ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (9): 759-767
0114-5916/12/0009-0759/$49.95/0

Drug Fever

A Descriptive Cohort Study from the French National Pharmacovigilance Database

Dominique Vodovar,[1,2,3] *Christine LeBeller*,[4] *Bruno Mégarbane*,[2,3] *Agnes Lillo-Le-Louet*[4] and *Thomas Hanslik*[1,5]

1 Department of Internal Medicine, AP-HP, Ambroise Paré Hospital, Boulogne-Billancourt, France
2 Medical and Toxicological Critical Care Department, AP-HP, Lariboisière Hospital, Paris, France
3 Paris-Diderot University, Paris, France
4 Regional Center of Pharmacovigilance, AP-HP, European Georges Pompidou Hospital, Paris, France
5 Versailles-Saint Quentin University, Versailles, France

Abstract

Background: Although known as a rare adverse drug reaction (ADR), drug fever (DF) remains an important issue in medicine, with the risk of leading to inappropriate and potentially harmful diagnostic and therapeutic interventions. Only sparse data regarding DF have been published.

Objective: The aim of the study was to investigate which drugs were associated with DF, and report outcomes.

Methods: Cases of DF without skin reactions were selected from all ADRs reported from 1986 to 2007 in the French National Pharmacovigilance Database. Drugs potentially responsible for DF were assessed using a qualitative case-by-case analysis (Naranjo's criteria) and quantitative measurement (proportional reporting ratio [PRR]). A drug was implicated as the cause of DF when the following criteria were validated: three or more cases and PRR of at least two with a Chi-squared value of at least four.

Results: A total of 167 DF cases involving 115 drugs were eligible. Based on the PRR, 22 drugs were significantly associated with DF. Antibacterials represented the most frequently reported drugs, including amikacin (PRR 39.6 [95% CI 23.6, 69.0], oxacillin (9.1 [3.6, 23.4]), cefotaxime (5.5 [2.0, 15.3]), ceftriaxone (5.4 [2.6, 11.3]), rifampicin (4.0 [1.8, 9.2]), vancomycin (4.0 [1.4, 11.5]), ciprofloxacin (3.1 [1.2, 8.0]), isoniazid (3.9 [1.4, 11.4]), pristinamycin (3.1 [1.0, 9.1]) and cotrimoxazole (2.6 [1.2, 5.8]). Median time [interquartile range] from drug administration to fever onset was 2 days [1.0–10.5]. A diagnosis of DF was made following cessation of the suspected drugs (3 days [1.0–11.5] after fever onset. Drug rechallenge was performed (38.0%), resulting in recurrence of DF in all cases. DF resulted in life-threatening events (0.6%), hospitalization or prolonged hospital stay (24.5%) and persistent

disability (0.6%). Final outcome was favourable in 96.9% of cases after drug discontinuation.

Conclusion: Diagnosing DF is challenging. Based on this large series, antibacterials remain the major class of drugs responsible for DF.

Background

Drug fever (DF) is a febrile reaction occurring with drug administration and disappearing after drug discontinuation, in the absence of other causes of fever as ascertained through careful physical examination and appropriate laboratory tests.[1] DF is generally defined as a febrile response to a drug without any skin reaction.[2]

DF as an isolated symptom is rare, representing 0.01–5% of all adverse drug reactions (ADR) among inpatients.[1,3-6] However, it remains underrecognized.[2] The diagnosis of DF is challenging as (i) risk factors have not been clearly identified;[1] (ii) the disease requiring the drug may manifest initially with fever, potentially obscuring the diagnosis;[2,7] and (iii) final diagnosis requires drug discontinuation, which is not easy if the drug is essential for patient recovery.[8] To date, reports of DF have been based on single cases and small hospital series published in the 1980s and 1990s,[1-9] with the largest series from 1987 reporting 51 consecutive cases.[1] In the English literature, at least 81 different drugs have been implicated in inducing fever,[8] with the four most frequent pharmacological classes being antimicrobials (mostly antibacterials), anticonvulsives, antidysrhythmics and other cardiac agents.[1,10]

Previous reports identified DF using qualitative case-by-case analyses.[1,3,5-7,9] A quantitative analysis (proportional reporting ratios [PRRs]) was developed for signal generation from large databases of spontaneous ADR reports to find a statistical link between one studied ADR and one given drug.[11] To date, this quantitative methodology has never been used to identify causal drugs responsible for DF. We sought to evaluate cases of DF using both qualitative case analyses as well as PRR analyses, using 20 years of data from the large French National Pharmacovigilance Database (FNPD).

