

Drug-Induced Anaphylaxis

Case/Non-Case Study Based on an Italian Pharmacovigilance Database

Roberto Leone,¹ Anita Conforti,¹ Mauro Venegoni,² Domenico Motola,³ Ugo Moretti,¹ Ilaria Meneghelli,¹ Alfredo Cocci,² Giulia Sangiorgi Cellini,³ Stefania Scotto,² Nicola Montanaro³ and Giampaolo Velo¹

- 1 Clinical Pharmacology Unit, Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring, University of Verona, Verona, Italy
- 2 Lombardy Centre of Pharmacovigilance, Milan, Italy
- 3 Department of Pharmacology, Interuniversity Research Centre for Pharmacoepidemiology, University of Bologna, Bologna, Italy

Abstract

Objective: To identify the number of cases of anaphylaxis reported in association with different classes of drugs and compare it with other reports contained in the same database.

Methods: The data were obtained from a database containing all of the spontaneous reports of adverse drug reactions (ADRs) coming from the Italian regions of Emilia Romagna, Lombardy and the Veneto, which are the main contributors to the Italian spontaneous surveillance system. The ADRs reported between January 1990 and December 2003 with a causality assessment of certainly, probably or possibly drug related (according to the WHO criteria) were analysed using a case/non-case design. The cases were defined as the reactions already coded by the WHO preferred terms of 'anaphylactic shock' or 'anaphylactoid reaction' (this last term also included anaphylactic reaction) and those with a time of event onset that suggested an allergic reaction and involved at least two of the skin, respiratory, gastrointestinal, CNS or cardiovascular systems; the non-cases were all of the other ADR reports. The frequency of the association between anaphylaxis and the suspected drug in comparison with the frequency of anaphylaxis associated to all of the other drugs was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.

Results: Our database contained 744 cases (including 307 cases of anaphylactic shock with 10 deaths) and 27 512 non-cases. The percentage of anaphylaxis cases reported in inpatients was higher than that among outpatients (59.1% vs 40.9%). This distribution is significantly different from that of the other ADR reports that mainly refer to outpatients. After intravenous drug administrations, anaphylactic shock cases were more frequent than anaphylactoid reactions or other ADRs, but more than one-third of these reactions were caused by an oral drug. Blood substitutes and radiology contrast agents had the highest RORs. Among the systemic antibacterial agents, anaphylaxis was disproportionally reported more often for penicillins, quinolones, cephalosporins and glycopeptides, but diclofenac was the only NSAID with a significant ROR. As a category, vaccines

had a significantly lower ROR, thus indicating that anaphylaxis is reported proportionally less than other ADRs.

Conclusions: Anaphylaxis is a severe ADR that may also occur with commonly used drugs. It represents 2.7% of all of the ADRs reported in an Italian spontaneous reporting database.

Background

Although there is no universal definition of anaphylaxis because of its multi-faceted nature, it can be described as an immediate hypersensitivity reaction with a potentially life-threatening outcome that can affect virtually any organ and is due to the union of an allergen with the IgE of basophils and mast cells. This interaction leads to the rapid release of preformed mediators, such as histamine, and other mediators, such as leukotrienes, which are responsible for the clinical manifestations involving the pulmonary, circulatory, cutaneous, neurological and gastrointestinal systems.^[1-3]

Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions and acute management is the same for both, but anaphylactoid reactions do not necessarily require previous exposure to an inciting substance.^[4] They may be immunological and not IgE-mediated or non-immunological, in which case the mediators are directly released by basophils and mast cells.^[5]

The most common manifestations of anaphylaxis are erythema, pruritus, urticaria, angioedema, nausea, vomiting, diarrhoea, bronchospasm, laryngeal oedema, hypotension and cardiovascular collapse with shock.^[6] There is a direct relationship between the time of onset of the symptoms after antigen administration and their severity: the more rapid the onset, the more severe the episode.^[7]

The incidence of anaphylaxis in the general population varies and is often under-reported, partially because of the absence of a standard definition. As only a few epidemiological studies have been published, its exact incidence is difficult to define, but seems to be increasing.^[8,9] A collaborative study conducted in Hungary, India, Spain and Sweden and based on definite and probable cases of anaphylaxis, estimated that the overall risk of severe anaphylaxis

is 154 per million hospital admissions (0.015%).^[10] In the US, it is estimated that 1 in every 2700 inpatients (0.037%) experiences a drug-induced anaphylactic reaction^[11] and a recent review of the current medical literature concerning anaphylaxis in the US has estimated that it affects between 1.21% and 15.04% of the general population.^[5] Another general population study of anaphylaxis carried out in Olmsted County (MN/US) found an average annual incidence of 21 per 100 000 person years (95% CI 17, 25), with an occurrence rate of 30 per 100 000 person years (95% CI 25, 35).^[12]

