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Drug-Related Deaths

An Analysis of the Italian Spontaneous Reporting Database

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Abstract

Background: Adverse drug reactions (ADRs) represent a major public health concern, with death as the ultimate adverse drug outcome. Despite the relevance of this, the frequency of fatal ADRs (FADRs) is to a large extent unknown. Although spontaneous reporting data cannot give an exact estimate of the magnitude of drug-related mortality, it may highlight the importance and large dimensions of this public health problem.

Objective: To describe the types and pattern of reported FADRs by analysing data from the national spontaneous reporting system in Italy.

Methods: The Italian Medicines Agency (AIFA) runs a pharmacovigilance database where all the individual case safety reports (since January 2001) are stored. We selected and then analysed in detail all the case reports (to the end of December 2006) in which death was reported as the outcome. We included in the study only FADR case reports with a probable or possible causality assessment, according to the criteria established by the WHO. In line with the Italian reporting form, we divided FADR reports into two groups: (i) suspected ADRs that caused death; and (ii) suspected ADRs that contributed to death.

Results: In the AIFA database 38 507 suspected ADR case reports were collected, of which 641 (1.66%) had a fatal outcome. We analysed 450 case reports (1.17% of total reports), 159 (35.33%) of them causing the patient's death and 291 (64.67%) contributing to death. The annual percentage of FADR reports followed a constant trend during the 6-year period. The majority of fatal reports (79%) were sent by hospital doctors. In total, 222 different drugs were suspected as causes of FADRs. 'Systemic anti-infective drugs' was the drug category associated with the highest percentage of FADRs (21.9%), followed by antineoplastic and immunomodulating agents (18.8%), and then by nervous system drugs (14.8%). Other drug categories involved in the fatal case reports were antithrombotic agents, NSAIDs and contrast media.

Conclusions: The drugs most frequently involved in FADRs were drugs of wide usage with a narrow therapeutic range or those that caused serious skin or systemic allergic reactions. Ceftriaxone, ticlopidine and nimesulide were associated with the highest number of fatal case reports; the related FADRs were already known and recognized for each of these drugs. We highlight some cases reflecting probable inappropriate drug use by Italian physicians. This suggests a

need for continued clinical pharmacology training and that many FADRs might be preventable through better medical and prescribing practice.

Background

Adverse drug reactions (ADRs) represent a major public health problem in terms of hospitalization, morbidity and cost, as reported by many studies conducted in hospitals, emergency departments and ambulatory care settings.[1-9] Death is the ultimate adverse drug outcome. Despite its importance, there are only a few studies on the incidence of fatal ADRs (FADRs). Mortality incidence ranges from 0.05% to 0.95% in hospitalized patients, depending on the source.[3,7,10-14] The difference may partly be explained by the fact that there were some methodological differences between the studies, e.g. in the criteria of classification and definition of drug-related deaths. Some authors analysed fatal adverse drug events (ADEs), which include injuries resulting from drug administration, intoxication and drug abuse. However, most studies used the WHO definition of an ADR.[15]

In a large meta-analysis of 39 prospective studies (from 1966 to 1996) it was estimated that in 1994 in the US, 106 000 hospitalized patients died from an ADR, with an overall incidence of 0.32%. This figure was based on a 0.13% incidence of FADRs in patients admitted to hospital, and a 0.19% incidence in patients who developed an ADR while in hospital. The authors deduced that ADRs may rank from the fourth to the sixth most frequent cause of death (after heart disease, cancer, stroke, pulmonary disease and accidents).[3] These findings were also supported by another study showing that in 1997, a total of 16 500 patients died from the gastrointestinal toxic effects of NSAIDs, suggesting that these effects would constitute the fifteenth most common cause of death in the US.[16] A later UK study estimated a 0.15% incidence of FADRs among inpatients, which is similar to the US figure. The authors suggested that the true rate of death, taking into account all ADRs, may be >10 000 per year.[7] In a Canadian study, ADRs were ranked as approximately the nineteenth most common cause of death in hospitalized patients.[11] Their estimate, 1824 drug-associated deaths annually, was higher than that of a study based on data collected by the Canadian voluntary reporting system, where only 1417 cases of drug-related deaths over a 10-year period were found.[17] In a recently published Swedish study, 3.1% of the total number of spontaneously submitted reports documented a fatal outcome. Taking into consideration an assumed degree of under-reporting, the authors suggested that FADRs might be estimated to be at least the twelfth most common cause of death in Sweden.[18] Finally, fatal ADEs reported to the US FDA Adverse Event Reporting System increased 2.7-fold (from 5519 to 15 107 deaths) between 1998 and 2005. It is the world's largest database of voluntary submitted reports of ADEs (including ADRs, medication errors, accidental and intentional overdoses and product problems), and these data show that a growing number of patients are experiencing very serious injuries from drug therapy.[19] Although, by using these kinds of data, it is not possible to estimate the real magnitude of drug-related mortality, these results highlight the importance and magnitude of this public health problem.