Methods

Source of Data

Created in 1986, the FNPD collects all ADRs from in- and outpatient settings, as spontaneously reported by physicians, dentists, midwives and pharmacists to the network of the 31 Regional Centers of Pharmacovigilance (RCPV) in France. The FNPD has been previously described.[12] In 2001, a total of 197 580 spontaneous reports of ADRs were present in the FNPD; in November 2011, this number has grown to more than 431 000 cases. Case records contain minimal information about the patient (including demographics and medical history), the suspected drug and ADR description. It has been previously estimated that no more than 5% of serious ADRs are reported in the FNDP.[13]

Definition of Drug Fever (DF)

We used the following diagnostic criteria adapted from those described by Young et al.[6] and modified by Pleasants et al.[14] and Johnson and Cunha:[2] (i) an oral or rectal body temperature above 38°C; (ii) the absence of other causes of fever as determined by physical examination and appropriate biological and microbiological tests (i.e. absence of any infection); (iii) the absence of any underlying condition causing fever by itself; (iv) the absence of skin reactions; (v) the coincidence of fever onset with drug administration; (vi) disappearance of the fever within 72 hours following drug discontinuation without any other intervention; (vii) no recurrence of fever within at least 72 hours after normalization of temperature; and (viii) exclusion of other differential diagnoses for hyperthermia, including antipsychotic malignant syndrome, serum sickness-like reactions, serotonin syndrome and malignant hyperthermia. Although debated in the literature,[1,2] we did not

consider fevers associated with skin reactions as DF in this study, since isolated fevers represent the most challenging situations for clinicians. Moreover, we included DF independently from their related mechanisms, although, based on the literature,[8] the majority of these mechanisms are related to hypersensitivity.

Case Selection

To assess the causal drugs responsible for DF, reports recorded in the FNPD between January 1986 and December 2007 were reviewed by searching for 'DF' (based on the Medical Dictionary for Regulatory Activities [MedDRA®])[15] and preselected if meeting the criteria for DF. Each suspected drug was classified according to the Anatomical Therapeutic Chemical (ATC) classification first-level code.[16] Preselected cases were subjected to Naranjo scoring (table I): to assess causality for individual cases (i.e. the likelihood that fever was caused in each selected report by the suspected drug),[17] a weighted score from +2 to –2 was determined for each of ten questions. Where insufficient data was available, the question received a score of '0'. A total score corresponding to the likelihood of DF as 'doubtful', 'possible', 'probable' or 'definite' was calculated for each case. Only reports with 'possible', 'probable' or 'definite' were considered for further evaluation using a description of DF (qualitative case-by case analysis) and PRR calculation (quantitative methodology). Blinded chart reviewing was performed by two experienced specialists in pharmacovigilance (Drs LeBeller and Lillo-Le-Louet). In case of disagreement between the two evaluators, the lowest Naranjo score was considered.

Description of DF Cases

For cases selected from the Naranjo criteria, the following data were collected: demographics, medical history, fever characteristics (continuous vs intermittent), general symptoms, biological data (C-reactive protein, aminotransferases, haemoglobin, platelet and white blood cell counts) and outcome. Patients' underlying health disorders were classified according to the International Statistical Classification of Diseases and Related Health Problems – 10th revision (ICD-10).[18] DF cases were codified according to the WHO Adverse Reaction Terminology,[19] and classified as 'non-serious' or 'serious'. Cases were considered 'serious' if resulting in death, life-threatening event, hospitalization, prolonged hospital stay or persistent disability. The following periods of time were collected: onset of fever after drug administration, onset of fever to drug discontinuation, discontinuation of drug to disappearance of fever and drug discontinuation to drug rechallenge if performed. For unavailable data in the FNPD, a personalized questionnaire was sent

Table I. The Naranjo's adverse drug reaction probability scale[a] (reprinted by permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics,[17] © 1981)

	Yes	No	Do not know
1. Are there previous *conclusive* reports on this reaction?	+1	0	0
2. Did the adverse event occur after the suspected drug was administered?	+2	–1	0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	–1	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	–1	+2	0
6. Did the reaction reappear when a placebo was given?	–1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

a The Naranjo criteria assess the probability that an adverse event is related to drug therapy based on a list of weighted questions. Where insufficient data are available, the question received a score of '0'. A total score corresponding to the likelihood of drug fever as 'doubtful' (0), 'possible' (1–4), 'probable' (5–8) or 'definite' (9 or greater) was calculated for each case.

to the corresponding RCPV to retrieve additional information. The completion rate was 80%.

