ORIGINAL RESEARCH ARTICLE

Drug Safety 2009; 32 (5): 429-440
0114-5916/09/0005-0429/$49.95/0

Avoidability of Adverse Drug Reactions Spontaneously Reported to a French Regional Drug Monitoring Centre

Annie Pierre Jonville-Béra,[1] *Hassan Saissi*,[1] *Lamiae Bensouda-Grimaldi*,[2] *Frederique Beau-Salinas*,[1] *Haware Cissoko*,[1] *Bruno Giraudeau*[3] and *Elisabeth Autret-Leca*[2]

1 Pharmacoepidemiology and Clinical Pharmacology Unit/Regional Drug Monitoring Centre, CHRU de Tours, Tours, France
2 Pharmacoepidemiology and Clinical Pharmacology Unit/Regional Drug Monitoring Centre, Université François Rabelais Tours, CHRU de Tours, Tours, France
3 INSERM, CIC 202, Université François Rabelais Tours, CHRU de Tours, Tours, France

Abstract

Background: Adverse drug reactions (ADRs) are now recognized as a major category of iatrogenic illness in terms of morbidity and mortality.

Objective: To describe the type and frequency of avoidable ADRs spontaneously reported to a regional drug monitoring centre following inappropriate prescribing, as a basis for preventive actions.

Methods: A prospective, observational study of ADRs reported to the Regional Drug Monitoring Centre of Tours, France, between 26 November 2002 and 28 November 2003. The outcome measure was ADRs secondary to inappropriate prescribing that were defined as entirely or partly avoidable, i.e. at least one of the recommendations in various sections of the summary of product characteristics (SPC; indication, route of administration, dose, duration of treatment, dose adaptation, precautions for use, monitoring of treatment, absolute contraindications and contraindicated interactions) had not been respected. The link between the lack of conformity of the drug prescription with the SPC and occurrence of the ADR was evaluated by a working group using two criteria: (i) is nonconformity of the prescription of this drug a known and validated risk factor for this ADR?; and (ii) are there other aetiologies or other risk factors for this ADR?

Results: Three hundred and sixty ADRs in 294 adults and 66 children were analysed. The prescription was considered inappropriate for 213 of the 659 (32%) drugs implicated in ADRs, corresponding to 161 patients (45%). The ADR was adjudged entirely avoidable for 32 (9%) patients, partly avoidable for 28 (8%) patients and unavoidable for 300 (83%) patients. Not taking into account a history of allergy or altered renal function and not respecting the recommended dose were the most frequent causes of entirely avoidable ADRs. Allopurinol and lamotrigine were the drugs most frequently involved in serious avoidable ADRs.

Conclusions: Preventive actions should focus on more systematic allergy checks when prescribing drugs and on dose adaptation in cases of altered renal function.

Background

Adverse drug reactions (ADRs) are one of the most important categories of iatrogenic illness in terms of morbidity and mortality. In France, between 32% and 80% of ADRs may be considered avoidable, depending on the site and criteria used to define the avoidability of ADRs (including whether the prescription was actually needed and administration errors).[1-4] As a consequence, reducing the number of avoidable undesirable effects of care, and ADRs in particular, was identified as a priority by the French national health conference in 2004.[5]

Avoidable ADRs may result from several levels of error during the process of drug treatment, i.e. prescribing, transcription/interpretation, dispensing and administration errors, with the last three of these types of errors considered distribution errors. Detailed analysis of medication errors reveals that the most serious ADRs are associated with prescriptions made by physicians.[6] These ADRs may be classified as avoidable if there was an alternative therapy at least as effective as the prescribed medication but with lower toxicity, or if the prescription did not meet the recommendations given in the product's authorization for market release (i.e. 'off label' drug use). The first of these two issues involves the pertinence of drug choice (appropriateness) with respect to other possible treatments and drugs and on the basis of the most favourable benefit/risk ratio. This aspect can be analysed only by detailed discussion with the prescriber. The second situation is easier to analyse if the prescription conditions are known and can be compared with the summary of product characteristics (SPC). The SPC is an appendix of the product's authorization for market release specifying the indications, contraindications, modes of use (dose, route of administration, duration of treatment, precautions for use, etc.) and undesirable effects of the drug.

According to French law, physicians must report 'serious' ADRs (those resulting in death, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity or that are life-threatening) or 'unexpected' ADRs to their regional drug monitoring centre (RDMC). The 31 RDMCs collect ADR reports on a standard form. These ADR reports are analysed by the RDMC – using the French method for assessing imputability[7] to evaluate the relationships between ADRs and drugs – and are then transmitted to the French health authorities.

In a previous study[8] of 182 ADRs reported to the RDMC of Tours, drugs for which one or several of the recommendations in the SPC (drug interactions, contraindication, indication not listed in the authorization for market release, inappropriate dose or treatment duration) had not been respected were found to be more frequently involved in ADRs than drugs correctly prescribed (76% vs 57%; $p < 0.0001$). These findings led us to conduct a second, prospective study, based on the nonconformity of a drug prescription with SPC recommendations (or inappropriate prescribing) as an indicator of the avoidability of ADRs. The identification of such ADRs is important for the guidance of educational programmes aiming to decrease the number of avoidable ADRs.