Spontaneous reporting has the great advantage of covering a large number of patients and wide range of drugs and of being a relatively cost-effective method of monitoring drug safety. It is well known that its main objective is to detect associations between drugs and previously unrecognized ADRs. The data from spontaneous reporting cannot provide an accurate estimate of the risk associated with a drug, which requires adequate denominator information on the utilization of the drug. The numerator is also inaccurate as it is subject to reporting bias. Under-reporting is probably the main problem since the absolute number of ADRs is not known. The reporting rate suffers from other influencing factors, such as 'notoriety bias' and the 'Weber effect', so it may vary among drugs and for the same drug over

time. The quality of reports is also very important; lack of information and details may make causality assessment impossible. Consequently, using spontaneous reporting as the sole source of data to determine the incidence of drug-related mortality is not appropriate and the information obtained has to be interpreted cautiously. Despite their limitations, spontaneous reporting systems remain an important tool for monitoring the safety of marketed products and this data may underscore some potential 'qualitative' problems.

Therefore, considering that little information is available on drug-related mortality, the objective of our study was primarily to describe the type and pattern of reported FADRs by analysing data from the national spontaneous reporting system in Italy.

Methods

In Italy pharmacovigilance activities are regulated by several laws issued in compliance with European directives. It is mandatory to report all suspected serious and unknown ADRs, and every suspected ADR to vaccines and recently marketed drugs, including known and non-serious reactions. The system is based on the activities of local public pharmacovigilance offices, where healthcare professionals have to send suspected ADR reports. These offices have to transmit the received ADR reports, via a computerized network, to the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]). In case of death, the pharmacovigilance offices have to request from physicians a clinical report and the results of the autopsy if one is performed.

The Italian Pharmacovigilance National Network has been operative since November 2001; through this network 21 Italian regions, 204 local health districts, 112 hospitals, 38 teaching hospitals and 561 pharmaceutical companies are connected to the AIFA.[20] The AIFA database contains all the Individual Case Safety Reports with date onset since January 2001. In this database, ADRs are coded using the Medical Dictionary for Regulatory Activities terminology[21] and drugs are classified following the Anatomical Therapeutic Chemical (ATC) classification. All the case reports in which death was reported as the outcome were selected from the AIFA database. These reports and related follow-up documentation were analysed in detail by a panel of experts, including physicians, pharmacists and pharmacologists. The panel excluded duplicates, reports in which the death was not ADR-related, and cases of overdose (intentional or accidental) in line with the WHO definition of an ADR.[15]

We evaluated causality between the suspected FADR and the related drug, considering also the potential contribution of concomitant drugs, following the criteria established by the WHO.[22] We included in the analysis only FADR case reports with a probable or possible causality assessment.

The Italian reporting card obliges the reporter to distinguish whether the ADR definitively caused or contributed to the fatal outcome. Therefore, on the basis of this judgement, the reports were divided into two groups: (i) suspected ADRs that caused death; and (ii) suspected ADRs that contributed to death. Furthermore, the expert panel assessed the reporter's judgement, death diagnosis and all other available information about potential contributing factors, such as age, concomitant diseases and patient health conditions.

We calculated the ADR reporting odds ratio (ROR), with a 95% confidence interval, associated with fatal reports for each first level ATC drug group. ROR is one of the measures of disproportionality that entail comparisons of observed with expected proportions of an adverse event associated with a drug; they do not require access to external data sets for exposure estimates.[23]

Results

From January 2001 to the end of December 2006, the AIFA pharmacovigilance database collected 38 507 (32% serious) suspected ADR case reports, of which 641 (1.7%) had a fatal outcome. We excluded 191 case reports after evaluating causality assessment and the relationship between the reported ADR and the fatal outcome. Thus, we analysed 450 case reports (1.2% of total reports stored in the AIFA database): 159 (35.3%) of the ADRs showed a causal association with the patient's death and 291

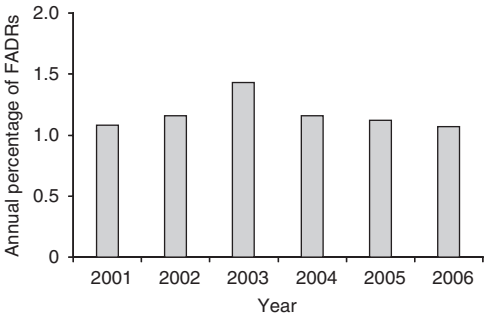

Fig. 1. Annual percentage of fatal adverse drug reactions (FADRs) in the Italian Medicines Agency (AIFA) database.