Quantitative Analysis

After a case-by-case evaluation using the Naranjo score and for all cases selected, a PRR was calculated. The PRR is currently used for signal generation (*quantitative methodology*) from spontaneous reporting data.[11] The PRR compares the proportion of DF linked to a particular drug with the corresponding proportion of all drugs in the database. It is recognized that the quantitative detection is a potentially useful adjunct to traditional pharmacovigilance practices such as case-by-case analysis;[20] PRR allows to quantify the strength of the association between the ADR and the suspected drug. In the case of DF, the disproportionality analysis using the PRR may be useful to evaluate potential signals for DF that could have been excluded due to underlying disease, such as fever induced by the infection that required the prescription of the incriminating antibiotic (*confounding by indication*).

Statistical Methods

To calculate the PRR with 95% CI, the proportion of DF with one drug was compared with the same proportion for all drugs in the database, in a 2×2 table. This measure of disproportionality was combined with an estimator of the statistical association, i.e. a Chi-squared test at one degree of freedom with Yate's correction. We used as the minimum criteria for a signal, three or more cases, a PRR of at least two (with a lower limit of the 95% CI >1) and Chi-squared test of at least four (threshold value at one degree of freedom with $p<0.05$ in a 2×2 table). These cut-off values are those usually applied by the UK Medicines and Healthcare products Regulatory Agency to routinely scan the Adverse Drug Reactions On-line Information Tracking database of spontaneous reports for signals.[21] When a specific drug-DF association met all the criteria mentioned above, it indicates that DF has been disproportionately reported for that drug. A significant increase in PRR supported by any other information on a particular drug-DF combination contributes to the creation of a signal. Results are expressed as median [interquartile range] or percentages when appropriate. Differences with p-values ≤0.05 were considered as significant. All calculations were performed using Prism v5.0 (GraphPad Software, Inc., San Diego, CA, USA).

Results

Overall, 174 recorded files over a 20-year period from the FNPD were eligible for further evaluation as potentially true DF cases. Three cases with missing data and four other cases with 'doubtful' Naranjo's assessment were excluded, leaving 167 cases enrolled in this study.

DF represented 0.05% of all ADR cases reported to the FNPD during the study period (167/323 340). The median number of DF cases notified per year was 7.5 [5.7–9.2] (figure 1). On the basis of Naranjo's criteria, 33% of the cases were 'possible', 47% were 'probable' and 20% were 'definite'. Patients (age 52 years [32–69]) were <18 years (16%) and >65 years (29%). Male/female sex ratio was 1.01. An underlying health disorder was present in 70% (116/167) of cases, including cardiovascular disease (40/167; 24%), cancer (26/167; 16%), endocrine disease (16/167; 10%) and unspecified allergy (6/167; 4%) [table II].

The reported median peak fever was 39°C [38.7–39.8] (103°F [102–104]) and DF pattern was continuous (71/137; 52%) or intermittent (66/137; 48%). Time from drug administration to fever onset was 2 days [1.0–10.5] (n = 133). DF appeared <12 hours after first exposure to the drug in 11% of

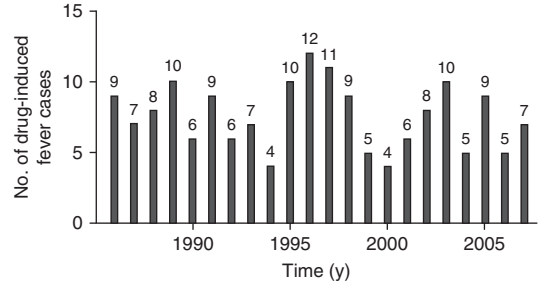

Fig. 1. Number of drug-induced fever cases reported each year to the Regional Centers of Pharmacovigilance in France from 1986 to 2007.