The aim of this study was to identify and describe avoidable ADRs secondary to inappropriate prescribing (nonconformity of drug prescription with SPC recommendations).

Methods

Setting

We carried out a prospective study to define a basis for preventive action in our region that includes a large region around Tours, France, with a population of 1 854 000 people. All the ADRs reported to the RDMC of Tours over a 1-year

period (from 26 November 2002 to 28 November 2003) were included.

Data Collection

ADRs for which causality was considered certain, probable/likely or possible were included in the study. We excluded ADRs for which too little information was available to assess the conformity of the prescription to the SPC, ADRs declared more than 1 year after their occurrence and ADRs following errors in drug administration or self-medication.

For each ADR, we compiled a file including information about patient characteristics (age, sex and medical history), the ADR (description, differential diagnoses, severity, outcome), clinical investigations and drugs taken by the patients at the time of or just before the occurrence of the ADR (indication, dose, dates of start and end of treatment). In addition to the information routinely collected, information was collected to estimate the conformity of the prescription to the recommendations of the SPC. This additional information was collected via telephone at the time the initial ADR report was made, followed by a telephone call to the prescriber of the drug if any information was missing. Information collected included the characteristics of the patient (age, renal function, hepatic function, medical history, including previous occurrence of similar adverse events) and whether dose adaptation and/or particular monitoring procedures recommended by the SPC (e.g. platelet counts, hepatic function tests, etc.) had been followed.

Data Analysis

For each ADR, the role of each drug taken by the patient was classified as 'likely', 'unlikely', 'unclear' or 'excluded', using the French method for determining imputability,[7] plus, for certain ADRs, criteria defined by published consensus conferences.[9-14]

Only drugs for which involvement in the ADR was not classified as 'excluded' were retained for the analysis of conformity of drug prescription with the SPC. For these drugs, we analysed the sections of the SPC dealing with indications, route of administration, dose, duration of treatment, dose adaptation, precautions, treatment monitoring, absolute contraindications and contraindicated interactions. The drug was defined as inappropriately prescribed if the recommendations in one or more of these sections had not been respected.

The extent to which the ADR was avoidable – the link between the lack of conformity of the drug prescription with the SPC and occurrence of the ADR – was evaluated by a working group consisting of two pharmacologists and a clinician (EAL, APJB, HS), using predefined criteria. We classified an ADR as avoidable only if the nonconformity of the prescription with the SPC was a known and validated risk factor for this ADR (figure 1). For example, the development of a rash in a child treated with a drug with no approved paediatric indication was not classified as avoidable. ADRs for which no other risk factors and no other possible aetiology could be identified were classified as entirely avoidable and ADRs for which another risk factor or another possible aetiology could be identified were classified as partly avoidable.

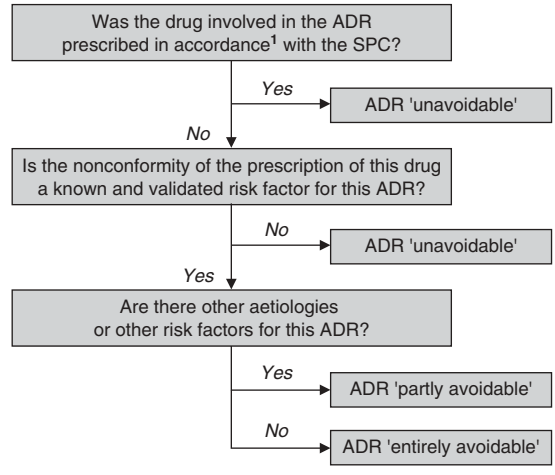

Fig. 1. Criteria used to evaluate the avoidability of each adverse drug reaction (ADR). **1** In accordance with the sections of SPC: indication, route of administration, dose, treatment duration, dose adaptation, precautions for use, treatment monitoring, absolute contraindications and contraindicated interactions. **SPC** = summary of product characteristics (in the Vidal® Dictionary 2002.[15])

Results

In the 1-year period studied, 440 ADRs were reported to the RDMC of Tours. Eighty of these ADRs were not included in the study because the time between the ADR and submission of the report was too long (n = 29), information required for estimating the conformity of the prescription to the SPC was lacking (n = 26), or because they were secondary to self-medication (n = 13), secondary to use of a drug without product authorization for market release (n = 7) or secondary to an administration error (n = 5). Thus, 360 ADRs, in 360 patients, were included in the analysis.

Characteristics of the Adverse Drug Reactions

ADRs were reported to the RDMC by a healthcare professional from the regional university hospital in 182 cases (51%), from another hospital in 81 cases (23%), by a doctor in private practice in 93 cases (26%) and by someone else in 4 cases (1%). The person reporting the ADR was a specialist in 278 cases (77%), a general practitioner in 59 cases (16%) and another healthcare professional in 23 cases (6%).