(64.7%) contributed to the death. Causality was classified as 'probable' in 50.2% and as 'possible' in 49.8% of these associations.

Each year the number of FADR reports ranged between 63 and 86; we found that the annual percentage rate followed a constant trend during the 6-year period, with only a slight increase in 2003 (figure 1). There was no statistically significant difference (Chi-squared test) between the female-male ratio of patients with suspected FADRs (1.12) and that of all patients (1.32).

The FADR and non-FADR reporting rate increased with age, suggesting that the elderly are more susceptible (figure 2). The age-related increase in FADR reports was more evident than in non-FADR reports, which show an exponential trend. The reporting rate of non-FADRs in the <18-years-of-age group was influenced by vaccine reactions reporting.

In the AIFA database as a whole, 41% of the ADR reports were sent by hospital doctors, 35% by general practitioners (GPs), and the remaining 24% by specialists or pharmacists. As expected, the majority of fatal reports (79%) were sent by hospital doctors and only a small percentage (10%) by GPs, and the rest by specialists (8%) or others (3%).

The types of reactions most frequently involved in the reports with fatal outcomes were blood and bone marrow dysfunction (71 reports, 15.8%), haemorrhages (65, 14.4%), anaphylactic shock (63, 14%), liver dysfunction (49, 10.9%), cardiovascular diseases (47, 10.4%), severe skin reactions (38, 8.4%) and acute renal failure (25, 5.6%).

Seventy percent of fatal case reports had only one drug suspected; in the remaining cases there were two (25%) or three (5%) suspected drugs. In total, 222 different drugs were suspected as being causes of FADRs. Table I shows all the drugs implicated in FADR reports, grouped according to the first level of ATC code. 'Systemic anti-infective drugs' was the drug category associated with the highest number of FADRs; within this drug category, antibacterials (86 FADRs) and antivirals (28) were the most common. Among antibacterials, cephalosporins (35), fluoroquinolones (15) and penicillins (15) were the most frequently implicated drugs. Antineoplastic and immunomodulating agents were the second most frequently implicated drug category,

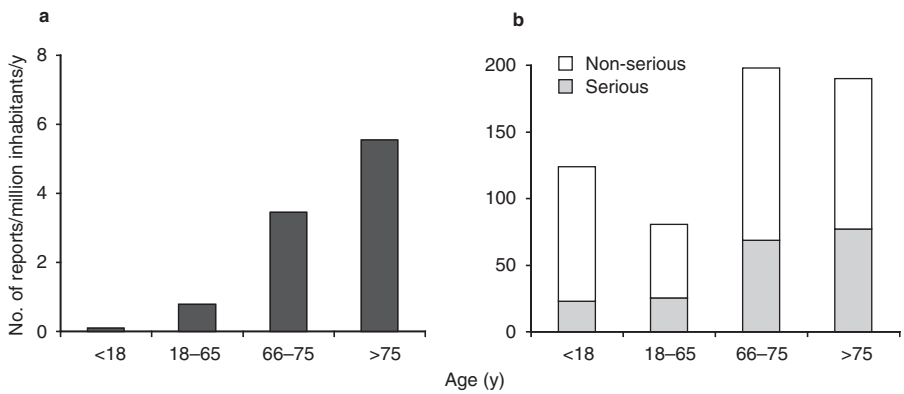

Fig. 2. Age-specific fatal (**a**) and non-fatal (**b**) adverse drug reaction reporting rates per million inhabitants per year in Italy from January 2001 to December 2006.

Table I. Drugs involved in the fatal adverse drug reaction (FADR) reports

ATC system group (first level)	No. of total ADR reports[a]	No. of FADR reports[a]	ROR (95% CI)
A. Alimentary tract and metabolism	2 071	24	0.74 (0.48, 1.14)
B. Blood and blood forming organs	2 298	77	2.40 (1.87, 3.08)
C. Cardiovascular system	5 039	51	0.62 (0.46, 0.94)
D. Dermatologicals	318	2	0.40 (0.07, 1.65)
G. Genito-urinary system and sex hormones	873	9	0.66 (0.32, 1.32)
H. Systemic hormonal preparations, excluding sex hormones and insulins	383	8	1.38 (0.63, 2.87)
J. Anti-infectives for systemic use	14 508	133	0.48 (0.39, 0.58)
L. Antineoplastic and immunomodulating agents	2 094	114	4.31 (3.48, 5.34)
M. Musculo-skeletal system	4 513	63	0.90 (0.68, 1.18)
N. Nervous system	4 348	90	1.42 (1.12, 1.79)
P. Antiparasitic products, insecticides and repellents	194	2	0.67 (0.17, 2.67)
R. Respiratory system	835	2	0.15 (0.03, 0.61)
V. Various	1 530	32	1.39 (0.95, 2.02)

a There are large number of reports because in many categories more than one drug was suspected.

