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Trends in Spontaneous Adverse Drug Reaction Reports to the French Pharmacovigilance System (1986–2001)

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Abstract

Background: The French pharmacovigilance system is based on a network of 31 regional centres located in teaching hospitals and coordinated by the French Medicines Agency ('Agence Française de Sécurité Sanitaire des Produits de Santé' [Afssaps]). Since 1984, they have shared a common database of adverse drug reactions (ADRs) that are spontaneously reported by healthcare professionals. The objective of this study is to describe the characteristics of the reports and the reporting trends in the French pharmacovigilance spontaneous reporting database from 1986 to 2001.

Methods: All the reports from January 1986 to December 2001 were included. Drugs and ADRs were translated to anatomical therapeutic chemical (ATC) codes and MedDRA classifications, respectively.

Results: The total number of reports was 197 580 over the 16-year period, with linearly increase over time. The median (interquartile range [IQR]) age of the patients was 53 (34–70) and the male/female ratio was 0.82. The median (IQR) time between the date of occurrence of the ADR and the date of report was 73 days (34–166). The reporter was a specialist in 74% of the reports and a general practitioner in 17%. The annual rate of reporting according to medical demography strongly increased for the specialists, especially since 1994. At least one ADR was considered as serious in 44.8% of the reports. The ADRs were most frequently related to nervous system drugs (23%), followed by cardiovascular drugs (19%) and systemic anti-infectives (17%). The latter class had the fastest progression mostly due to antiretroviral therapy since 1996. According to the Medical Dictionary for Regulatory Activities (MedDRA) coding, the system organ most often reported was skin and subcutaneous tissue disorders (29%), followed by nervous system disorders (19%), gastrointestinal disorders (12%), blood and lymphatic system disorders (12%), vascular disorders (12%) and general disorders and administration site conditions (12%).

Discussion: All spontaneous reporting systems are affected by under-reporting. One of their goals is to generate early signals, which might be more affected by reporting bias than by under-reporting. Some improvements should be made in the design of the French database, but data collected since 1986 constitute an essential tool for the routine work of the 31 pharmacovigilance centres.

Conclusion: This first description of the data of the French pharmacovigilance database involving all drugs and ADRs shows an increasing tendency to reporting

over time, especially in specialists and for systemic anti-infective drugs. The database that uses hierarchical international classifications for drugs and adverse reactions may be used for further studies and could be the basis for an automatic signal generation system.

Background

One of the goals of pharmacovigilance is to detect new drug-related adverse effects and detect early signals. After many tragedies concerning drug safety during the 20th century, a spontaneous reporting system was set up in France in 1979 with a network of 15 regional centres, which was extended to 29 centres in 1984 and 31 centres in 1994.[1] Since 1984, reporting of adverse drug reactions (ADRs) has been mandatory in France, both for prescribers and marketing authorisation holders.[2] Mandatory reporting was extended to include pharmacists in 1995. The regional centres are coordinated by the French Medicines Agency ('Agence Française de Sécurité Sanitaire des Produits de Santé' or Afssaps). The regional pharmacovigilance centres and Afssaps are connected via a national database that contains ADRs reported by healthcare professionals.[3] All reports are assessed at the level of the regional centres before data capture in the national database using a causality assessment method.[4] The national database was updated in 1985–1986 so that online input became possible and data could be accessed and shared between centres. In 1994–1995, the database structure was revised, mainly by adding new fields, according to the recommendations of the International Conference on Harmonisation (ICH).[5,6]

The objective of this study was to describe the characteristics of the reports and the reporting trends over a 16-year period using the data included in the French pharmacovigilance database from 1986 to 2001.

Material and Methods

Report Collection

The 31 regional centres collect ADR reports and store them in the French pharmacovigilance database after assessing causality for each drug. Pharmacovigilance centres are required to report all serious reactions to the Afssaps within 15 days. ADRs are 'spontaneously' reported to regional centres: there is an official form for healthcare professionals to use for reporting ADRs to regional centres,[7] but any other means of reporting is also acceptable. Regional pharmacovigilance centres also act as drug information centres.