Anaphylactic events seem to be related to both age and sex as they are more likely to occur in adults and women.^[10,13] An analysis of 4 years of English hospital admissions for anaphylaxis reported an increased incidence in females of child-bearing age, with a ratio of 1.38 (95% CI 1.27, 1.50), thus suggesting that endocrine factors may be important in the pathogenesis of allergic reactions.^[14]

The most common reported causes of anaphylaxis are medications, insect stings, food and latex, although any agent capable of stimulating mast cells or basophils is a potential cause.^[9] When the cause is not known, idiopathic anaphylaxis is supposed. The incidence of anaphylactic or anaphylactoid reactions varies among classes of drugs and it is known that reactions to antibacterials, especially penicillins, have been observed the most frequently.^[6,15] Allergic reactions to penicillins have been reported as occurring during 0.7–8% of treatment courses in different studies and anaphylactic reactions occur in 0.004–0.015%.^[16] The incidence of mortality is 0.0015–0.002% or one death per 50 000–100 000 treatment courses.^[16]

Other drugs that have been associated with anaphylaxis include aspirin (acetylsalicylic acid) and other NSAIDs, anaesthetic medications, radiology

contrast agents and vaccines; however, it is difficult to make a thorough evaluation of the incidence of anaphylaxis in relation to individual drugs because the reaction is rare and the available data are mainly based on case reports or small case series in which the denominator is unknown.

One case-control study of the risk of anaphylaxis following drug exposure during hospitalisation showed an incidence in the range of 5–15 cases per 100 000 patients for most analgesics and antibacterials, whereas dextran, parenteral penicillin, pentoxifylline and streptokinase were associated with an incidence of ≥ 30 cases per 100 000 patients.^[17]

Data concerning drug-related anaphylaxis that is obtained from spontaneous reporting systems in some countries have shown that dextran, radiology contrast agents, antibacterials and NSAIDs are the most frequently involved drugs.^[18–20] For some drugs, this adverse reaction was unknown at the time of reporting, thus confirming that pharmacovigilance remains essential for signal generation.

Various measures have been taken to decrease the risk of anaphylaxis on the basis of the results of these studies, e.g. the development of non-ionic radiology contrast agents, the marketing of dextran 1 and the worldwide withdrawal of the analgesic glafenine.

It is known that the incidence of an adverse drug reaction (ADR) cannot be estimated on the basis of spontaneous reports, but the development of quantitative methods for measuring signals does make it possible to detect a disproportional number of a reaction when specific knowledge of the composition of a database is presented.^[21,22]

Objective

The aim of this study, which was based on an Italian spontaneous reporting database, was to identify the number of cases of anaphylaxis reported in association with different drug classes and compare the data with the other reports present in the database.

Methods

The data were obtained from a database containing all of the voluntarily submitted reports of ADRs from the Italian regions of Emilia Romagna, Lombardy and the Veneto. These regions had an estimated population of approximately 18 000 000 inhabitants in January 2000 (about 32% of the Italian population) and are the main contributors to the Italian spontaneous surveillance system (accounting for approximately 54% of all Italian reports). We analysed the spontaneous reports collected between January 1990 and December 2003 in terms of the following information: reporter category, patient's age and sex, reporter's ADR diagnosis, characteristics of the underlying diseases, drug exposure (indication, duration of treatment and dose), the time of onset of the event and its outcome. The reports were classified according to the WHO criteria for causality assessment^[23] and only those with a 'certain', 'probable' or 'possible' causality assessment were included.

The association between drugs and anaphylaxis was analysed using a case/non-case design according to the method described by van Puijenbroek et al.^[24] The cases (defined with the general term of anaphylaxis) were the reports describing reactions already coded with the WHO preferred terms 'anaphylactic shock' or 'anaphylactoid reaction'. The anaphylactoid reactions also included the anaphylactic reactions, since they share the same clinical features and can not be distinguished on clinical grounds. Moreover, a case by case analysis was made on reports with a time of event onset that suggested an allergic reaction and involved at least two of the skin, respiratory, gastrointestinal, CNS or cardiovascular systems. Among these, reports with allergic symptoms were classified as anaphylactoid reactions, whereas those that included shock-like symptoms and decreased blood pressure were classified as anaphylactic shock. The non-cases were all of the other ADR reports included in the database.

All of the cases were analysed in detail by a specially constituted *ad hoc* panel of experts, including internists, pharmacologists and immunologists,

whose main task was to check the diagnosis of anaphylaxis and the causality relationship.