ADRs were reported in 294 adults (82%), with a mean age of 55.2 ± 19.2 years and in 66 children. The age distribution of the affected children was as follows: 12 neonates (<28 days; 18%), 19 infants (1 month to 2 years; 29%) and 35 children (>2 years; 53%). The mean age of the children was 8.5 ± 4.5 years. In total, 167 of the patients were male (46.4%).

The most frequently reported ADRs were cutaneous (22%), haematological (10%), hepatic (9%), digestive (7%), cardiovascular (7%), osteomuscular (5%), neurological (5%), respiratory (4%), urogenital (4%) and endocrine (4%).

For the 358 ADRs for which information was available, 174 (49%) were considered serious. The outcome, which was known for 291 patients, was cure in 265 patients (74%), sequelae in 11 patients (3%) and death in 15 cases (4%), 13 of which were linked to the ADR.

Analysis of the Conformity of Drug Prescription with Summary of Product Characteristics Recommendations

At the time of the ADR, the 360 patients were taking a total of 1430 drugs (median of three drugs per patient; range 1–17). The involvement

Table I. Therapeutic classes of drugs involved in adverse drug reactions and not prescribed in accordance with the summary of product characteristics (SPC)

Therapeutic class	Total no. of drugs (n = 659)	Drugs not prescribed in accordance with the SPC (n = 213) [no. (%)]
Infectious/parasitic diseases	164	44 (27)
Cardiology/angiology	61	15 (25)
Psychiatry	59	13 (22)
Oncology/haematology	50	19 (38)
Anti-inflammatory drugs	48	22 (46)
Neurology	38	18 (47)
Analgesics, antipyretics	34	4 (1)
Gastroenterohepatology	32	12 (38)
Rheumatology	23	16 (70)
Haemostasis	22	8 (36)
Metabolism/diabetes/nutrition	17	9 (53)
Blood products	16	9 (56)
Pneumology	15	8 (53)
Gynaecology/obstetrics	13	3 (23)
Other	38	13 (34)

Table II. Type of inappropriate prescribing of the 213 drugs not prescribed in accordance with the summary of product characteristics (SPC)

Type of inappropriate prescribing	No. of instances of inappropriate prescribing (%) [n = 278[a]]	Main reasons implicated (no.)
Indication not approved	85 (30)	Indication not listed in product's authorization (64) Preventive rather than curative treatment (16) First-line rather than second-line treatment (3) Not prescribed in association with the recommended drug (2)
Precaution for use not respected	65 (23)	Continuation of treatment after the occurrence of the ADR (12) Recommended supplementation not given (9) Combination of drugs that should not be given together (8) Recommendations for administration not respected (6) Examinations not carried out before treatment (6)
Dose not respected	42 (15)	Dose too high (23); dose too low (5) Dose schedule not respected (13) No loading dose given (1)
Dose not adapted	24 (9)	Dose not appropriate for renal function (22) Dose not modified despite combination with another drug (2)
Absolute contraindication not respected	27 (10)	History of allergy to the drug (8) Contraindicated for reasons of age (5) Contraindicated due to severe renal insufficiency (5) Contraindicated due to the context (infection etc.) (4)
Treatment duration not respected	18 (7)	Duration of treatment longer than recommended (18)
Recommended monitoring not carried out	13 (5)	No haematological monitoring (4) No hepatic monitoring (4) No renal monitoring (3) No clinical monitoring (2)
Administration route not respected	4 (1)	Subcutaneous rather than intravenous administration (4)

a Two hundred and thirteen drug treatments were not prescribed in accordance with the SPC. For 161 drugs, only one section of the SPC was not respected, for 40 drugs two sections were not respected, for 11 drugs three sections were not respected and for 1 drug four sections were not respected. Therefore, 278 instances of nonconformity with the SPC were detected.

ADR = adverse drug reaction.

of the drug in the ADR was excluded (not related) for 771 drugs (54%), considered unclear for 204 drugs (14%), unlikely for 159 drugs (11%) and likely for 296 drugs (21%). The analysis of the conformity of drug prescription with the recommendations of the SPC focused on these last three groups, corresponding to 659 drug treatments.

Of these 659 drug treatments, 213 (32%), corresponding to 161 patients (45%), were not prescribed in accordance with the SPC. For 161 drugs only one section of the SPC was not respected, for 40 drugs two sections were not respected, for 11 drugs three sections were not respected and for 1 drug four sections of the SPC were not respected. Therefore for 213 drugs, 278 instances of nonconformity to the SPC were detected. The number of drugs taken at the time of the ADR (median of five) was greater in these 161 patients than in the 199 patients for whom all drugs were prescribed in accordance with the recommendations of the SPC (median of three drugs; Wilcoxon's rank sum test $p < 0.001$). The proportion of patients for whom at least one drug was not prescribed in accordance with the SPC was lower for neonates (25%) than for infants (42%), children (49%) and adults (45%). Therapeutic classes of drugs involved in ADRs (i.e. not classified as excluded) and inappropriately prescribed are presented in table I.

The most frequent types of inappropriate prescribing were 'indications not approved' and 'precautions for use not being respected' (table II).