ADR = adverse drug reaction; **ATC** = Anatomical Therapeutic Chemical; **ROR** = reporting odds ratio.

with antineoplastics cited in 77 FADR reports, followed by immunosuppressive (18) and immunostimulant (12) agents. Nervous system drugs were the third most commonly implicated drug category, with analgesics (24), antipsychotics (19) and antiepileptics (19) as the most frequently involved drugs. Other drug categories involved in fatal case reports were antithrombotic agents (73), NSAIDs (48) and contrast media (26). Most of the fatal cases associated with the use of contrast media (ten different drugs) were immediate allergy-like reactions to iodinated compounds.

Analysing the data using the case/non-case method, 'antineoplastic and immunomodulating agents' was the drug category associated with the highest ROR, followed by haematological agents and nervous system drugs (table I).

In table II the single drugs associated with at least ten fatal case reports are listed. Ceftriaxone was the most frequently involved drug (24 cases), followed by ticlopidine (22) and nimesulide (17). When we considered only ADRs causing death, ceftriaxone remained the most frequently implicated drug (18 cases), followed by allopurinol (8) and ticlopidine (7). In reports of ADRs contributing to death, the reporter or the expert panel recognized some risk factors that could have contributed to the fatal outcome, such as predisposing pathologies, serious health conditions or consumption of interacting drugs. For example, in six of nine warfarin-related reports with ADRs contributing to death, concomitant diseases included hypertension, diabetes mellitus, trauma and cardiac failure, which are conditions in which administration of warfarin requires caution.

The great majority of the fatal reactions associated with the drugs listed in table II are typical of each drug, e.g. haematological reactions for ticlopidine, anaphylactic shock for ceftriaxone, hepatotoxicity or gastrointestinal bleeding for nimesulide, etc. (table III). Some of these cases could reflect possible inappropriate prescription: e.g. administration of nimesulide to patients with chronic renal or hepatic diseases; use of ticlopidine in patients with predisposition to bleeding or severe liver disease; administration of amiodarone to patients with previous acute myocardial infarction and use of simvastatin in patients with renal insufficiency secondary to diabetes mellitus or active liver disease. We also observed, in some fatal reports, the concomitant use of known interacting drugs, such as warfarin and NSAIDs, and simvastatin and amiodarone or clarithromycin. Furthermore, some deaths from immune reactions occurred in patients

Table II. Reports of suspected drugs involved in at least ten fatal cases during the study period

Drugs	Total no. of reports of fatal cases	No. of reports with ADRs causing death	No. of reports with ADRs contributing to death
Ceftriaxone	24	18	6
Ticlopidine	22	7	15
Nimesulide	17	5	12
Amiodarone	13	3	10
Allopurinol	12	8	4
Simvastatin	12	0	12
Warfarin	12	3	9
Paracetamol (acetaminophen)	10	4	6

ADRs = adverse drug reactions.

with a previous history of allergy or because the suspected drug was not withdrawn at the first signs of allergy.

Discussion

To our knowledge, this is the first study conducted on drug-related mortality in Italy. Analysing the AIFA database we found 450 FADR case reports, with a relatively stable annual mean mortality during the 6-year study period. The slight increase observed in 2003 may have been due to a new Italian law on spontaneous reporting.

The FADR percentage found in our analysis is similar to that of the French Pharmacovigilance Database (1.7%)[24] but lower than that found in other studies using the same methodology.[17,18] Furthermore, although it does not constitute the aim of the present study, the possible estimated mortality from our data would be much lower than that reported in some previous studies on this topic.[3,7] Studies based on spontaneous reporting systems have many limitations of which the most important is underreporting. In Italy the ADR reporting rate (annual mean: 100 reports/100 000 inhabitants during the study period) is lower than in other industrialized countries (e.g. Sweden, Canada, UK, US, France, Spain). There are also limitations closely related to the reporting of FADRs. Identifying ADRs as a cause of death in a patient may be a complicated task, especially in patients with polypharmacy, comorbidity and long-term drug use, since other possible explanations often cannot be ruled out. In addition, there are problems unique to the assessment of FADRs, since it is impossible to dechallenge and rechallenge the patient with the suspected drug. Moreover, in fatal cases with a long period of disease, it is more likely that clinicians attribute deaths

Table III. Fatal adverse drug reactions (FADRs) caused by drugs involved in at least ten deaths during the study period