The frequency of the association between anaphylaxis and the suspected drug in comparison with the frequency of anaphylaxis associated to all the other drugs was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.^[24] The ROR is identical to the calculation of an odds ratio from a case-control study that compares each drug in turn to all other drugs. Odds ratios and their 95% CIs (adjusted for age, sex and patient typology) were calculated by means of logistic regression using SPSS statistical software. The χ^2 test or Student's t-test were used to compare cases and non-cases as appropriate. Differences were considered significant with p-values of <0.05.

Results

As of December 2003, the database contained 30 975 ADR reports, of which 2276 (7.3%) were excluded because they were unclassifiable or the causality assessment was 'unlikely'. The primary selection identified a total of 1187 cases of anaphylaxis, but the expert panel excluded 443 cases because the diagnosis of anaphylaxis was uncertain. The analysis was, therefore, based on 744 cases (including 307 cases of anaphylactic shock with 10 deaths) and 27 512 non-cases. Among the included reports, the causality assessment was certain in 5%, probable in 59% and possible in 36%, with no significant differences between the cases and non-cases.

Table I shows the main characteristics of the patients. There were no significant differences between the cases and non-cases in terms of age and sex. Patients were also divided, on the basis of the reporter categories, into outpatients (reports coming from general practitioners and emergency rooms) and inpatients (from other hospital wards). The percentage of anaphylaxis cases was higher among hospital patients than outpatients (see table I); this was particularly evident for anaphylactic shock (69.6% vs 30.4%). This distribution was significantly different from that of the other ADR reports, which mainly referred to outpatients.

Table I. Main patient characteristics

Patient characteristics	Cases (n = 744)	Non-cases (n = 27 512)	p-Value
Sex [n (%)]			
females	423 (56.9)	16 540 (60.1)	NS ^a
males	321 (43.1)	10 972 (39.9)	
Mean age (years) $\pm$ SD	49.0 $\pm$ 21.2	49.0 $\pm$ 24.4	NS ^b
Patient typology [n (%)]			
outpatients	304 (40.9)	17 920 (65.1)	<0.001 ^a
inpatients	440 (59.1)	9592 (34.9)	

a χ^2 test.

b Student's t-test.

NS = not significant.

Two hundred and sixty different drugs were suspected of causing anaphylaxis. Ninety-two percent of cases were attributed to only one suspected drug; a similar percentage was observed in non-cases (91%). Table II shows the differences between cases and non-cases in relation to the drug administration route: anaphylactic shock was more frequently reported after intravenous administration than either anaphylactoid reactions or other ADRs; however, more than one-third of the cases of anaphylactic shock were caused by an oral drug.

Table III shows the main six drug categories that were associated with an outcome of anaphylaxis, with the corresponding number of other reported ADRs and the ROR. Among the systemic antibacterial agents, anaphylaxis was disproportionately more often reported in relation to penicillins, quinolones, cephalosporins and glycopeptides with a significant ROR (table IV). The individual antibacterial agents (with a total of ≥ 30 reports) that were suspected of causing anaphylaxis are listed in table V.

As shown in table VI, diclofenac was the only NSAID with a significant ROR. There was significant disproportionality between the cases and non-cases for all of the radiology contrast agents (table VII). Propyphenazone (ROR 5.81; 95% CI 3.52, 9.59) and dipyrone (ROR 2.39; 95% CI 1.22, 4.72) were the analgesic drugs that were mainly responsible for anaphylaxis. There were also reports of anaphylaxis that were related to all blood substitutes and perfusion solutions, but the only agents with a

number of reports suitable for analysis were polyethylene (ROR 16.62; 95% CI 9.90, 27.90) and human albumin (ROR 7.75; 95% CI 2.95, 20.37). As a category, vaccines had a significantly lower ROR, thus indicating that anaphylaxis is reported proportionally less than other ADRs.

Discussion

This study originated from spontaneous reporting data concerning anaphylaxis and so the results should be interpreted in this context. The main aim of spontaneous reporting systems is to detect previously unknown adverse drug-related events or those occurring in a quantitatively or qualitatively different manner from that expected. Quantitative methods have recently been developed to supplement the simple inspection of reports, all of which are based on an assessment of how much the observed reporting frequency of a given ADR deviates from that expected within a database.^[25]

Analysis of databases should take into account any possible bias that is related to spontaneous reporting. One well known problem is under reporting, but when all drug reactions are similarly under reported it is assumed that this would not lead to a systematic bias in the analysis of large databases.^[26] However, uneven under reporting may be a significant problem. High reporting of a reaction can be related to a temporary special attention by doctors (e.g. new reactions to a new drug, media claims, specific guidelines, etc.), whereas a well known reaction may not be reported. Moreover, when using disproportionality measures in analysis of spontane-

ous reporting, the association between a drug and a reaction may be artificially decreased if another drug-specific reaction is widely reported because this dilutes the association by increasing the presence of the drug in non-case reports.^[27]

In this study, we applied the case/non-case method to an Italian spontaneous reporting database by comparing the ratio of anaphylaxis reports (cases) that were identified by clinical signs and chronology with those referring to all other ADRs (non-cases) and looked for associations with patient characteristics and specific drugs or drug classes. Given the characteristics of spontaneous reporting and the variability in terminology used by doctors to report an ADR, the cases included both anaphylactic and anaphylactoid reactions because although their physiopathology differs, their clinical manifestations are often not clearly distinguishable.