Analysis of Avoidable ADRs

The ADR was considered entirely avoidable in 32 cases (9% of patients), partly avoidable in 28 cases (8% of patients) and unavoidable in 300 cases (83% of patients) [figure 2]. The entirely

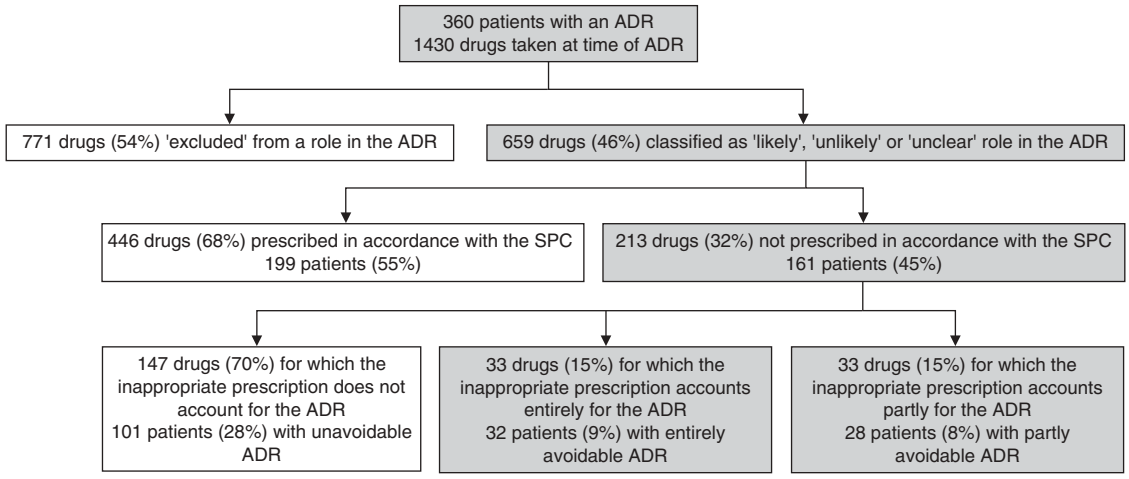

Fig. 2. Analysis of avoidability of adverse drug reaction (ADR). **SPC** = summary of product characteristics (in the Vidal® Dictionary 2002[15]).

avoidable ADRs, 16 (50%) of which were serious, involved 22 adults and 10 children. Their outcome was known in 29 cases: cure (26 cases), sequelae (2 cases: pulmonary fibrosis secondary to continuous nitrofurantoin treatment in one case and abnormal ossification of the skull and anamnios in a neonate exposed *in utero* to candesartan until 31 weeks of gestation in the other) and death (a drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome secondary to treatment with an inappropriate dose of allopurinol in a patient with renal insufficiency) in one case. The partly avoidable ADRs involved 22 adults and 6 children. Their outcome was known in 24 cases: cure (22 cases) and death (lactic acidosis during metformin treatment in a context of infection and renal insufficiency; severe infectious complication in a patient treated with adalimumab) in two cases. The most frequent types of inappropriate prescribing of the drugs responsible for an entirely avoidable ADR were a contraindication or a precaution for use not being respected (table III). These causes include not taking into account a history of allergy to the specific drug (19% of entirely avoidable ADRs) or altered renal function (16%). Allopurinol was the drug most frequently implicated among those involved in more than one entirely or partly avoidable ADR (table IV).

Discussion

In our study, 32% of the drugs implicated in ADRs were inappropriately prescribed, as defined by drug use beyond the recommendations of the SPC. This incorrect drug use was implicated in the occurrence of the ADR in 9% of patients. Not taking into account a history of allergy to the specific drug or altered renal function and not respecting the recommended dose were frequently responsible for entirely avoidable ADRs. Avoidable ADRs of iatrogenic origin should be the subject of preventive actions. This would involve an analysis of the circumstances favouring the occurrence of the ADR, so as to identify situations associated with higher risk. As our ultimate aim was to improve the training of doctors concerning prescription practice, we deliberately excluded drug delivery and administration conditions from our analysis. We also included no consideration of the pertinence of the prescription (appropriateness of choice of treatment or drug) in this analysis of medical interventions, because such analyses are based on less objective criteria.

There is currently no consensus definition of an 'avoidable' ADR and no internationally validated tool for measuring avoidability. In the principal studies carried out, in which the proportion

of avoidable ADRs varies between 13% and 83%,[16,17] the avoidability or preventability of ADRs is evaluated by two methods: subjective analysis by one or several experts of the conditions in which the ADR occurred (implicit criteria),[18-22] or the use of predefined criteria (explicit criteria).[23-28] These predefined criteria often take into account the appropriateness of the prescription, respect of conditions for use (particularly as a function of age, weight and

Table III. Type of inappropriate prescribing of the 32 drugs involved in adverse drug reactions (ADRs) classified as entirely avoidable; serious ADRs are shown in italics