Table II. Patients' underlying health disorders according to the International Statistical Classification of Diseases and Related Health Problems – 10th revision

Underlying health disorders (N = 167)	N (%)
No medical background	**47 (30.0)**
Medical background	**120 (70.0)**
Diseases of the circulatory system	40 (24.0)
Neoplasms	26 (15.6)
Endocrine, nutritional, and metabolic diseases	16 (9.6)
Infectious and parasitic diseases	15 (9.0)
Mental and behavioural disorders	15 (9.0)
Diseases of the digestive system	14 (8.4)
Diseases of the genitourinary system	14 (8.4)
Diseases of the musculoskeletal system and connective tissue	12 (7.2)
Diseases of the nervous system	11 (6.6)
Diseases of the respiratory system	9 (5.4)
Diseases of the blood	8 (4.8)
Allergy (unspecified)	6 (3.6)
Diseases of the skin and subcutaneous tissue	5 (3.0)
Diseases of the ear and mastoid process	2 (1.2)

patients (14/137) and within 10 days in 74% of patients (101/137). The responsible drug was discontinued 3 [1.0–11.5] days after fever onset (n = 128). DF duration was 1 [1.0–2.0] days after drug cessation (n = 101).

General symptoms were reported in 18.4% (22/120) of the cases, including chills (18/120; 15%) and fatigue (4/120; 3.4%). Biological disorders (22/112; 19.8%) included increased C-reactive protein (10/112; 8.9%), increased aminotransferases (9/112; 8.0%), thrombocytopenia (3/112; 2.7%), hypereosinophilia (1/112; 0.9%) and neutropenia (1/112; 0.9%). Cases were classified as 'serious' (43/167; 25.7%) if requiring hospitalization or prolonged hospitalization (41/167; 24.5%) or resulting in persistent disabilities (1/167; 0.6%) and life-threatening events (1/167; 0.6%). Outcome (n = 159) was favourable with complete recovery (154/167; 96.9%), incomplete recovery (3/157; 1.9%) and recovering (1/157; 0.6%). One death (1/157; 0.6%) occurred during follow-up with no relation to DF (cardiac infarction). Rechallenge was performed in 38.0% (63/167) of cases resulting in DF recurrence in all cases.

Based on Naranjo's criteria, 115 different drugs were shown to be responsible for DF (table III). The median number of suspected drugs implicated in each case was 1.0 [1.0–1.0]. Antibacterials (43 cases), immune sera and globulins (21 cases) and antineoplastic drugs (15 cases) were the most frequently reported drugs. Based on the PRR method, drugs significantly associated with fever are listed in table IV. Antimicrobial agents were the most frequently reported drugs associated with DF (figure 2).

Discussion

We report the largest series of 167 DF cases based on a national pharmacovigilance database analysis collected by the French National Pharmacovigilance Database from 1986 to 2007.

DF diagnosis remains difficult. About 1.3% of fevers of unknown origin could correspond to DF.[22-35] As previously reported, DF is rarely associated with severe symptoms (as generally well tolerated by patients) or blood abnormalities,[8] although it may mimic sepsis.[1,5,9] DF appeared mostly within 10 days from drug administration (74%); however, in some cases, onset could be delayed up to several months.[1] Rapid DF resolution after drug discontinuation is the key to diagnosis.[2,36] However, time from fever onset to drug discontinuation was prolonged (3.0 days [1.0–11.5]) in our series, in relation to the time required to make the diagnosis. Consistent with this, in another cases series, 14.8% of DFs were diagnosed 21 days after fever onset, fulfilling the criteria of fever of an unknown origin[32] and thus underlining the difficulty of diagnosis.

DF is not generally a serious ADR;[8] however, it may be the reason for the patient's hospitalization or prolonged hospitalization (25% of cases in our series). Additional hospitalization days attributable to DF have been estimated to be about 5.49–8.7 days.[3,37] Additional costs, including diagnostic procedures and treatments, have been estimated to be upwards of $US9022 per inpatient (year of costing 1997).[3] In our series, no death was directly related to DF although six deaths were reported in the other large series.[1] Rechallenge rate with the suspected drug was surprisingly high in the current series (38%) but DF was not worse than when it developed following the first exposure.