Structure of the Database and Data Collected in the Reports

For this study, all reports that were validated by regional centres from January 1986 to December 2001 in the French pharmacovigilance database were extracted. Three relational tables constitute the majority of the database: the report table, the drugs table and the ADR table. A single report can thus be linked with one or more drugs and with one or more ADRs.

The reports contain fields describing the patient (age, sex, height, weight, place of residence) and the type of reporter (general practitioner [GP], specialist, pharmacist, dentist, paramedic, other), as well as their type of practice (teaching hospital, other hospital, private practice, other).

The date of ADR reporting, date of data capture and ADR outcome are also collected. The seriousness of the ADR is assessed by pharmacovigilance centres before recording in the database, according to the ICH definition.[5]

Each drug considered to be associated with the ADR or not is coded according to a three-level classification (active ingredient, brand name, with or without dose). A maximum of six different drugs can be coded and stored with additional drugs being recorded in the comments section. If more than six drugs are reported, the ones with the higher causality score are coded and stored and the others are put in the comments section. In order to establish a hierarchical coding and to compare data in further studies, Afssaps' drug codes using active ingredients have been translated into anatomical therapeutic chemical

(ATC) codes.[8-10] For each suspected drug, the dose, the dates of beginning of treatment and withdrawal, the frequency and route of administration are collected.

ADRs are coded with the WHO-Adverse Reaction Terminology (WHO-ART). Each ADR is ranked as a primary or secondary effect. For the same reasons, as for the ATC recoding, the ADRs were recoded from WHO-ART to Medical Dictionary for Regulatory Activities (MedDRA), US 5th version coding[11,12] using the translation included with the preferred terms (PTs) or with the high-level terms (HLTs) when the PT was missing. Since 1995, the database also includes the date of occurrence, date of reporting and seriousness of the ADR. The database was imported into the SQL Server database management system (DBMS) and data were checked and corrected if necessary.

For each report, the causality of the drug-ADR combination is assessed using the French method as updated in 1985.[4] Causality is assessed by a medical doctor or a pharmacist in the regional centres. This method is an algorithmic approach that considers the chronological and semiological data contained in the reports, the combination of which results in the classification of the drug's causality for the ADR into five classes: certain, probable, possible, doubtful and excluded. To assess the novelty of drug-ADR pairs, reports are classified into four categories according to bibliographic data: well known (labelled in the summary of product characteristics and/or in reference books); not well known (published once or twice); not described (not mentioned in the above sources); and never described before (not found after an extensive literature search).

Data Analysis

The age-specific reporting rates of adverse reactions were computed according to sex and age by dividing the average number of ADRs in each category (1997–2001) by the number of people according to the last national census (1999). Reports with missing data were not excluded, but missing values were omitted from totals and percentages. Analyses were performed using Stata software version 6.0.[13]

Results

From 1986 to 2001, 197 580 reports were recorded in the French pharmacovigilance database. As shown in figure 1, the number of reports increased linearly over the 16-year period. For example 7264 and 18 253 cases of ADRs were reported in 1986 and 2001, respectively.

The reports over the study period referred to a total of 301 726 ADRs (1333 different ADRs) involving a total of 484 945 drugs (12 005 different drugs) or 566 460 active ingredients (1877 different active ingredients). Each report involved a mean of approximately 1.5 ADRs and 3 active ingredients. When using ADRs recoded using MedDRA's PTs and active ingredients recoded using ATC codes, we obtained 883 829 drug-ADR pairs.

Characteristics of the Reports

The median age of the patients was 53 years old (interquartile range [IQR]) 34–70); 8.3% were <15 years old and 34.7% were >65 years old. Reports related to children <1 year old were 3-fold more frequent than reported related to children 1 or 2 years old (figure 2); half of the reports related to children <1 year old involved children <1 month old and 9% concerned neonates in the first hours of life. Except for children, the patients' reported ages were more often a rounded value (e.g. 40 or 50 years) or an intermediate value of the 10 year intervals (e.g. 45 or 55 years).