Drugs	FADRs (no. of reports)
Ceftriaxone	Anaphylactic shock (15), Lyell's disease (5), hepatitis (2), cutaneous necrosis (1), pseudomembranous colitis (1)
Ticlopidine	Thrombotic thrombocytopenic purpura (7), agranulocytosis (4), serious leukopenia (4), cholestatic jaundice (3), aplastic anaemia (2), hepatic and renal failure (2)
Nimesulide	Acute liver failure (7), gastrointestinal bleeding (5), acute renal failure (4), acute liver and renal failure (1)
Amiodarone	Pulmonary fibrosis (7), anaphylactic shock (2), congestive cardiac failure (2), acute liver failure (1), rhabdomyolysis (1)
Allopurinol	Lyell's disease (6), exfoliative dermatitis (2), Stevens-Johnson syndrome (2), cholestatic hepatitis (1), cutaneous necrosis (1),
Simvastatin	Myopathies/rhabdomyolysis (10), cardiac arrest (1), acute myocardial infarction (1)
Warfarin	Cerebral bleeding (7), blood coagulation disorder (2), hepatitis (2), gastrointestinal bleeding (1)
Paracetamol (acetaminophen)	Lyell's disease (5), disseminated intravascular coagulation (2), thrombotic thrombocytopenic purpura (1), anaphylactic shock (1), acute liver and renal failure (1)

to underlying diseases than to the therapies provided.

'Elderly people' was the age grouping most frequently involved in FADRs. This result is expected and common to other studies on drug-related mortality.[17,18] Age-related changes, such as those arising from changes in pharmacokinetics and pharmacodynamics, interindividual variability, polypharmacy and other drug consumption that leads to drug interactions are known risk factors for ADRs. It is known that the percentage of hospitalizations attributed to ADRs is highest for the elderly.[6,7,9,25]

By comparing the pattern of suspected FADRs with that in a recent Swedish study,[18] we observed some differences in the ranking. In our context, blood and bone marrow dysfunction, haemorrhage and anaphylactic shock jointly account for one-half of FADR reports (about one-sixth each), whereas in Sweden, haemorrhages account for approximately 61% of FADRs and anaphylactic shock is not reported. It is difficult to explain these differences, but they may be due to the different attitudes of physicians to ADR reporting or differences in drug utilization patterns.

A relatively high number of drugs were associated with FADRs in our study, indicating that numerous drugs from various pharmacological groups can cause fatalities. Antibacterials, antineoplastics, antithrombotics and NSAIDs were the drugs most frequently cited in fatal case reports. However, ROR analyses show an increased risk only for antineoplastic and immunomodulating agents, haematological agents and nervous system drugs. In other spontaneous reporting-based studies, the drug classes most commonly suspected of causing FADRs were similar, with some variations among the ranking. Anticoagulants were most frequently involved in spontaneous fatal reports in a German study[26] and in the Swedish study.[18] Moreover, 'anticoagulants' was one of the most frequently implicated drug classes in some Nordic studies investigating FADRs in hospital settings.[13,14] In a US study,[27] antineoplastic and immunosuppressive agents were the drugs most frequently suspected in spontaneously reported deaths. In a Canadian study,[17] nervous system agents were most frequently reported as being associated with deaths, followed by anti-infective agents for systemic use, musculoskeletal and cardiovascular system agents, and musculoskeletal agents in another Canadian study.[28]

In our study, ceftriaxone, a systemic third-generation cephalosporin indicated for treating serious infections, was associated with the highest number of FADRs. In particular, we found 15 cases of fatal anaphylactic shock. This is a known serious adverse reaction to ceftriaxone and is reported in the Summary of Product Characteristics among rare events.[29] Its frequency is not known, because it depends on both the population exposed and the route of drug administration.[30] Our data may reflect the well known and controversial Italian prescribers' habit of administering antibacterials parenterally. This prescription habit seems to be peculiar to Italian doctors.[31] It is noteworthy that in the WHO-UMC (Uppsala Monitoring Centre) ADR database (accessed online on May 2007), 13% of all anaphylactic shock cases related to injectable cephalosporins had been sent from Italy, whereas <1% of total reports are Italian. Furthermore, during 2005 an increase of third- and fourth-generation cephalosporin consumption was observed in Italy, which was almost entirely attributed to ceftriaxone prescribing (0.3 defined daily dose [DDD]/1000 inhabitants/day) related to the lowering of its price.[32] As shown in several studies, a marked variability exists in the choice of antibacterials across Europe.[33-38] In Southern European countries such as Italy, Spain and Greece, the antibacterial consumption pattern appeared similar, with a prevalent use of the extended-spectrum and newer antibacterials. Moreover, there is a broad variation among the Italian regions, with a higher consumption of antibacterials in the South. A high proportion of patients were shown to have been treated unnecessarily with antibacterials.[31] In Italy, cephalosporins are the antibacterials most frequently prescribed both to children and older people, although there is no evidence to indicate cephalosporins as the drug of

choice for these age groups.[37] Therefore, their frequent use in Italy seems not to reflect actual therapeutic needs, but rather to be induced by motivations such as patient pressure and advertising. Moreover, this prescribing habit does not comply with recommendations issued by the WHO and Centers for Disease Control and Prevention in order to control the spread of resistance to antibacterials.[39,40] The correct strategy, in our opinion, is a closer adherence to the international antibacterial prescription guidelines, which will also help to avoid FADRs.