Type of inappropriate prescribing (no.)	Drug	ADR	Reason the prescription was inappropriate
Absolute contraindication (10)	*Colchicine*	*Medullary aplasia*	*Severe renal insufficiency*
	Candesartan cilexetil	*Anamnios*	*Continuation of treatment until wk 31 of pregnancy*
	Levonorgestrel implant	*Late miscarriage*	*Implantation on day + 8 of the cycle*
	Cefotaxime	*Quinke's oedema*	*History of allergy to cefotaxime*
	Tiaprofenic acid	*Anaphylactic shock*	*History of allergy to aspirin (acetylsalicylic acid)*
	Amoxicillin	Massive urticaria	History of allergy to amoxicillin
	Fluindione	Maculous rash	History of skin rash
	Imatinib	Photosensitive reaction	History of photosensitivity on imatinib
	Infliximab	Malaise, shivering	Clinical manifestations during previous treatments
	Ketoprofen gel	Photosensitivity	Exposure to sunlight
Precautions for use (7)	*Oxaliplatin*	*Quinke's oedema*	*Signs of allergy during previous treatment*
	Zoledronic acid	Hypocalcaemia	Non-monitoring of calcaemia despite renal insufficiency
	Immunoglobulins	Fever	Perfusion flow rate too fast
	Immunoglobulins	Lumbar pain	Perfusion flow rate too fast
	Escitalopram	Hyperglycaemia	No adjustment of insulin treatment
	Carbamazepine	Diplopia, dizziness	Combination with dextropropoxyphene
	Indinavir	Inefficacy in interaction	Combination with an enzyme inducer (bosentan)
Dose not respected (5)	*Pyrimethamine*	*Pancytopenia*	*Dose too high with no folinic acid supplementation*
	Metoclopramide	*Methaemoglobinaemia*	*Dose too high*
	Lamotrigine	*Facial oedema*	*Initial dose too high*
	Salbutamol	Ventricular extrasystole	Dose too high
	Pimozide	Extrapyramidal *syndrome*	Dose too high
Administration route not respected (4)	Ceftriaxone	Pain at the site of injection	Subcutaneous rather than intravenous administration
Lack of dose adaptation (4)	*Allopurinol*	*DRESS syndrome* *Medullary aplasia* *Stevens-Johnson syndrome*	*No adaptation for renal function* *No adaptation for renal function* *No adaptation for renal function*
	Lamotrigine	*Skin rash*	*High dose and combination with valproic acid*
Inappropriate duration of treatment (2)	*Nitrofurantoin*	*Pulmonary fibrosis*	*Continuous treatment for 3 years*
	Niflumic acid	*Bleeding, digestive ulcer*	*Prolonged treatment (10 days rather than 5 days)*
Indication not listed in SPC (1)	*Methylprednisolone*	*Anaphylactic shock*	*Injection for a wasp sting without clinical signs*

DRESS = drug rash with eosinophilia and systemic symptoms; **SPC** = summary of product characteristics.

Table IV. Drugs involved in more than one entirely or partially avoidable adverse drug reaction (ADR; n = 60)

Drug involved in the ADR	No. of cases	Type of inappropriate prescription (no.)
Allopurinol	6	No adaptation for renal function (5) Treatment continued after occurrence of ADR (1)
Ceftriaxone	5	Incorrect administration route (4) Treatment continued after occurrence of ADR (1)
Lamotrigine	3	Initial dose too high (2) Dose schedule not respected (1)
Polyvalent immunoglobulins	3	Perfusion flow rate too fast (3)
Metformin	2	Contraindication not respected (2)
Fluindione	2	History of allergy (1) Not recommended in cases of renal insufficiency (1)
Vancomycin	2	High dose (1) Dose not adapted for renal function (1)
Isotretinoin	2	Recommendations for administration not respected (2)

associated diseases), respect of the recommended clinical and/or biological monitoring procedures, history of allergy or drug intolerance, excessively high plasma concentrations and patient compliance. Other studies have also taken into account a lack of patient information,[29] respect of the SPC[30] and mode of administration.[31] The first French scale, based on a critical analysis of pharmacovigilance experiences, proposes a scheme to evaluate the degree of avoidability of adverse drug effects.[32] This scheme contains three groups of items concerning the drug, the patient and the prescription. It assesses the prescription and the therapeutic approach used for a specific patient within the context of medical knowledge as well as the risk factors presented by the patient. This scale has been developed further, but additional improvements are required to meet all the criteria of validity for a measurement scale.[33]

In this study, the most frequent causes of entirely avoidable adverse drug reactions were failure to take into account a history of allergy to the specific drug, and the prescription of too high a dose. Such errors are also known as medication errors. According to the definition accepted by the US National Coordinating Council for Medication Error and Prevention: ''A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.''[34] Under this definition, all ADRs that can be explained by the use of the drug without following the recommendations of the SPC (as defined in our study) may be considered medication errors, because they are preventable (i.e. they would not have occurred if the prescriber had prescribed the drug in accordance with the SPC).[34] As claimed by Bates et al.,[21] ''all unprevented adverse events are errors''. In other words, it may be considered erroneous not to prevent an adverse effect if that event could be prevented.