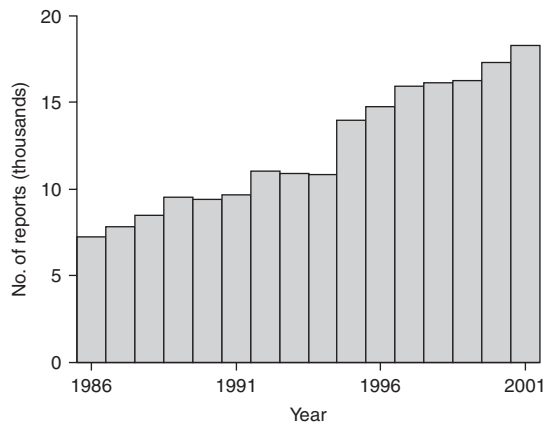

Fig. 1. Evolution of the number of reports in the French pharmacovigilance database (1986–2001).

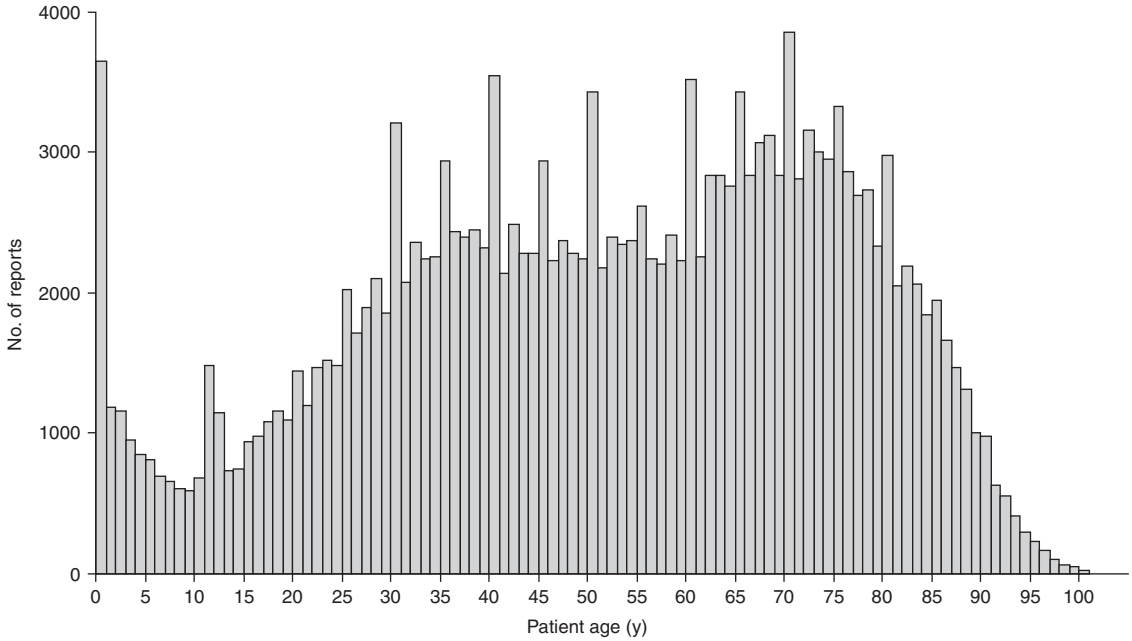

Fig. 2. Distribution of the number of reports in the French pharmacovigilance database (1986–2001) according to patient age.

The male/female ratio was 0.82 in the reports, while the male/female ratio was 0.94 in the French population according to the national census of 1999. For this year, the age- and gender-specific rates of adverse effects reported according to the national census are presented in figure 3. A slight rise in the annual rate was observed with age, both in men and women. Reporting rate for children <1 year was 4-fold the rate for older children.

For the reports transmitted after 1995, dates of occurrence, reporting and capture were considered when available. The median time between the date of occurrence of the ADR and the date of reporting was 73 days (IQR 34–166) [>10 years and negative delays, which represented 0.4% of the reports, were excluded]. The median time between the date of reporting and the date of capture in the database was 19 days (IQR 8–51) [>10 years and negative delays, which represented 0.1% of the reports, were excluded].