However, caution with drug rechallenging is advised as more severe reactions could be triggered. The suspected drug must be withdrawn while an alternative treatment is chosen.[2]

Consistent with previous reports,[1,2,5,8] anti-infective agents were most frequently related to DF in our series (113), followed by drugs acting on the nervous system (28), antineoplastics and immunomodulating drugs (27), and cardiovascular agents (12) [table III]. Overreporting of DF from antimicrobials when compared with other drugs is likely due to the more difficult diagnosis in the setting of infection. In our series, when the antibiotic was administered to treat an evidenced infection, DF diagnosis was suspected due to the remaining or persistent fever while other markers

Table III. Classification of the drugs reported to induce fever based on Naranjo's criteria (i.e. 'possible', 'probable' or 'definite') in the French National Pharmacovigilance Database according to the Anatomical Therapeutic Chemical classification

ATC classification first-level code	Number of drugs	Drugs responsible for drug fever (number of cases)
A – Alimentary tract and metabolism	2	Calcium phosphate (1), sulfasalazine (2)
B – Blood and blood forming organs	11	Acenocoumarol (1), albumin (2), dalteparin (1), darbepoetin alfa (1), enoxaparin (1), etamsylate (1), ferrous fumarate (1), fluindione (4), gelatin agents (1), heparin (1), streptokinase (1)
C – Cardiovascular system	8	Atenolol (1), bisoprolol (3), clonidine (1), dobutamine (1), fenofibrate (1), furosemide (1), captopril (1), methyldopa (3)
G – Genito-urinary system and sex hormones	5	Cyproterone (1), lynestrenol (2), medrogestone (1), misoprostol (1), nomegestrol (4)
H – Systemic hormonal preparations, excluding sex hormones and insulins	1	Hydrocortisone (3)
J – Anti-infectives for systemic use	34	*Penicillins (13):* amoxicillin (3), amoxicillin + enzyme inhibitor (3), bacampicillin (1), oxacillin (3), piperacillin (2), piperacillin + enzyme inhibitor (1) *Cephalosporins (12):* cefotaxime (3), ceftazidime (2), ceftriaxone (6), cephalexin (1) *Aminoglycosides (7):* amikacin (5), tobramycin (2) *Glycopeptides (5):* vancomycin (3), teicoplanin (2) *Fluoroquinolones (9):* ciprofloxacin (4), enoxacin (1), levofloxacin (1), ofloxacin (2), pefloxacin (1) *Antituberculosis agents (11):* ethambutol (2), isoniazid (3), pyrazinamid (1), rifampicin (5) *Other antibacterials (13):* metronidazole (2), nitrofurantoin (1), pristinamycin (3), roxithromycin (1), cotrimoxazole (6) *Other antimicrobials (43):* abacavir (1), acyclovir (3), amphotericin B (6), flucytosine (2), human polyvalent immune globulins (21), vaccines (10)
L – Antineoplastic and immunomodulating agents	20	Adalimumab (1), antilymphocyte immunoglobulin [horse] (1), azathioprine (2), carboplatin (1), chlorambucil (1), cisplatin (1), cyclophosphamide (1), cytarabine (3), daunorubicin (1), doxorubicin (2), hydroxycarbamide (3) , interferon α-2a (1), L-asparaginase (1), methotrexate (1), molgramostim (1), oxaliplatin (2), rituximab (1), thalidomide (1), triptorelin (1), vincristine (1)
M – Musculo-skeletal system	6	Allopurinol (1), flurbiprofen (1), ketoprofen (1), pamidronic acid (2), phenylbutazone (1), urate oxidase (1)
N – Nervous system	19	Carbamazepine (3), chlorpromazine (1), clomipramine (2), fipexide (1), fluoxetine (1), haloperidol (2), imipramine (1), lorazepam (2), metapramine (5), mianserin (1), nomifensin (1), periciazine (1), phenobarbital (1), clorazepate dipotassium (1), sulpiride (1), valproic acid (1), venlafaxine (1), viloxazine (1), zuclopenthixol (1)
P – Antiparasitic products, insecticides and repellents	1	Primaquine (1)
V – various	2	Edetates (1), mesna [2-mercaptoethane sulfonate sodium] (1)

ATC = Anatomical Therapeutic Chemical.