In our study, ticlopidine, an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation, used to prevent strokes in high-risk populations or following coronary artery stent placement, was the second most frequently involved drug in FADRs; most reported deaths were associated with haematological reactions. Serious adverse reactions to ticlopidine have been found during postmarketing surveillance with 85.6% of deaths being associated with haematological effects.[41] Although they were reported as infrequent reactions, thrombocytopenia and thrombotic thrombocytopenic purpura (TTP) appeared to be more common causes of death than leukopenia and agranulocytosis,[41] and this was also shown in our analysis. TTP is a life-threatening multisystem disease characterized by thrombocytopenia, microangiopathic haemolytic anaemia, neurological changes, progressive renal failure and fever. The aetiology of TTP is still partially unknown.[42] The estimated incidence of ticlopidine-associated TTP is 1 per 1600 and its mortality rate is 33%.[42,43] Since TTP usually sets in within the first 3 months of therapy, ticlopidine use requires frequent physician visits and laboratory tests during this period. The revision of the ticlopidine black box warnings made by the manufacturer in 1998, the 'Dear Doctor' letter sent in the same year in the US and competition from clopidogrel, a potentially less toxic alternative antiplatelet agent, have limited ticlopidine use in recent years throughout the world. However, in Italy during 2005, ticlopidine was still the most commonly used antiplatelet drug (5.2 DDD/1000 inhabitants/day) after aspirin (acetylsalicylic acid).[32] The Italian Medicines Agency assessed the benefit-risk ratio of ticlopidine as positive only for the patients with individual hypersensitivity to aspirin or in cases of aspirin ineffectiveness. In the other cases, considering the high incidence of serious ADRs, it would be preferable to use aspirin. Therefore, the high Italian reporting rate of haematological ADRs with ticlopidine[44] may be the consequence of inappropriate prescription. Ticlopidine, together with amiodarone, have been found to be the most commonly prescribed potentially inappropriate medications in Italy.[45,46]

In our analysis, nimesulide was associated with 17 fatal case reports. Nimesulide is the most frequently administered NSAID in Italy (7.3 DDD/1000 inhabitants/day; prevalence of use: 18.4%).[32,47] Wide use of nimesulide is a peculiarity of Italy, whereas in other countries, e.g. Denmark or Sweden,[48] consumption is very low. Nimesulide is not available on the US market or in other European countries (e.g. UK); in 2002 it was withdrawn because of reports of serious hepatotoxicity, firstly in Finland, then a few months later in Spain and, in 2007, in Ireland. In Italy it is still available following a toxicity evaluation by the European Medicines Agency, which was essentially based on an epidemiological study documenting a small risk of liver toxicity.[49] However, this study also documented that nimesulide appears more hepatotoxic than other NSAIDs, even although the results failed to reach statistical significance. For these reasons, a 'Dear Doctor' letter was issued in 2002 by the Italian Ministry of Health to advise about appropriate use and remind doctors that it is a prescription drug. However, most of the reported FADRs attributed to nimesulide were sent after the Finnish alarm, and therefore a 'notoriety bias' cannot be excluded, even if this bias is less likely in fatal cases. In addition, wide use among the elderly and a high rate of self-treatment suggest that more attention should be paid by doctors and pharmacists, in particular to patients with hepatic or renal diseases.

It is not surprising to find amiodarone and warfarin in the list of the drugs most implicated in FADRs because of their narrow therapeutic range, whereas the presence of simvastatin and paracetamol (aceta-

minophen) in this list associated with known and expected ADRs, such as rhabdomyolysis or serious cutaneous reactions, is probably related to their very wide use (e.g. in 2005 their use was at a level of 17 and 5.5 DDD/1000 inhabitants/day, respectively).[32]

Although allopurinol is a very commonly used hypouricemic agent,[50] it may be unexpected to find this drug among the eight drugs most implicated in FADRs, since the other listed drugs are more widely used. In our analysis, allopurinol-related fatal cases were mainly associated with serious cutaneous ADRs, especially with toxic epidermal necrolysis (TEN), which supports this well known and documented association.[51] In addition, TEN may be one of the symptoms of drug hypersensitivity syndrome, which has been associated with allopurinol and has a mortality rate that may reach 25%.[52] Fatal allopurinol hypersensitivity syndrome most often presents as a consequence of inappropriate treatment of asymptomatic hyperuricemia or inadequate administration in patients with renal failure. In the latter patients, allopurinol administration must be adjusted because accumulation of oxypurinol, its principal metabolite, is considered a crucial factor for the development of this syndrome. Therefore, it could be reduced by strictly following recommendations for gout management.[52,53]