In the period 1990–2003, the reports of anaphylaxis accounted for 2.7% of all of the ADR reports in the database. This percentage is about four times higher than that found by van Puijenbroek et al.^[24] in a Dutch study that shared many characteristics with our own in terms of the total number of reports in the spontaneous reporting database, the time of observation and the case selection criteria. We have no data concerning under reporting in the two countries, but we have no reason to think that it would be specifically different for anaphylaxis.

A number of studies have shown marked variability among European countries in the consumption of some classes of drugs, such as antibacterials,^[28] NSAIDs^[29] and lipid-lowering agents.^[30] The an-

Table II. Administration route of suspected drugs

Administration route	Drugs suspected in cases [n (%)]		Drugs suspected in non-cases [n (%)]	p-Value ^a
	anaphylactoid reaction ^b	anaphylactic shock		
Oral	221 (46.4)	125 (36.2)	16 154 (52.9)	<0.001
Intravenous	144 (30.3)	159 (46.1)	1911 (6.3)	<0.001
Other parenteral	83 (17.4)	44 (12.7)	4490 (14.7)	NS
Other routes	25 (5.3)	14 (4.1)	1019 (3.3)	NS
Undefined	3 (0.6)	3 (0.9)	6961 (22.8)	NA
Total	476 (100)	345 (100)	30 535 (100)	

a χ^2 test (cases vs non-cases).

b WHO Adverse Reaction Terminology (WHO-ART) term that also includes anaphylactic reaction.

NA = not applied; NS = not significant.

Table III. Drug categories suspected of causing anaphylaxis (cases) and other reported adverse drug reactions (non-cases)

Drug categories ^a	Cases [n (%)] ^b	Non-cases [n (%)] ^b	Reporting odds ratio (95% CI)
Antibacterials for systemic use	255 (34.3)	5833 (21.2)	1.94 (1.66, 2.26)
NSAIDs and aspirin (acetylsalicylic acid)	104 (14.0)	3131 (11.4)	1.27 (1.03, 1.56)
Radiology contrast agents	100 (13.4)	576 (2.1)	7.26 (5.79, 9.11)
Vaccines	50 (6.7)	3315 (12.0)	0.53 (0.39, 0.70)
Analgesic drugs	40 (5.4)	806 (2.9)	1.88 (1.36, 2.61)
Blood substitutes and perfusion solutions	33 (4.4)	118 (0.4)	10.78 (7.27, 15.96)

a Categories with ≥30 reports of anaphylaxis.

b The percentages refer to the total number of cases or non-cases.

tibacterial sales data for 1997 show that sales were three times higher in Italy than in The Netherlands^[31] and a possible overuse, particularly of injectable antibacterials, may partially explain the higher number of anaphylaxis reports. In the WHO database, which collates spontaneous reports from more than 70 countries worldwide, 27% of the reports of anaphylactic shock that are associated with injectable antibacterials come from Italy (Leone R, personal research: WHO database). This is an extremely high figure as ADR reports from Italy account for no more than 1% of the WHO database.

The distribution of drugs among cases and non-cases by an administration route clearly shows the association between anaphylactic shock and intravenous drug administration, thus confirming that “anaphylactic reactions are usually more dramatic when the drug is given by injection than when it is given orally”.^[32] Intravenous drug administration is almost exclusively used in hospital settings, which may explain the greater frequency of anaphylaxis in inpatients in comparison with other ADRs. On the contrary, ADRs other than anaphylaxis are more frequently reported in outpatients and are associated with orally administered drugs (obviously because this is the most common route of drug administration).

We did not find any differences in the distribution of age and sex among the cases and non-cases. Females were more likely to develop anaphylaxis as well as the other ADRs. A common finding of several studies that were based on spontaneous reporting and other surveillance systems was that women experience more ADRs than men.^[9,33,34] This is probably related to multiple factors that depend on

the type of reaction, such as differences in pharmacokinetics, the influence of circulating hormones on drug metabolism, the greater consumption of drugs by women and their higher reporting rate to doctors.^[35]