Table IV. Drugs reported in the French National Pharmacovigilance Database to significantly induce fever onset using the proportional reporting ratios method

Drugs	Chi-squared	PRR (95% CI)
Anti-infectives		
Antibacterials		
Classes		
Aminoglycosides	25.3	5.6 (2.9, 11.0)
β-lactams	14.2	2.2 (1.5, 3.4)
Glycopeptides	14.3	4.7 (2.1, 10.6)
Streptogramins	4.1	3.1 (1.1, 9.1)
Subclasses		
Third-generation cephalosporins	27.2	4.4 (2.5, 7.8)
Molecules		
Amikacin	82.4	39.6 (23.6, 69.0)
Cefotaxime	11.0	5.5 (2.0, 15.3)
Ceftriaxone	21.0	5.4 (2.6, 11.3)
Ciprofloxacin	5.5	3.1 (1.2, 8.0)
Isoniazid	6.5	3.9 (1.4, 11.4)
Oxacillin	21.2	9.1 (3.6, 23.4)
Pristinamycin	4.1	3.1 (1.0, 9.1)
Rifampicin	11.0	4.0 (1.8, 9.2)
Cotrimoxazole	5.7	2.6 (1.2, 5.8)
Vancomycin	6.6	4.0 (1.4, 11.5)
Other anti-infectives		
Acyclovir	12.3	6.0 (2.21, 16.4)
Amphotericin B	74.2	14.8 (8.04, 27.4)
Attenuated diphtheria, *Haemophilus influenzae, Bordetella pertussis*, poliomyelitis, tetanus vaccine	113.5	40.5 (20.9, 81.9)
No anti-infectives		
Bisoprolol	11.7	5.8 (2.12, 15.9)
Cytarabine	20.3	8.8 (3.4, 22.7)
Hydroxycarbamide	27.5	11.2 (4.6, 28.0)
Hydrocortisone	103.8	37.2 (18.8, 76.2)
Human immunoglobulins	581.1	33.6 (25.6, 45.5)
Metapramine	422.6	98.1 (60.5, 143.6)
Methyldopa	22.0	9.4 (3.7, 24.0)
Nomegestrol	105.4	28.9 (15.4, 56.0)

PRR = proportional reporting ratios.

of infection resolved. When the antibiotic was administered for prophylaxis, diagnosis was suspected based on the occurrence of fever while no infection was evidenced. About 13% of the patients receiving more than 7 days of intravenous antibacterials were estimated to experience DF in one study.[9] In our study, antibacterials significantly associated with DF occurrence included β-lactams, third-generation cephalosporins, antituberculous agents and glycopeptides, as previously reported,[8] while streptogramins and aminoglycosides, which we found to be significantly associated with DF, have not been previously reported. Regarding aminoglycosides, we could not eliminate a bias related to their frequent co-prescription with other antibacterials. Surprisingly, ciprofloxacin was also significantly associated with DF, as only levofloxacin had previously been reported to induce fever.[38]

DF involves either a single drug molecule or a whole pharmacological class. The syndrome is related to six possible mechanisms: (i) altered regulation of body temperature due to increased heat production or diminished heat dissipation with drugs such as antipsychotics or thyroid hormones;[5,7,39] (ii) presence of pyrogenic impurities during manufacturing processes (e.g. vancomycin as described in historical cases);[40-42] (iii) complications due to intravenous drug administration such as phlebitis; (iv) pyrogenic particle release (e.g. endotoxins/lipopolysaccharides from bacterial

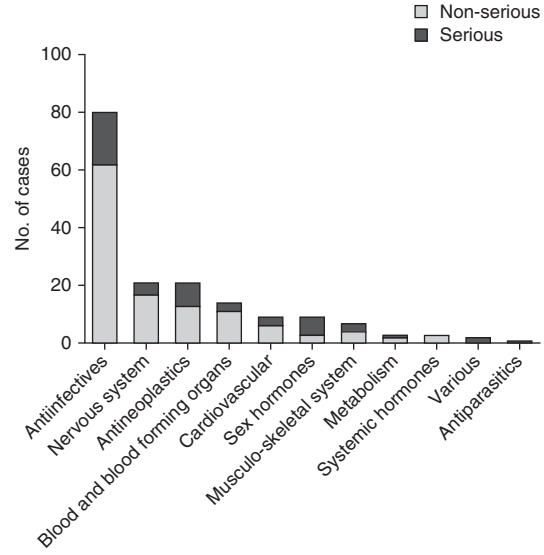

Fig. 2. Drugs classified according to Anatomical Therapeutic Chemical classification first-level code and implicated in the reports classified as 'serious' or 'not serious' according to the WHO Adverse Reaction Terminology.

antibiotic-induced wall destruction or cytokine release following tumour destruction with anticancer agents); (v) idiosyncratic reactions, including genetically-determined variations in drug pharmacokinetics or pharmacodynamics; (vi) hypersensitivity explaining the tricky frontier between DF and allergy.

