like diarrhea, stomach inflammation, pain and burning, nausea, constipation and vomiting (52%) and other like lack of efficacy (7%), headache (6%) and dizziness (4%). Seven cardiovascular events were experienced which were considered not related (cardiac arrest post-abdominal surgery, 1 tachycardia and 1 chest pain) to Tegaserod and 4 reports were classified suspected for reporting purposes (1 myocardial infarction, the patient got recovered and continued taking Tegaserod; Peripheral thrombosis, the patient had peripheral vein insufficiency; 1 angina and 1 heart attack did not have enough information for doing a complete evaluation of the cases). There were no reports of cerebral vascular accidents.

Conclusions: This work described the safety profile of Tegaserod and was found that corresponds with the basic prescribing information of the product. Seeger et al. and Schmulson[1,2,4] published that there is not evidence of an increasing risk of ischemic events related with Tegaserod therapy. The results showed in our study group suggest a similar pattern respecting to the ischemic events. Based on these results, Tegaserod maintains its status of being a recommended therapy for the treatment of Intestinal Bowel Syndrome accordingly with the current prescription recommendations.

References

1. Seeger J, Loughlin J, Rivero E, et al. NO Evidence for Association of Tegaserod with Cardiovascular Adverse Ischemic Events (Cvie) in Routine Clinical Practice. Am J Gastroenterol 2008; 103: S465

2. FDA News release March 30, 2007. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108879.htm

3. Notification to Health Care Providers. Tegaserod (Zelmac) 18 de Junio de 2008. http://www.cofepris.gob.mx/bv/tegaserod.pdf

4. Schmulson Wasserman MJ, Pulido London D. Comorbilidad cardiovascular, tegaserod y otros tratamientos en pacientes con trastornos funcionales gastrointestinales (tfgi), síndrome de intestino irritable (sii) y estreñimiento crónico (ec). Rev Gastroenterol Mex 2007; 72 Suppl. 2: 180

266. Drug-Induced QT Prolongation and Sudden Cardiac Death: A Case Report and Review of the Literature

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A large number of drugs are known to prolong the QT interval, thereby increasing the risk of torsades de pointes and sudden cardiac death. The most common reason for removing a prescription drug from the U.S. market in the past decade has been prolongation of the QT interval. A recent study has demonstrated that typical and atypical antipsychotic drug users have a similar, dose-related increased risk of sudden cardiac death. QT prolongation occurs when a drug affects ion channels in cardiac cells and leads to prolongation of the action potential during depolarization. This step may lead to a reduced reserve for normal repolarization, which then increases the risk of developing torsades de pointes. The degree of QT prolongation caused by a given medication can be influenced by the concomitant use of other agents that inhibit drug elimination or by other factors, such as genetic long QT syndrome (LQTS). Consequently, when physicians need to use a medication known to have the effect of prolonging the QT interval, a review of other risk factors that may increase the likelihood that torsades de pointes will develop, is mandatory, and a close clinical and electrocardiographic monitoring should be prudent during treatment. LQTS-patients should always inform their doctor(s) about their disease and make sure they know there are many medications which are contraindicated in this condition.Among others, AFSSAPS and Arizona Center for Research and Education on Therapeutics (Arizona CERT) have published recommendations and lists of drugs responsible for QT prolongation. Deaths occurring in patients treated by such drugs may have medicolegal implications. We will report on an autopsy case involving a patient, whose death was caused by antipsychotic drugs. We will discuss the possible role of additional factors and resulting malpractice issues. On the basis of the literature, we will examine the mechanisms by which these drugs and additional factors cause sudden cardiac death.

267. Osteonecrosis of the Jaw with Bisphosphonates: French Pharmacovigilance Data

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Introduction: Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates.[1-4] Bisphosphonates are used widely in the management of bone diseases including osteoporosis, Paget's disease and hypercalcemia related to malignancy.

Methods: We conducted a retrospective analysis of the French Pharmacovigilance database. A systematic review of the suspected adverse drug reactions (ADRs) with bisphosphonates was used to identify cases of ONJ until 31 march 2009.

Results: A total of 272 cases of osteonecrosis of the jaw with bisphosphonates as suspected drug were identified in the French Pharmacovigilance database. In the database, the ADRs denomination was various, sometimes the ONJ is described in the text. The mean patient age was 65.2 years, the sex ration 0.45. In 168 reports (61.8%), zoledronate was the only suspected drug. In 29 reports (10.7%), pamidronate and zoledronate were co-suspected. Thirty eight cases of ONJ were identified among patients who were bisphosphonates prescribed for a benign indication.