The drug categories that were most frequently reported as the cause of anaphylaxis were in line with the medical literature (antibacterials, NSAIDs, etc.). Blood substitutes (polygeline and human albumin) and radiology contrast agents were the categories with the highest ROR, thus indicating that anaphylaxis is probably their most frequent serious adverse event. Polygeline, a polymerised gelatin used as a plasma volume expander, is known to cause anaphylaxis with an incidence ranging from 0.78% to 26%.^[36,37] Histamine release is also a well known effect of human albumin,^[38] although to a lesser extent than polygeline, but the incidence of allergic reactions due to albumin seems to be low.^[39,40]

It is well known that low-osmolality, non-ionic radiology contrast agents cause fewer life-threatening

Table IV. Number of cases and non-cases attributed to the different classes of antibacterials for systemic use

Drug categories	Cases	Non-cases	Reporting odds ratio (95% CI)
Penicillins	88	2085	1.64 (1.30, 2.05)
Quinolones	72	1292	2.17 (1.69, 2.79)
Cephalosporins	50	815	2.36 (1.76, 3.17)
Macrolides	14	883	0.58 (0.34, 0.99)
Glycopeptides	7	106	2.46 (1.14, 5.30)
Aminoglycosides	5	86	2.16 (0.87, 5.33)
Other β-lactams	3	60	1.85 (0.58, 5.92)
Tetracyclines	1	91	0.41 (0.06, 2.91)
Other antibacterials	3	164	0.68 (0.22, 2.12)

Table V. Individual antibacterial agents suspected of causing anaphylaxis

Drug ^a	Reporting odds ratio (95% CI)
Cinoxacin	11.97 (6.53, 21.94)
Piperacillin	4.74 (2.15, 10.45)
Ceftriaxone	3.75 (2.43, 5.79)
Teicoplanin	3.43 (1.48, 7.95)
Levofloxacin	3.01 (1.98, 4.60)

a Agents with ≥ 30 reports of anaphylaxis.

ing adverse reactions than higher-osmolality molecules.^[41-43] As a consequence, they are widely used in Italy despite their higher cost. Some cases of anaphylaxis related to non-ionic radiology contrast agents have been reported,^[44-48] although the mechanisms involved are still a matter of debate.^[49-52] We found a high ROR for all of these agents, with no particular differences between the individual compounds. This finding suggests that the risk of anaphylaxis with non-ionic radiology contrast agents should not be disregarded and emphasises the need to train radiologists to recognise, prevent and treat the anaphylaxis induced by contrast media.^[53]

In this study, antibacterials were responsible for the highest number of reports of anaphylaxis and three of the four classes showing significant disproportionality (penicillins, quinolones and cephalosporins) are among the most widely prescribed antibacterials in Italy. In particular, ceftriaxone (a third-generation injectable cephalosporin) and the fluoroquinolone levofloxacin were the third and fourth antibacterial, respectively, used in Italy in 2003, ranked by cost.^[54] It is estimated that anaphylaxis occurs in 0.46–1.2 per 100 000 patients treated with fluoroquinolones and several case reports and case series have been associated with individual quinolones.^[55,56] Our results indicate a higher disproportionality of anaphylaxis for levofloxacin and cinoxacin.

Cinoxacin product information states that the most frequently reported adverse events in the postmarketing surveillance of cinoxacin have been rash and anaphylactic reactions.^[57] Several case reports have also been published on anaphylactic reactions associated with the use of cinoxacin.^[58,59]

Among the glycopeptide antibacterials, we found a higher ROR for teicoplanin even though it is generally reported to be better tolerated than vancomycin (ROR 0.90; 95% CI 0.12, 6.56).^[60] There are no published case reports of anaphylaxis and the first case of hypersensitivity was published in May 2004.^[61] However, the WHO database contains 29 reports of anaphylactic shock and 25 of anaphylactoid reactions that are associated with teicoplanin, including those that come from Italy (Leone R, personal research: WHO database).

Our analysis indicates that diclofenac is the NSAID that is most frequently associated with anaphylaxis and it is worth noting that this result is similar to that found by van Puijenbroek et al.^[24] in The Netherlands. There are some published cases of diclofenac-induced anaphylaxis after oral administration and patch testing.^[62-66] In a case-cohort study of 934 hospital admissions for anaphylaxis in The Netherlands, diclofenac was one of the most common drug-related causes; the authors estimated an incidence of diclofenac-induced anaphylaxis of 1 in 10 000 to 1 in 20 000 prescriptions.^[67] It has been suggested that diclofenac is associated with selective hypersensitivity without cross-reactivity with other NSAIDs^[68] and in an experimental setting, the drug induces a direct T cell-dependent popliteal lymph node reaction and has intrinsic adjuvant activity that selectively induces the interleukin-4 mediated production of IgG₁ and IgE.^[69]

Table VI. Number of cases and non-cases attributed to NSAIDs and aspirin (acetylsalicylic acid)

Drug ^a	Cases	Non-cases	Reporting odds ratio (95% CI)
Diclofenac	30	353	3.23 (2.21, 4.73)
Ketoprofen	15	339	1.65 (0.98, 2.78)
Aspirin	15	566	0.98 (0.58, 1.64)
Nimesulide	8	495	0.59 (0.29, 1.20)
Naproxen	7	141	1.84 (0.86, 3.95)
Ketorolac	6	150	1.48 (0.65, 3.36)
Ibuprofen	4	128	1.16 (0.43, 3.14)
Rofecoxib	3	234	0.47 (0.15, 1.48)
Celecoxib	2	254	0.29 (0.07, 1.17)
Piroxicam	1	167	0.22 (0.03, 1.58)

a Only the drugs with ≥ 100 reports.