Our study has significant strengths. No cases of antipsychotic malignant syndrome, serum sickness-like reaction, serotonin syndrome and malignant hyperthermia misdiagnosed as DF were considered in this study. Imputability of the suspected drug for DF was determined in all the cases and no 'doubtful' cases were included. A two-step approach based on initial qualitative individual case analysis followed by quantitative PRR methodology was used to ascertain the observed causal link between each DF case and its corresponding drug. While PRR is useful to determine a signal in a database of spontaneous reporting, allowing investigators to study the strength of the association between the ADR and each drug identified by the qualitative approach, care is needed on how to interpret the PRR. The results of quantitative signal detection should be considered as an additional source of information, complementary to the traditional analysis.[20]

However, several limitations also exist. Cases were based on spontaneous reporting which clearly suffered from underreporting.[13,43] DF prevalence among all ADRs reported to the RCPV was 0.05% in this study, while retrospective series monitoring ADRs or DF with associated skin reactions reported higher rates up to 5%.[1,2,4,5,8] Clinical data were not always available despite additional information requests sent to the RCPV. The disproportionality measurement used here is a statistical tool requiring at least three cases.[44-46] For some drugs, Chi-squared and PRR tests were significant but the reported number of cases was lower than three, leading to exclusion. Thus, other drugs potentially responsible for DF may have remained undisclosed in our study.

Conclusions

DF is induced by a wide variety of drugs and probably remains underdiagnosed and underreported. The quantitative PRR approach improves the analysis to assess a causal relationship of a specific pharmaceutical agent to DF. We observed that DF occurs more frequently with antibacterials. Outcome is generally favourable; however, DF may lead to costly hospitalizations and unnecessary laboratory testing and imaging for patients.

Acknowledgements

No sources of funding were used to conduct this study or prepare this manuscript. None of the authors has any conflict of interest.

The authors would like to acknowledge Jenny Lu, MD, from Toxikon Consortium, Chicago, IL, USA, for her review of this manuscript and François Maignen, from the European Medicines Agency, London, UK, for his methodological help. We appreciate the assistance of the French pharmacovigilance centers in our work.

References

1. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. Ann Intern Med 1987; 106: 728-33
2. Johnson DH, Cunha BA. Drug fever. Infect Dis Clin North Am 1996 Mar; 10: 85-91
3. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. JAMA 1997; 277: 301-6
4. Kumar KL, Reuler JB. Drug fever. West J Med 1986; 144: 753-5
5. Lipsky BA, Hirschmann JV. Drug fever. JAMA 1981; 245: 851-4
6. Young EJ, Fainstein V, Musher DM. Drug-induced fever: cases seen in the evaluation of unexplained fever in a general hospital population. Rev Infect Dis 1982; 4: 69-77
7. Tabor PA. Drug-induced fever. Drug Intell Clin Pharm 1986; 20: 413-20
8. Patel RA, Gallagher JC. Drug fever. Pharmacotherapy 2010; 30: 57-69
9. Oizumi K, Onuma K, Watanabe A, et al. Clinical study of drug fever induced by parenteral administration of antibiotics. Tohoku J Exp Med 1989; 159: 45-56
10. Tisdale J, Miller D. Drug induced disease: prevention, detection, management. Bethesda (MD): American Society of Health System Pharmacists, 2010
11. 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; 10: 483-6
12. 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: 731-40