The reporter was a specialist in 74% of the reports, a GP in 17%, a pharmacist in 5%, a paramedic in 3% and another type of reporter in <1%. The number of reports according to reporter type was constant over time, except for the specialists. For specialists and GPs, we calculated the annual rate of reporting according to medical demography at the same time. Changes over time of specialist and GP reporting were clearly different: the annual rate decreased slightly for GPs while it increased strongly for specialists, especially since 1994 (figure 4); in 1986 and 2001, 28 and 18 reports, respectively, were made per 1000 GPs, compared with 71 and 133 per 1000 specialists. Reporters came from teaching hospitals (42%), private practice (41%) and non-teaching hospitals (17%).

Characteristics of Drugs

The median number of drugs per report was two (IQR one to four). Only one drug was suspected in 43% of the reports, two in 19%, three in 13%, four in 9% and five or more in 16%. There was no relevant difference in the median number of drugs per report according to patient sex.

The most frequent route of administration of suspected drugs was oral (74%), followed by intravenous (11%), intramuscular (5%), subcutaneous (4%), topical (3%) and other routes (3%). The ADRs were most frequently related to nervous system drugs (23%), followed by cardiovascular drugs

(19%), systemic anti-infectives (including antiretroviral agents and vaccines) [17%] and alimentary tract and metabolism drugs (11%). All other therapeutic classes were less often involved (<6% of the reports). Over the study period, the number of reports related to anti-infectives increased the fastest, i.e. fairly steady till 1991 (4th rank) and then first-ranking in 2001 (figure 5). In 2000 and 2001, >12% of the reports concerned at least one antiretroviral drug. Forty-four percent of the ADRs reported for children <1 year old were associated with systemic anti-infectives and 28.6% with a vaccine.

Characteristics of Adverse Drug Reactions (ADRs)

At least one ADR was considered serious in 44.8% of the reports: 37.3% of the ADRs required hospitalisation or prolongation of an existing hospitalisation, 1.7% resulted in persistent or significant disability/incapacity, 4.1% were life-threatening and 1.7% resulted in death. Fifty-two percent of the cases were not serious and this figure did not change over the study period. The evolution of ADRs was generally good, with 80.6% of patients recovering and 13.1% of patients noted as having improved at the time of reporting and follow-up. On the negative side, 2.46% of patients had sequelae, 1.5% died because of the ADR, 1.2% died possibly of the ADR and 1.1% died from a non-ADR-related cause.

ADRs were initially coded with a PT in 73% of the reports and with a HLT in 27%. This proportion did not change during the study period. The distribution of the number of PTs and HLTs per report was very similar, with 42% with one ADR term per report, 17% with two, 13% with three, 10% with four, 7% with five and 11% with six or more ADR terms for the same report. The most often reported system organ was skin and subcutaneous tissue disorders (29%), followed by nervous system disorders (19%), gastrointestinal disorders (12%), blood and lymphatic system disorders (12%), vascular disorders (12%), general disorders and administration site conditions (12%) and immune system disorders