Table VII. Number of cases and non-cases attributed to radiology contrast agents

Drugs ^a	Cases	Non-cases	Reporting odds ratio (95% CI)
lopromide	29	157	7.07 (4.72, 10.57)
lomeprol	24	150	6.08 (3.93, 9.41)
lopamidol	15	99	5.70 (3.29, 9.86)
lodixanol	5	46	4.04 (1.60, 10.20)
loversol	4	30	4.95 (1.74, 14.09)

a Only the agents with ≥ 30 reports.

The results concerning analgesic-related anaphylaxis suggest caution when using propyphenazone or dipyrone. The estimated incidence of propyphenazone-induced anaphylaxis is 0.2%, whereas the incidence of dipyrone-related anaphylaxis is 0.02%.^[70] In Italy, propyphenazone is also available over the counter in association with a peripheral cough suppressant and the suppository formulation is widely used in children. The administration of dipyrone is controversial because of life-threatening adverse events, such as agranulocytosis and aplastic anaemia, and its use is banned in various countries. Cases of anaphylaxis following dipyrone therapy have mainly been reported in Spain, Germany and Russia.^[71-73]

Over the 14 years of our pharmacovigilance system, 3365 adverse reactions related to vaccines have been reported, including 50 cases of anaphylaxis. Unlike in the case of other drugs, we found that the ROR for vaccines was <1 , which may reflect a bias related to the tendency of Italian doctors to report any (serious and non-serious) adverse vaccine reaction (as also required by a recent law), thus leading to a high proportion of non-cases. However, a low rate of anaphylaxis after the vaccination of children and adolescents has also been observed in a study population, with an estimated risk of 0.65 cases per million vaccine doses (95% CI 0.21, 1.53).^[74]

Conclusion

This analysis of 744 reports of anaphylaxis in an Italian spontaneous reporting database using case/non-case methodology confirms the drug categories with the highest risk and shows that the possibility of anaphylaxis should not be disregarded, since any

agent capable of activating mast cells or basophils can potentially cause anaphylactic or anaphylactoid reactions. Levofloxacin, cinoxacin, ceftriaxone, diclofenac, propyphenazone and dipyrone are widely used in Italy, but showed a significant disproportionality for anaphylaxis in comparison with other ADRs.

The most important point to bear in mind regarding anaphylaxis is that it is preferable to prevent it occurring rather than having to treat a reaction. Unfortunately, these ADRs are characterised by their unpredictable nature and a predisposition to anaphylaxis is not easily recognisable or testable. In clinical practice prevention methods are to collect background information about the history of previous anaphylactic episodes and replace the offending agent with another that is not cross-reactive. Other useful measures could be the proper recognition of anaphylaxis when it occurs and employment of a 20–30-minute observation period after the administration of parenteral medications.

At the same time, much work remains to be done to describe these reactions accurately and we believe that morbidity and mortality due to anaphylaxis can only be minimised by improving our knowledge of its epidemiology and risk factors, and ensuring that drugs are used rationally and safely.

Acknowledgements

We are very grateful to the Pharmaceutical Departments of Emilia Romagna, Lombardy and the Veneto and their local Health Districts for collecting the adverse reaction forms.

We would also like to thank the Uppsala Monitoring Centre for allowing us to consult the WHO database. No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

- Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991; 324: 1785-90
- Ewan PW. Anaphylaxis. *BMJ* 1998; 316: 1442-5
- O'Hollaren MT. Anaphylaxis: new clues to clinical patterns and optimum treatment. *Medscape Allergy & Clinical Immunology* 2002; 2 (2) [online]. Available from URL: <http://www.medscape.com/viewarticle/439721> [Accessed 2005 Apr 21]
- Anderson JA. Allergic reactions to drugs and biological agents. *JAMA* 1992; 268: 2845-57

5. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med* 2001; 161: 15-21
6. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol* 2002; 110: 341-8
7. Lieberman PL. Anaphylaxis. *Medscape General Medicine* 1999; 1 (1) [online]. Available from URL: <http://www.medscape.com/viewarticle/408706> [Accessed 2005 Apr 21]
8. Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *BMJ* 2000; 320: 1441
9. Brown AFT, McKinnon D. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001; 108: 861-6
10. International Collaborative Study of Severe Anaphylaxis. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks. *Epidemiology* 1998; 9: 141-6
11. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986; 78: 76-83
12. Yocum MW, Butterfield LH, Klein JS, et al. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999; 104: 452-6
13. Haddi E, Cherpin D, Taffareau M, et al. Atopy and systemic reactions to drugs. *Allergy* 1990; 45: 236-9
14. Sheikh A, Alves B. Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy* 2001; 31: 1571-6
15. Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Saf* 2001; 24: 843-53
16. Weiss WE, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; 18: 515-40
17. Kaufman DW, Kelly JP. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf* 2003; 12: 195-202
18. Wang D-Y, Forslund C, Persson U, et al. Drug-attributed anaphylaxis. *Pharmacoepidemiol Drug Saf* 1998; 7: 269-74
19. Lenler-Petersen P, Hansen D, Andersen M, et al. Drug-related anaphylactic shock in Denmark 1968-1990: a study based on notifications to the Committee on Adverse Drug Reactions. *J Clin Epidemiol* 1995; 48: 1185-8
20. Van der Klauw MM, Wilson JHP, Stricker BH. Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974-1994) and review of the literature. *Clin Exp Allergy* 1996; 26: 1355-63
21. van Puijenbroek EP, Bate A, Leufkens GM, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002; 1: 3-10
22. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. *Br J Clin Pharmacol* 2003; 57: 127-34
23. Meyboom RHB, Hekster YA, Egberts ACG, et al. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf* 1997; 17: 374-89
24. van Puijenbroek EP, Egberts ACG, Meyboom RHB, et al. Different risks for NSAID induced anaphylaxis. *Ann Pharmacother* 2002; 36: 24-9
25. Hauben M, Zhou X. Quantitative methods in pharmacovigilance. *Drug Saf* 2003; 26: 159-86
26. Van der Heijden PGM, 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 ratio. *Stat Med* 2002; 21: 2027-44
27. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; 44: 513-8
28. 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
29. Bergman U, Andersen M, Vaccheri A, et al. Deviation from evidence-based prescribing of non-steroidal anti-inflammatory drugs in three European Regions. *Eur J Clin Pharmacol* 2000; 56: 269-72
30. Magrini N, Einarsson T, Vaccheri A, et al. Use of lipid-lowering drugs from 1990 to 1994: an international comparison among Australia, Finland, Italy (Emilia Romagna region), Norway and Sweden. *Eur J Clin Pharmacol* 1997; 53: 185-9
31. Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. *Lancet* 2001; 357: 1851-3
32. Assem E-SK. Drug allergy and tests for its detection. In: Davies DM, Ferner RE, de Glanville H, editors. *Davies's textbook of adverse drug reactions*. 5th ed. London: Chapman & Hall Medical, 1998: 791-815
33. Naldi L, Conforti A, Venegoni M, et al. Cutaneous reactions to drugs: an analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999; 48: 839-46
34. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-hepatic injuries: a French population-based study. *Hepatology* 2002; 36: 451-5
35. Miller MA. Gender-based differences in the toxicity of pharmaceuticals: Food and Drug Administration's perspective. *Int J Toxicol* 2001; 20: 149-52
36. Weis KH. Haemacel 35: adverse reactions in a multicentric, prospective study. *Anaesthesist* 1983; 32: 488-93
37. Lorenz W, Duda D, Dick W, et al. Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Trial Group Mainz/Marburg. Lancet* 1994; 343: 933-40
38. Celik I, Duda D, Stinner B, et al. Early and late histamine release induced by albumin, hetastarch and polygeline: some unexpected findings. *Inflamm Res* 2003; 52: 408-16
39. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1: 466-9
40. Koch C. Blood, blood components, plasma and plasma products. In: Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs*. 14th ed. Amsterdam: Elsevier, 2000: 1111-39
41. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; 175: 621-8
42. Thomsen HS, Bush WH. Adverse effects of contrast media: incidence, prevention and management. *Drug Saf* 1998; 19: 313-24
43. Maddox TG. Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician* 2002; 66: 1229-34
44. Zuckerman GB, Riess PL, Patel L, et al. Development of a life-threatening anaphylactoid reaction following administration of ioversol in a child. *Pediatr Radiol* 1999; 29: 295-7
45. Alvarez Fernandez JA, Valero AM, Pulido Z, et al. Hypersensitivity reaction to ioversol. *Allergy* 2000; 55: 581-2