A relatively high number of FADRs associated with contrast media were reported in the AIFA database. Currently, contrast media are an indispensable part of modern diagnostic medicine. Minor adverse reactions have been reported in 3–12% of all recipients, with mortality rates of <1 in 100 000 patients. Physicians should be aware of the risk factors and prophylactic measures involved in procedures with contrast media. They should also be better prepared and ready to treat immediate allergic reactions to contrast media in an emergency situation.[54,55]

Conclusion

ADRs are a significant cause of death and the relatively low incidence of drug-related mortality found to date should not preclude further studies. Although spontaneous reporting system studies are flawed by under-reporting, they provide information of value. In this study we found that the drugs most involved in FADRs were drugs of wide usage (e.g. antibacterials, NSAIDs, cardiovascular agents and analgesics), drugs with a narrow therapeutic range (e.g. antitumour and antithrombotic agents) or drugs that caused serious skin or systemic allergic reactions (e.g. contrast media, allopurinol and β-lactams). Ceftriaxone, ticlopidine and nimesulide were associated with the highest number of FADRs.

In our analysis, we observed some cases that might, at least partially, reflect inappropriate prescription practice. The collection of data coming from spontaneous reporting does not allow precise measurement of these practices. For this purpose, other methodologies are more appropriate. However, our findings underline the need for continuing clinical pharmacology training, since many ADRs, including the fatal ones, may be preventable through improved medical practice.

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References

1. Ives TJ, Bentz EJ, Gwyther RE. Drug-related admissions to a family medicine inpatient service. Arch Intern Med 1987; 147: 1117-20
2. Stoukides CE, D'Agostino PR, Kaufman MB. Adverse drug reaction surveillance in an emergency room. Am J Hosp Pharm 1993; 50: 712-4
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. JAMA 1998; 279: 1200-5
4. Muehlberger N, Schneeweiss S, Hasford J. Adverse drug reaction monitoring-cost and benefit considerations. Part I: frequency of adverse drug reactions causing hospital admissions. Pharmacoepidemiol Drug Saf 1997; 6 Suppl. 3: S71-7
5. 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; 56: 181-6
6. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci 2002; 24: 46-54
7. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ 2004; 329: 15-9
8. Samoy LJ, Zed PJ, Wilbur K, et al. Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian

hospital: a prospective study. Pharmacotherapy 2006; 26: 1578-86
9. van der Hooft CS, Sturkenboom M, van Grootheest K, et al. Adverse drug reaction-related hospitalisations: a nationwide study in the Netherlands. Drug Saf 2006; 29: 161-8
10. Porter J, Jick H. Drug-related deaths among medical inpatients. JAMA 1977; 237: 879-81
11. Bains N, Hunter D. Adverse reporting on adverse reactions. CMAJ 1999; 160: 350-1
12. Zoppi M, Braunschweig S, Kuenzi UP, et al. Incidence of lethal adverse drug reactions in the comprehensive hospital drug monitoring, a 20-year survey, 1974-1993, based on the data of Berne/St Gallen. Eur J Clin Pharmacol 2000; 56: 427-30
13. Ebbesen J, Buajordet I, Erikssen J, et al. Drug-related deaths in a department of internal medicine. Arch Intern Med 2001; 161: 2317-23
14. Juntti-Patinen L, Neuvonen PJ. Drug-related deaths in a university central hospital. Eur J Clin Pharmacol 2002; 58: 479-82
15. WHO. International drug monitoring: the role of the hospital. Geneva: WHO, 1966. Technical report series N. 425
16. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999; 340: 1888-99
17. Mittmann N, Liu BA, Iskedjian M, et al. Drug-related mortality in Canada (1984-1994). Pharmacoepidemiol Drug Saf 1997; 6: 157-68
18. Wester K, Jönsson A, Spigset O, et al. Spontaneously reported fatal suspected adverse drug reactions: a 10-year survey from Sweden. Pharmacoepidemiol Drug Saf 2007; 16: 173-80
19. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. Arch Intern Med 2007; 167: 1752-9
20. Agenzia Italiana del Farmaco. Pharmacovigilance [online]. Available from URL: http://www.agenziafarmaco.it/ [Accessed 2007 Apr 16]
21. Bousquet C, Lagier G, Lillo-Le Louet A, et al. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. Drug Saf 2005; 28: 19-34
22. Uppsala Monitoring Centre. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Uppsala: The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, 2000
23. van der Heijden PG, van Puijenbroek EP, van Buuren S, et al. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. Stat Med 2002; 21: 2027-44
24. 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
25. Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 2002; 50: 1962-8
26. Tiaden JD, Wenzel E, Berthold HK, et al. Adverse reactions to anticoagulants and to antiplatelet drugs recorded by the German spontaneous reporting system. Semin Thromb Hemost 2005; 31: 371-80
27. Chyka PA. How many deaths occur annually from adverse drug reactions in the United States? Am J Med 2000; 109: 122-30
28. Liu BA, Knowles SR, Mittmann N, et al. Reporting of fatal adverse drug reactions. Can J Clin Pharmacol 2001; 8: 84–8
29. Repertorio Farmaceutico Italiano [CD ROM]. 15th ed. Milan: Masson, 2006
30. Baldo BA, Pham NH, Zhao Z. Chemistry of drug allergenicity. Curr Opin Allergy Clin Immunol 2001; 1: 327-35
31. Vaccheri A, Castelvetri C, Esaka E, et al. Pattern of antibiotic use in primary health care in Italy. Eur J Clin Pharmacol 2000; 56: 417-25
32. Agenzia Italiana del Farmaco. Drug utilization in Italy: National Report year 2005 [online]. Available from URL: http://www.agenziafarmaco.it/ [Accessed 2007 Feb 14]
33. Ortqvist A. Antibiotic treatment of community-acquired pneumonia in clinical practice: a European perspective. J Antimicrob Chemother 1995; 35: 205-12
34. Gulbinovic J, Myrback KE, Bytautiene J, et al. Marked differences in antibiotic use and resistance between university hospitals in Vilnius, Lithuania, and Huddinge, Sweden. Microb Drug Resist 2001; 7: 383-9
35. Bremon AR, Ruiz-Tovar M, Gorricho BP, et al. Non-hospital consumption of antibiotics in Spain: 1987-1997. J Antimicrob Chemother 2000; 45: 395-400
36. Mazzaglia G, Arcoraci V, Greco S, et al. Prescribing habits of general practitioners in choosing an empirical antibiotic regimen for lower respiratory tract infections in adults in Sicily. Pharm Res 1999; 40: 47-52
37. Vaccheri A, Bjerrum L, Resi D, et al. Antibiotic prescribing in general practice: striking differences between Italy (Ravenna) and Denmark (Funen). J Antimicrob Chemother 2002; 50: 989-97
38. Elseviers MM, Ferech M, Vander Stichele RH, et al. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf 2007; 16: 115-23
39. WHO. WHO Global Strategy for Containment of Antimicrobial Resistance [online]. Available from URL: http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_2001_2_EN/en/ [Accessed 2007 May 10]
40. Centers for Disease Control and Prevention. A public health action plan to combat antimicrobial resistance [online]. Available from URL: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf [Accessed 2007 May 10]
41. Bennett CL, Davidson CJ, Raisch DW, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. Arch Intern Med 1999; 159: 2524-8
42. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. Ann Intern Med 1998; 128: 541-4
43. Bennett CL, Kiss JE, Weinberg PD, et al. Thrombotic thrombocytopenic purpura after stenting and ticlopidine. Lancet 1998; 352: 1036-7
44. Venegoni M, Conforti A, Cocci A, et al. Spontaneous reports of ticlopidine-associated thrombotic thrombocytopenic purpura from two Italian regions [letter]. Arch Intern Med 1999; 159: 2227
45. Fialova D, Topinkova E, Gambassi G, et al. Potentially inappropriate medication use among elderly home care patients in Europe. JAMA 2005; 293: 1348-58
46. Onder G, Landi F, Liperoti R, et al. Impact of inappropriate drug use among hospitalized older adults. Eur J Clin Pharm 2005; 61: 453-9

47. Motola D, Vaccheri A, Silvani MC, et al. Pattern of NSAID use in the Italian general population: a questionnaire based survey. Eur J Clin Pharmacol 2004; 60: 731-8
48. Bergman U, Andersen M, Vaccheri A, et al. Deviations from evidence based prescribing of non-steroidal anti-inflammatory drugs in three European regions. Eur J Clin Pharmacol 2000; 56: 269-72
49. Traversa G, Bianchi C, Da Cas R, et al. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ 2003; 327: 18-22
50. Pascual E, Sivera F. Therapeutic advances in gout. Curr Opin Rheumatol 2007; 19: 122-7
51. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333: 1600-7
52. 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
53. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006; 65: 1312-24
54. Caro JJ, Trindade E, McGregor M. The risks of death and of severe non fatal reactions with high vs low-osmolality contrast media: a meta-analysis. AJR Am J Roentgenol 1991; 156: 825-32
55. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. Drug Saf 2006; 29: 133-41

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