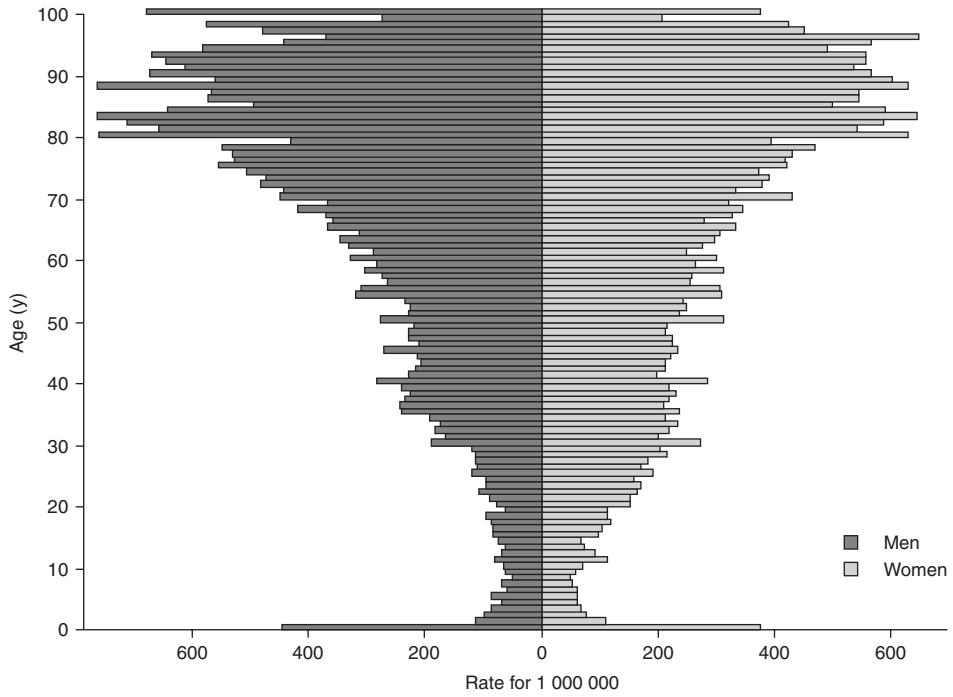

Fig. 3. Patient age-specific rates of adverse drug reactions reported in 1997–2001 (French pharmacovigilance database 1997–2001/ French census 1999).

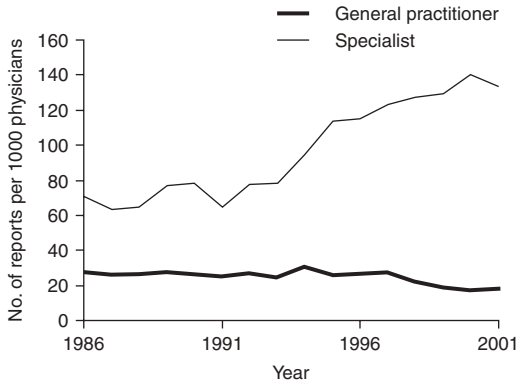

Fig. 4. French pharmacovigilance database (1986–2001): average annual reporting rate per physician per year.

(11%). All other system organs were involved less commonly (< 8%) [figure 6]. Owing to the multiaxial structure of the MedDRA classification and to the fact that the same patient could present with more than one ADR, the sum of the frequencies was >100%.

Characteristics of Drug-ADR Pairs

The causality of an ADR was assessed as certain for 1% of the drugs, probable for 8%, possible for 17%, doubtful for 74% and excluded for 1% of the drugs. The novelty of drug-ADR pairs was as follows: 54% were well known, 15% not well known, 28% not described and 3% never described before. We studied the trends of the assessments made by the centres about the novelty of drug-ADR pairs for the 28 most frequent drug-ADR pairs over the study period (representing 14% of the database). Those assessments remained almost constant over time and even after 10 years or more, a few percent of the pairs were still coded as 'not described' or 'never described before' (data not shown). The level of 'not described' and 'never described before' pairs was very steady: the mean proportion of not described pairs was 8.7% (SD 11.5%) for the 1985–1990 period and 9.2% (10.1%) for 1996–2001, and the mean difference between those two periods for the 24 pairs already present in the earlier years was 1.2% (SD 2.8%).

Considering the HLTs and chemical class, the most frequent pairs were thrombocytopenia with heparin group, followed by rashes, eruptions and exanthema with penicillins with extended spectrum, and metabolic disorders with class III antiarrhythmics (table I).

Discussion

Spontaneous reporting of ADRs is still the most frequently used and efficient method to identify new ADRs after approval,[14,15] but it is hampered by under-reporting (both qualitative and quantitative). Rates of spontaneous reporting of ADRs were studied in France and were usually low (<5%[16-19]). Nevertheless, under-reporting in France does not seem to differ from under-reporting in other countries.[20-22] Spontaneous reporting is neither a convenient system from which to derive information on drug-utilisation, nor information on the real incidence of ADRs. This study only describes trends of the data of the French pharmacovigilance database.