46. Dewachter P, Mouton-Faivre C, Felden F. Allergy and contrast media. *Allergy* 2001; 56: 250-1
47. Nakamura I, Hori S, Funabiki T, et al. Cardiopulmonary arrest induced by anaphylactoid reaction with contrast media. *Resuscitation* 2002; 53: 223-6
48. Ketkar M, Shrier D. An allergic reaction to intraarterial non-ionic contrast material [letter]. *AJNR Am J Neuroradiol* 2003; 24: 292
49. Laroche D, Aimone-Gastin I, Dubois F, et al. Mechanisms of severe, immediate reactions to iodinated contrast material. *Radiology* 1998; 209: 183-90
50. Laroche D, Namour F, Lefrancois C, et al. Anaphylactoid and anaphylactic reactions to iodinated contrast material. *Allergy* 1999; 54 Suppl. 58: 13-6
51. Lasser EC. The multipotential pseudoantigenicity of X-ray contrast media: pseudoantigen excess may downregulate the release of hypotensive mediators. *Int Arch Allergy Immunol* 2000; 123: 282-90
52. Lasser EC. The radiocontrast molecule in anaphylaxis: a surprising antigen. *Novartis Found Symp* 2004; 257: 211-24
53. Bartlett MJ, Bynevelt M. Acute contrast reaction management by radiologists: a local audit study. *Australas Radiol* 2003; 47: 363-7
54. Ministero della Salute. Drug utilization in Italy. National report year 2003 [online]. Available from URL: <http://www.ministerosalute.it/medicinali/osmed/osmed.jsp> [Accessed 2005 Apr 22]
55. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000; 20: 1520-3
56. Ho D, Song J, Wang C. Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003; 37: 1018-23
57. Cinobac® product information. Corona (CA): Oclassen Pharmaceuticals, Inc., a division of Watson Labs, Inc., 1999 Jun 23
58. Stricker BH, Slagboom G, Demaeseneer R, et al. Anaphylactic reactions to cinoxacin. *BMJ* 1988; 297: 1434-5
59. Quercia O, Pafanelli S, Emiliani F, et al. Anaphylactic reaction to cinoxacin: report of one case associated with inferior acute myocardial infarction. *Allerg Immunol (Paris)* 2003; 35: 61-3
60. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. *J Antimicrob Chemother* 1991; 27 Suppl. B: 17-29
61. Perrett CM, McBride SR. Teicoplanin induced drug hypersensitivity syndrome. *BMJ* 2004; 328: 1292
62. Dux S, Groslop I, Garty M, et al. Anaphylactic shock induced by diclofenac. *Brit Med J (Clin Res Ed)* 1983; 286: 1861
63. Alkhawajah AM, Eifawal M, Mahmoud SF. Fatal anaphylactic reaction to diclofenac. *Forensic Sci Int* 1993; 60: 107-10
64. Schabitz WR, Berger C, Knauth M, et al. Hypoxic brain damage after intramuscular self-injection of diclofenac for acute back pain. *Eur J Anaesth* 2001; 18: 763-5
65. Sen I, Mitra S, Gombur KK. Fatal anaphylactic reaction to oral diclofenac sodium [letter]. *Can J Anaesth* 2001; 48: 421
66. Jonker MJ, Bruynzeel DP. Anaphylactic reaction elicited by patch testing with diclofenac. *Contact Dermatitis* 2003; 49: 114-5
67. Van der Klauw MM, Stricker BHCH, Herings RMC, et al. A population based case-cohort study of drug-induced anaphylaxis. *Br J Clin Pharmacol* 1993; 35: 400-8
68. Del Pozo MD, Lobera T, Blasco A. Selective hypersensitivity to diclofenac. *Allergy* 2000; 55: 412-3
69. Gutting BW, Updyke LW, Amacher DE. Diclofenac activates T cells in the direct popliteal lymph node assay and selectively induces IgG1 and IgE against co-injected TNP-OVA. *Toxicol Lett* 2002; 131: 167-80
70. Klasco RK, editor. *DRUGDEX® System*. Greenwood Village (CO): Thomson MICROMEDEX, 2004
71. Hernandez C, Aragones N, Estanyol N. Two cases of anaphylactic shock after metamizol given during postoperative recovery. *Rev Esp Anestesiol Reanim* 2004; 51: 168-9
72. Janke C, Schmeck J, Passami D, et al. Anaphylactic cardiocirculatory failure after intraoperative application of dipyrone. *Anaesthesist* 2003; 52: 321-5
73. Priima OB. The clinical picture and ambulatory treatment of drug-induced anaphylactic shock with a favourable course. *Feldsher Akush* 1991; 56: 33-5
74. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112: 815-20

Correspondence and offprints: Dr *Roberto Leone*, Clinical Pharmacology Unit, Policlinico G.B. Rossi, Piazzale L. Scuro 10, 37134 Verona, Italy.
E-mail: rl Leone@sfm.univr.it