13. Bégaud B, Martin K, Haramburu F, et al. Rates of spontaneous reporting of adverse drug reactions in France [letter]. JAMA 2002; 288: 1588
14. Pleasants RA, Walker TR, Samuelson WM. Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. Chest 1994; 106: 1124-8
15. Wood K, on behalf of the MedDRA Working Party. The medical dictionary for drug regulatory affairs (MedDRA). Pharmacoepidemiol Drug Saf 1994; 3: 7-13
16. World Health Organization Collaborating Center for Drug Statistics Methodology. ATC/DDD index 2012 [online]. Available from URL: http://www.whocc.no/atc_ddd_index/ [Accessed 2012 Jun 26]
17. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45
18. World Health Organization. International classification of diseases and related health problems 10th revision, 2007 [online]. Available from URL: http://www.who.int/classifications/icd/en/ [Accessed 2012 Jun 26]
19. CIOMS. Basic requirements for the use of terms for reporting adverse drug reactions. Pharmacoepidemiol Drug Saf 1992; 1: 39-45
20. Almenoff J, Tonning JM, Gould AL, et al. Perspectives on the use of data mining in pharmacovigilance. Drug Saf 2005; 28: 981-1007
21. Evans SJ. Pharmacovigilance: a science or fielding emergencies? Stat Med 2000; 19: 3199-209
22. Barbado FJ, Gómez-Cerezo J, Peña JM, et al. Fever of unknown origin: classic and associated with human immunodeficiency virus infection. a comparative study. J Med 2001; 32: 152-62
23. Barbado FJ, Vazquez JJ, Peña JM, et al. Fever of unknown origin: a survey on 133 patients. J Med 1984; 15: 185-92
24. Colpan A, Onguru P, Erbay A, et al. Fever of unknown origin: analysis of 71 consecutive cases. Am J Med Sci 2007; 334: 92-6
25. de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO): I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997; 76: 392-400
26. Erten N, Saka B, Ozturk G, et al. Fever of unknown origin: a report of 57 cases. Int J Clin Pract 2005; 59: 958-60
27. Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis 1992; 15: 968-73
28. Knockaert DC, Vanneste LJ, Vanneste SB, et al. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. Arch Intern Med 1992 Jan; 152: 51-5
29. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003 Mar; 253: 263-75
30. Larson EB, Featherstone HJ, Petersdorf RG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970-1980. Medicine (Baltimore) 1982; 61: 269-92
31. Liu K-S, Sheng W-H, Chen Y-C, et al. Fever of unknown origin: a retrospective study of 78 adult patients in Taiwan. J Microbiol Immunol Infect 2003; 36: 243-7
32. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40: 1-30
33. Saltoglu N, Tasova Y, Midikli D, et al. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect 2004; 48: 81-5
34. Tabak F, Mert A, Celik AD, et al. Fever of unknown origin in Turkey. Infection 2003; 31: 417-20
35. Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006; 38: 632-8
36. Roush MK, Nelson KM. Understanding drug-induced febrile reactions. Am Pharm 1993; NS33 (10): 39-42
37. Harris LF, Holdsambeck HK. Drug fever: surprisingly common and costly. Ala Med 1986; 56: 19-22
38. Grépinet C, Guillocheau E, Berteloot A, et al. Drug-induced fever during treatment with levofloxacin: a case-report [in French]. Therapie 2008; 63: 341-3
39. Sprague JE, Banks ML, Cook VJ, et al. Hypothalamic-pituitary-thyroid axis and sympathetic nervous system involvement in hyperthermia induced by 3,4-methylenedioxymethamphetamine (ecstasy). J Pharmacol Exp Ther 2003; 305: 159-66
40. Elting LS, Rubenstein EB, Kurtin D, et al. Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. Cancer 1998; 83: 2597-607
41. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity: a review. Med Toxicol Adverse Drug Exp 1988; 3: 376-86
42. Darko W, Medicis JJ, Smith A, et al. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. Pharmacotherapy 2003; 23: 643-50
43. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006; 29: 385-96
44. Mannesse CK, van Puijenbroek EP, Jansen PAF, et al. Hyponatraemia as an adverse drug reaction of antipsychotic drugs: a case-control study in VigiBase. Drug Saf 2010; 33: 569-78
45. Poluzzi E, Raschi E, Motola D, et al. Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. Drug Saf 2010; 33: 303-14
46. Strandell J, Bate A, Hägg S, et al. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009; 68: 427-34

Correspondence: Professor *Thomas Hanslik,* MD, Service de médecine interne-Centre Hospitalier Ambroise Paré, 9 avenue Charles-de-Gaulle, 92100 Boulogne-Billancourt, France.
E-mail: thomas.hanslik@apr.aphp.fr