This description of trends in spontaneous reporting in France is the first concerning all drugs and ADRs. The number of reports has steadily increased over the 16-year period. This could be due to an increasing occurrence of ADRs because the number of patients treated has increased, to an increasing occurrence of ADRs in the same number of treated patients, to an increasing rate of reporting with regard to a stable number of ADRs by more safety

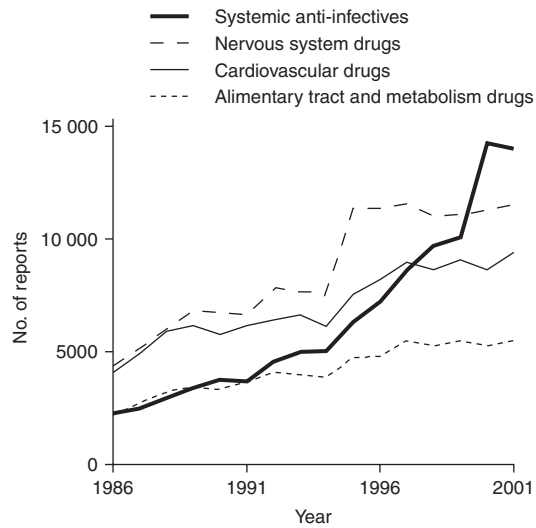

Fig. 5. French pharmacovigilance database (1986–2001): evolution of the four most frequently involved therapeutic classes.

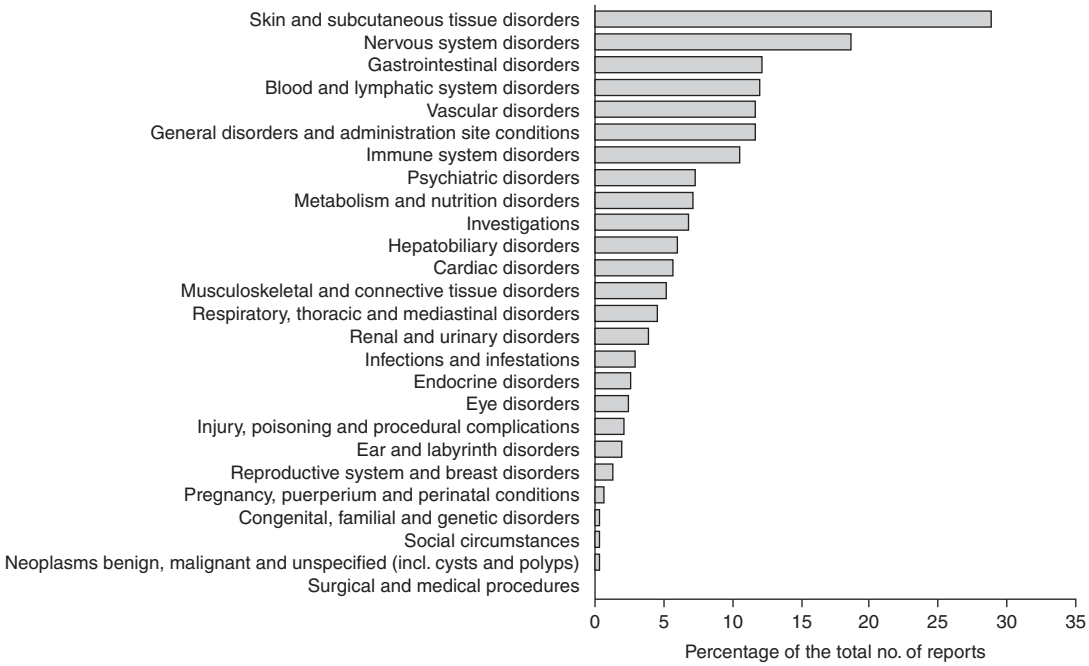

Fig. 6. French pharmacovigilance database (1986–2001): distribution of the System Organ Class (SOC) of adverse drug reactions

conscious physicians (our preferred hypothesis) or to any combination of the above.