In French studies focusing on iatrogenic effects, the proportion of ADRs adjudged avoidable has been estimated at between 9% and 73%.[1-4,35-38] It is difficult to compare the proportion of avoidable ADRs in our study with those in other studies because, to our knowledge, no other study with a similar design (i.e. based on spontaneously reported cases) has been reported, and because only the conformity of the prescription of the drug implicated was taken into account. However, this incidence is higher than that reported in another French study assessing the prevalence of ADRs on a given day in a representative sample of 2132 patients hospitalized in France.[39] On the day of the survey, 221 patients had an ADR (10.3% prevalence) and the

drug had not been prescribed in accordance with the SPC in 13 of these patients (5.3%)

Entirely avoidable ADRs did not differ from partly avoidable and unavoidable ADRs in terms of their severity (53% vs 48% serious ADRs; 3% vs 4% resulting in death) or the age of the patients affected (mean of 61 vs 55 years). Due to differences in data sources and methodology, we cannot compare this finding with previous reports, in which the incidence of avoidable ADRs was greater in subjects aged >65 years.[40-43] This greater incidence of avoidable ADRs in older patients was observed despite greater attention on the part of prescribers: a previous study reported that general practitioners collect more data if there are risk factors for undesirable effects when dealing with the elderly, to ensure that the prescription is appropriate.[44] In children, the incidence of avoidable ADRs in our study was higher than that in adults (10/66 [15%] vs 22/294 [7%]) and was similar to that reported by Temple et al.[45]

Our finding that the two most frequent causes of entirely avoidable ADRs were failure to take a history of allergy to the specific drug into account and the prescription of too high a dose as a consequence of the absence of dose adaptation in cases of altered renal function, is consistent with previous studies.[3,27,40] Ignoring a history of allergy is identified as the likely cause of ADRs in 1–13% of all avoidable ADRs.[27,45-50] As in our study, these errors are mostly associated with the prescription of antibacterials.[46,47] The administration of an inappropriate dose is frequently implicated in avoidable ADRs.[16,27,31,46,50,51] The dose may initially have been too high or inappropriate for the patient concerned, particularly in terms of renal function.[31,46] Failure to adapt the dose is frequent, particularly for elderly subjects with moderate renal insufficiency occurring insidiously during chronic treatment, with creatinaemia within the normal range but low creatinine clearance.[52] Fauchais et al.[53] showed that 40% of the 58 ADRs affecting study patients aged >75 years could have been avoided if renal function had been monitored regularly. In two other French studies,[54,55] the prescribers were not sufficiently aware of the requirement for dose adjustment of the drug in subjects with altered renal function and underestimated the consequences of not considering impaired renal function when prescribing. The major role of dose adaptation to renal function is illustrated by allopurinol, the drug most frequently implicated in avoidable ADRs in our study. Failure to adapt the dose of allopurinol to renal function has been found to be frequent in other studies,[56,57] and may lead to serious ADRs, including, in particular, DRESS syndrome.[58-60] DRESS is a severe reaction and the most common triggering agents are antiepileptic drugs, sulfonamides and allopurinol. Patients may have diffuse skin reactions, periorbital or facial oedema, fever, lymphadenopathy, organ dysfunction and leukocytosis. DRESS syndrome triggered by allopurinol has several unusual clinical features, and mortality rates may reach 25%. The exact mechanism underlying the development of allopurinol DRESS syndrome is unknown, but the accumulation of oxypurinol (the principal metabolite of allopurinol) in renal insufficiency is considered a crucial factor.[61,62]

In our study, lamotrigine was also implicated in several avoidable ADRs, as the cutaneous complications of treatment with this drug, which may be serious, are also worsened by a lack of respect for the dose schedule or by a failure to decrease the dose for patients also treated with valproic acid.[63]

Several limitations of our study should be noted. First, the major limitation of our study – which was based on spontaneous reporting of ADRs – was the well known under-reporting of ADRs. Estimation of the actual incidence of ADRs following off-label drug use requires the identification of all cases of off-label prescribing in a given setting and follow-up of the patients to see how many ADRs occur. As the denominator for off-label use is unknown, we cannot provide a general estimate of the incidence of ADRs following off-label use. The collection of ADR data through spontaneous reporting by healthcare professionals, rather than by systematic collection in a hospital department, made it possible to include several prescription situations, but may have led to underestimation of the incidence of

ADRs following inappropriate prescriptions (whether deliberately so or not). Such ADRs may be less readily declared to the RDMC, particularly if they are serious. Second, the study was restricted to the data for 1 year. However, given the estimated incidence of avoidable ADRs reported, the sample was sufficiently large to detect the most frequent situations in which inappropriate prescribing led to avoidable ADRs. Third, data from only one regional drug monitoring centre were included. However, the ultimate objective was to define the basis for regional preventive actions to reduce ADRs secondary to inappropriate prescribing. As medical practices and the profile of patients may differ between regions, it seemed appropriate for our aims to limit the collection of data to our region, to guide appropriate training. Thus, the results of this study should not be simply extrapolated to the rest of France. Fourth, the prescriber may, in certain circumstances, be unable to follow the recommendations of the SPC, and our study was unable to distinguish such deliberate acts from inadvertent non-respect of the SPC. Finally, retrospective analysis of the prescription may have resulted in some cases of nonconformity not being identified, as it was not always possible to contact the prescriber and, in cases of doubt, prescriptions were systematically considered to be compatible with the SPC for the evaluation of avoidability.