The mean duration of treatment with zoledronate (23.8 ± 18.5 months) or pamidronate (45.5 ± 23.9 months) was significantly shorter than with the other bisphosphonates ($p < 0.01$).

When the site of ONJ is identified, the ONJ occurs essentially in the mandible ($n = 160$), most of the remainder accurred in the maxilla ($n = 65$), and in eleven cases at both sites. Some reports include abscess or fistule formation.

94 patients (34.7%) had a dental procedure before the onset of ONJ. In 66 cases, a chirurgical debridement was realized (24.3%).

Discussion-Conclusion: In France, recommendations on dental care of patients treated with bisphosphonates have been published. No treatment has been established to be effective and so the current approach is conservative management with antibiotherapy.

The largest number of reports on ONJ has been observed with zoledronic acid.
The pathophysiological mechanism is not established. Investigation of the underlying pathological mechanisms is needed. The terminology used in the reporting must be harmonise.
Practitioners and patients must be educated.

References

1. Hess LM, et al. Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med 2008; 121: 475-83

2. Haff AO, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008; 23: 826-36

3. Trenque T, et al. Osteonecrosis of the jaw with bisphosphonates: a safety review. Drug Safety 2006; 29: 969

4. Ruggiero SL, et al. Osteonecrosis of the jaw associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004; 62: 527-34

268. Pharmacovigilance and Patients: Symbolic Logics and Ethical Aspects

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Whereas pharmacovigilance as a process of drug testing and drug control is, by definition, essentially a practice of health professionals in the service of other health professionals, patients are also largely present in the scene of pharmacovigilance, and this, at no less than two levels:

- at the level of the patients' own behaviours aimed at reducing the undesirable effects of drugs,
- at the level of the discourse that medical doctors sometimes deliver to patients, regarding their prescriptions.

The gaze of the anthropologist as outsider allows us to approach this issue from the angle of the symbolic logics and ethical aspects which are at stake.

269. Managing Safety Signals Associated with Manufacturing in GlaxoSmithKline Biologicals

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Throughout a product's life cycle, from clinical studies to post-marketing experience, subjects' safety is always of primary importance. One particularly significant aspect of Pharmacovigilance is the detection of potential safety issues that might be associated to manufacturing-related processes.
In this session we describe the methodology by which safety signals detected within the spontaneous adverse events reporting system are used in routine practice to identify potential manufacturing issues. Screening for safety signals is performed in relation to production lots. Where associations are detected, a quantitative disproportionality measure is applied to determine the strength of the association within any particular lot by estimating whether the concentration of adverse event reports is more than what might be expected to occur under the null hypothesis of independence. The signal detection follow mainly a set of four categories:
1. any disproportionate concentration of adverse event reports that indicates possible lack of sterility,
2. any disproportionate concentration of adverse event reports that indicates possible lack of efficacy,
3. any disproportionate concentration of serious or non-serious adverse event reports,
4. any reports of unexplained fatalities. In addition, technical complaint trends are evaluated for safety signals.

Any signal identified through the above set of screening analyses is subject to qualitative medical and manufacturing investigations to determine whether preventive or corrective actions are necessary. This process for detecting and managing safety signals is an important component of the Company's manufacturing quality program and is an important component of its proactive Pharmacovigilance system.

270. A Pharmaceutical Collaborative Initiative: An Innovative Approach to RISK Mitigation Strategies for a Rare Event: Progressive Multifocal Leukoencephalopathy

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Progressive Multifocal Leukoencephalopathy (PML) is a rare, potentially fatal, demyelinating disease of the brain caused by JC virus (JCV) with no generally accepted existing treatment. Approximately 60% of the adults are believed to be infected with JC virus. Most people infected with JC virus, however, do not develop PML. PML is usually associated with chronic immunosuppression resulting from diseases such as AIDS, or immunosuppressive treatments. Several new medicines have been associated with PML resulting in either extensive risk management plans or market withdrawal. Because PML occurs so rarely, it would be very difficult for any single pharmaceutical company, research center, or agency on its own to obtain sufficient data and specimens to conduct research to comprehensively evaluate the disease and identify causes and treatments. Therefore, a cooperative effort to make PML manageable through preventive strategies such as identification of risk factors, and treatment strategies such as early diagnosis and effective treatment, is needed. Several pharmaceutical companies are exploring the concept of such a cooperative effort to achieve this goal through pooling resources and sharing data. Ultimately, the objective is to gather sufficient information to mitigate risk and to conduct research in collaboration with academia, health authorities and other stakeholders, essential for achieving patients' best care and protection.