The regional pharmacovigilance centres were set up progressively, increasing in number from 6 in 1973 to 15 in 1979, 29 in 1984 and 31 since 1994 (the online database was created in 1984).[1] Good pharmacovigilance practices were written and widely distributed in 1994 to health professionals because of concern over the lack of reporting.[23] However, there seems to be a regular linear increasing trend over time. The annual number of reports is now very similar in France and in the UK (18 314 and 21 171 reports in 2001, respectively).[24]

The median time between the date of occurrence of the ADR and the date of reporting was rather long (73 days). In some cases, reporters wait to get enough information about differential diagnosis, evolution of the ADR, etc. before reporting and if this is the case then it is beneficial overall as it increases the quality of the data. For the very widely publicised drug-ADR pairs, such as hepatitis B vaccination and multiple sclerosis in France, reporting can occur a few years after the use of the drug (in this case, median time between the date of occurrence of the ADR and the date of reporting was 1207 days [IQR 559–2035]).

The distributions of patient age and sex have remained stable over time. The number of reports increases with age, even if placed in the context of the national census. In fact, this tendency might be due to increasing drug use with age, rather than to any specific awareness or specific increased risk in the elderly.[25,26] Proportions of reports involving the youngest children appear to be very similar to the US FDA's spontaneous ADR reports, with 81% of the reports concerning children <1 year old, of which 38% concerned children <1 month old.[27] Several reasons could account for this higher number of reports in infants. They may receive more drugs, including vaccinations, and because of immature detoxification mechanisms they are more prone to experience ADRs and drug-drug interactions. Moreover, some medical errors such as overdosing and accidental exposure may result from limited information about clinical pharmacology and ADRs in the paediatric population[28] or from an inadequate dose for the child's weight. Because of the frequent lack of clinical trials in pediatrics, spontaneous re-

Table I. Most frequent anatomical therapeutic chemical (ATC) chemical class and high-level term (HLT) pairs (data from the French pharmacovigilance database 1986–2001).

Adverse drug reaction	Drug	ATC	No. of reports	% of the reports[a]
Thrombocytopenias	Heparins	B01AB	2987	1.51
Rashes, eruptions and exanthems NEC	Penicillins with extended spectrum	J01CA	2015	1.02
Metabolic disorders NEC	Antiarrhythmics, class III	C01BD	1331	0.67
Urticarias	Penicillins with extended spectrum	J01CA	1314	0.67
Erythemas	Penicillins with extended spectrum	J01CA	1267	0.64
Rashes, eruptions and exanthems NEC	Anilides[b]	N02BE	1153	0.58
Dyskinesias and movement disorders NEC	Propulsives[c]	A03FA	1128	0.57
Liver function analyses	Anticholinesterases	N06DA	1107	0.56
Renal failure and impairment	ACE inhibitors, plain	C09AA	1037	0.52
Urticarias	Anilides[b]	N02BE	1000	0.51
Coagulation and bleeding analyses	Vitamin K antagonists	B01AA	979	0.50
Tendon disorders	Fluoroquinolones	J01MA	972	0.49

a Because individual reports may contain more than one HLT-ATC pair, the sum of all percents would be >100%.

b Anilides include paracetamol (acetaminophen), phenacetin, bucetin and propacetamol.

c Propulsives include metoclopramide, cisapride, domperidone, bromopride, alizapride and clebopride.

NEC = not elsewhere classified.

porting is a valuable source of information on the risk of drugs in this age class.[27] Reports related to neonates in the first hours of life also include neonatal effects of drugs given to the mother (fetal abnormalities and perinatal events).

The over-representation of ages with a rounded value is typically a reporting problem that could bias analyses. The date of birth was removed from the database at the request of the French Data Protection Act. Children are probably not affected by this because all prescriptions for children must include their age.