Conclusions

This study identifies elements that can be used to target preventive actions to decrease the incidence of avoidable ADRs. Training for doctors in our region could focus on two areas: (i) detailed interviewing of patients on their history of drug allergies and possible episodes of intolerance during prior treatment; and (ii) the screening of elderly subjects for changes in renal function through the regular evaluation of creatinine clearance (Cockcroft's formula) and, in cases in which creatinine clearance is <60 mL/min, systematic checking, before prescription or represcription of a drug, that dose adaptation is not required and that the drug is not contraindicated.

Acknowledgements

This study was funded by a Regional Clinical Research Hospital Programme (CRHP) grant from the University and Regional Hospital of Tours, Tours, France. The authors have no conflicts of interest directly relevant to the content of this study.

References

1. 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
2. Olivier P, Boulbès O, Tubery M, et al. Evitabilité des effets indésirables dans un service d'admissions médicales. Therapie 2001; 56: 275-8
3. Bannwarth B, Queneau P, Carpentier F, et al. Hospital visits caused by adverse drug reactions. Drug Saf 2003; 26: 133-4
4. Peyriere H, Cassan S, Floutard E, et al. Adverse drug events associated with hospital admission. Ann Pharmacother 2003; 37: 5-10
5. Law no. 2004-806 of August 9, 2004 relating to the policy of public health. Hundred objectives of public health. J Off Repub Fr Ed Lois Decrets 2004 Aug; (185): 14277
6. Thürmann PA. Prescribing errors resulting in adverse drug events: how can they be prevented? Expert Opin Drug Saf 2006; 5: 489-93
7. Bégaud B, Evreux JC, Jouglard J, et al. Imputabilité des effets inattendus ou toxiques des medicaments: actualisation de la méthode utilisée en France. Therapie 1985; 40: 111-8
8. Jonville-Bera AP, Bera F, Autret-Leca E. Are incorrectly used drugs more frequently involved in adverse drug reactions? A prospective study. Eur J Clin Pharmacol 2005; 61: 231-6
9. Standardization of definitions and criteria of causality assessment of adverse drug reactions: drug-induced cytopenia. Int J Clin Pharmacol Ther Toxicol 1991; 29: 75-81
10. Benichou C. Criteria of drug-induced liver disorders: report of an international consensus meeting. J Hepatol 1990; 11: 272-6
11. Vigeral P, Baumelou A, Bénichou C, et al. Drug-induced renal insufficiency: results of consensus meetings [in French]. Nephrologie 1989; 10: 157-61
12. Fournier M, Camus P, Benichou C, et al. Interstitial pneumopathies: criteria of drug side-effects: results of consensus meetings [in French]. Presse Med 1989; 18: 1333-6
13. Guillaume JC, Roujeau JC, Chevrant-Breton J, et al. How to diagnose a cutaneous complication of a drug: application to vascular purpura [in French]. Ann Dermatol Venereol 1987; 114: 721-4
14. Habibi B, Solal-Celigny P, Benichou C, et al. Drug-induced hemolytic anemia: results of consensus conferences [in French]. Therapie 1988; 43: 117-20

15. Dictionnaire vidal. 78th rev. ed. Paris: Editions du Vidal, 2002
16. Kanjanarat P, Winterstein AG, Johns TE, et al. Nature of preventable adverse drug events in hospitals: a literature review. Am J Health Syst Pharm 2003; 60: 1750-9
17. Von Laue NC, Schwappach DLB, Koech CM. The epidemiology of medical errors: a review of the literature. Wien Klin Wochenschr 2003; 115: 318-5
18. Dubois RW, Brook RH. Preventable deaths: who, how often, and why? Ann Intern Med 1988; 109: 582-9
19. Hallas J, Harvarld B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990; 228: 83-90
20. Petersen LA, Brennan TA, O'Neil AC, et al. Does housestaff discontinuity of care increase the risk for preventable adverse events? Ann Intern Med 1994; 121: 866-72
21. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. JAMA 1995; 274: 29-34
22. Cunningham G, Dodd TRP, Grant DJ, et al. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. Age Ageing 1997; 26: 375-82
23. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions [letter]. Hosp Pharm 1992; 27: 538
24. Pearson TF, Pittman DG, Longley JM, et al. Factors associated with preventable adverse drug reactions. Am J Hosp Pharm 1994; 51: 2268-72
25. Nelson KM, Talbert RL. Drug-related hospital admissions. Pharmacotherapy 1996; 16: 701-7
26. Lakshmanan MC, Hershey CO, Breslau D. Hospital admissions caused by iatrogenic disease. Arch Intern Med 1986; 146: 1931-4
27. McDonnell P, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36: 1331-2
28. Lau PM, Stewart K, Dooley MJ. Hospital admissions resulting from preventable adverse drug reactions [comment]. Ann Pharmacother 2003; 37: 303-4
29. Courtman BJ, Stallings SB. Characterization of drug-related problems in elderly patients on admission to a medical ward. Can J Hosp Pharm 1995; 48: 161-6
30. Dartnell JGA, Anderson RP, Chohan V, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996; 164: 659-62
31. Bero LA, Lipton HL, Adair Bird J. Characterization of geriatric drug-related hospital readmissions. Med Care 1991; 29: 989-1003
32. Imbs JL, Pletan Y, Spriet A, et al. Les membres de la table ronde n°2 de Giens XIII: evaluation de la iatrogénie médicamenteuse évitable: méthodologie. Therapie 1998; 53: 365-70
33. Olivier P, Caron J, Haramburu F, et al. Validation d'une échelle de mesure: exemple de l'échelle française d'évitabilité des effets indésirables médicamenteux. Therapie 2005; 60: 39-45
34. National Council focuses on coordinating error reduction efforts. USP quality review 1997, 57 [online]. Available from URL: http://www.usp.org/hqi/practitionerPrograms/newsletters/qualityReview/qr571997-01-01e.html [Accessed 2009 Feb 1]
35. Trunet P, Le Gall JR, Lhoste F, et al. The role of iatrogenic disease in admissions to intensive care. JAMA 1980; 244: 2617-20
36. Trunet P, Borda IT, Rouget AV, et al. The role of drug-induced illness in admissions to an intensive care unit. Intensive Care Med 1986; 12: 43-6
37. Darchy B, Le Mière E, Figueredo B, et al. Iatrogenic diseases as a reason for admission to the intensive care unit. Arch Intern Med 1999; 159: 71-8
38. Letrilliart L, Hanslik T, Biour M, et al. Postdischarge adverse drug reactions in primary care originating from hospital care in France. Drug Saf 2001; 24: 781-92
39. Imbs JL, Pouyanne P, Haramburu F, et al. Iatrogénie médicamenteuse: estimation de sa prévalence dans les hôpitaux publics français. Therapie 1999; 54: 21-7
40. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. BMJ 2000; 320: 741-4
41. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. Drugs Aging 2005; 22: 767-7
42. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003; 289: 1107-16
43. Lindley CM, Tully MP, Paramsothy V, et al. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing 1992; 21: 294-300
44. Fantino B, Voirin N, Laforest L, et al. Primary care physicians' behaviors toward risk of iatrogenesis in elderly patients. Eur J Clin Pharmacol 2006; 62: 563-70
45. Temple ME, Robinson RF, Miller JC, et al. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Saf 2004; 27: 819-29
46. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997; 277: 312-7
47. Winterstein AG, Hatton RC, Gonzalez-Rothi R, et al. Identifying clinically significant preventable adverse drug events through a hospital's database of drug reaction reports. Am J Health Syst Pharm 2002; 59: 1742-9
48. Jones TA, Como JA. Assessment of medication errors that involved drug allergies at a university hospital. Pharmacotherapy 2003; 23: 855-60
49. Krähenbühl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007; 30: 379-407
50. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA 1995; 274: 35-43
51. Dean B, Schachter M, Vincent C, et al. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care 2002; 11: 340-4
52. Corsonello A, Pedone C, Corica F, et al. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. Arch Intern Med 2005; 165: 790-5

53. Fauchais AL, Ploquin I, Ly K, et al. Iatrogénie chez le sujet âgé de plus de 75 ans dans un service de posturgences: etude prospective de cohorte avec suivi à six mois. Rev Med Interne 2006; 27: 375-81
54. Salomon L, Deray G, Jaudon MC, et al. Medication misuse in hospitalized patients with renal impairment. Int J Qual Health Care 2003; 15: 331-5
55. Salomon L, Levu S, Deray G, et al. Assessing residents' prescribing behavior in renal impairment. Int J Qual Health Care 2003; 15: 235-40
56. Smith P, Karlson N, Nair BR. Quality use of allopurinol in the elderly. J Qual Clin Pract 2000; 20: 42-3
57. Mikuls TR, Curtis JR, Allison JJ, et al. Medication errors with the use of allopurinol and colchicine: a retrospective study of a national, anonymous internet-accessible error reporting system. J Rheumatol 2006; 33: 562-6
58. Perez-Ruiz F, Hernando I, Villar I, et al. Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels: another insight to allopurinol-related toxicity. J Clin Rheumatol 2005; 11: 129-33
59. Gutierrez-Macias A, Lizarralde-Palacios E, Martinez-Odriozola P, et al. Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. BMJ 2005; 331: 623-4
60. Chao SC, Yang CC, Lee JY. Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. Ann Pharmacother 2005; 39: 1552-6
61. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother 1993; 27: 337-43
62. Kumar A, Edward N, White MI, et al. Allopurinol, erythema multiforme, and renal insufficiency. BMJ 1996; 312: 173-4
63. Hirsch LJ, Weintraub DB, Buchsbaum R, et al. Predictors of lamotrigine-associated rash. Epilepsia 2006; 47: 318-22

Correspondence: Dr *Annie Pierre Jonville-Béra*, Pharmacoepidemiology and Clinical Pharmacology Unit, CHRU de Tours, 2 boulevard Tonnellé, 37044 Tours, Cedex 9, France. E-mail: jonville-bera@chu-tours.fr