As shown in some previous studies, more reports involve female than male patients regardless of the male/female ratio in the population. The possible explanations given were the higher drug utilisation and consulting rate for women than for men in general practice and the lower body size and weight in women.[29,30]

This study only concerns the spontaneous reporting by healthcare professionals and does not include reports coming through industry or directly from patients.

The number of reports from GPs remained very low and stable over time, which is usual.[19] Ninety-one percent of reports came from physicians (GPs or specialists). It is not the case in some other countries because ADRs are mainly reported by pharmacists[31] or are reported to the industry[32] or because patients are encouraged to self report.[33,34]

Characteristics of Drugs

The mean number of drugs per report was 2.46 and this needs to be compared to real consumption data to put it into perspective. To do this, data on the consumption of drugs in France in 2000 stratified by age[35] was adjusted to the age structure of the patients involved in the French pharmacovigilance reports. The estimated mean number of drugs per patient in our database was 3.0. This 'under-reporting' of the drugs used by the patient might be an 'under-capturing' because some regional centres only record drugs considered as suspect. The dramatic increase of the number of reports concerning anti-infectives is mostly due to the introduction of antiretroviral drugs after 1996.

Characteristics of ADRs

Concerning the level of coding for ADRs, PTs (which are more precise and in accordance with recommendations) are used 3-fold more often than HLTs. HLTs might be used to describe a syndrome or a disease rather than a set of symptoms (for instance hepatitis rather than jaundice, asthenia, rise in aminotransferase levels, etc.).

Characteristics of Drug-ADR Pairs

The French causality assessment method is to use two scores instead of combining the bibliographic knowledge in the causality assessment as other methods do and the scoring is not always convergent.[36] Most of the drug-ADR pairs had a low causality score (75% were assessed as doubtful or excluded). Drug-ADR pairs can be reported even if the confidence in the causality is low because all the drugs used at the time of the ADR should be reported. A previous study showed marked differences between physicians' opinions about causality of the drug for the ADR reported and the causality assessment made by the regional centre where those ADRs were reported.[37] Physicians assessed the causality of the drug-ADR pair as certain or probable in 60% of the pairs, compared with 9% after the causality assessment by the regional centre. In France, the causality assessment is made by a trained medical doctor or pharmacist at the level of the regional pharmacovigilance centres, not by the health professional reporting the case.

The bibliographic scores showed that 69% of the drug-ADR pairs were already well known at the time of occurrence. The very steady level of the most frequent 'never described before' pairs was surprising because they were expected to decrease within few years. We only focused on the most frequent pairs to obtain trends over the study period (all the pairs corresponding to >500 reports) that corresponded to very well known pairs. Therefore, the bibliographic scores were high since the beginning of the period. The relatively high level of pairs classified as 'never described before' after many years might be due to a lack of homogeneity in bibliographic scoring between regional centres. Another possible explanation could be a mistake in the design of the French database: the same score is linked to other ADRs if more than one is associated with the considered drug. This would have to be corrected in a future database. If possible, bibliographic score should be consensual at a given time and thus its coding could be centralised.

The number of drugs captured for the same report should not have any limitations. More capture controls should be added to minimise the number of mistakes at the recording time. The date of birth should be included again instead of the age. Drugs should be directly coded with a hierarchical international classification.

Independent of these technical problems, the limitations of the present study are mainly those related to the limitations of the spontaneous reporting system itself (under-reporting, reporting biases and absence of information on population exposure).

Despite the limitations described here and possible improvements, the French pharmacovigilance database constitutes an essential tool for routine practice with a quality control provided at each reporting stage: only healthcare professionals can report and causality criteria are assessed for each drug-adverse reaction pair by pharmacovigilance professionals.

Conclusion

The present description of the whole French pharmacovigilance database shows a trend to increased reporting over time, especially by specialists and for systemic anti-infective drugs. There has been no significant change according to other characteristics, in particular the seriousness of ADRs. The transcodification of the database with hierarchical international classifications for drugs and ADRs makes the analysis of grouped data easier (e.g. for a therapeutic class or for a system organ class). This database may be used for further studies and for automatic signal generation system if the classifications mentioned previously are used.

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