

Epidemiology of drug allergy

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Adverse drug reactions occur in 10–20% of hospitalized patients, and up to one-third of these are of an allergic or pseudo-allergic nature. Allergic reactions are unpredictable adverse effects that are linked to immunological mechanisms. Pseudo-allergic reactions are unpredictable adverse reactions that are clinically similar to allergic reactions, but for which there are no drug-specific antibodies or T lymphocytes. There is a paucity of tools that allow a definite diagnosis, and most of the available ones still require validation. Therefore, there are few true epidemiological data, and most of those that are available, including incidence, mortality and socioeconomic impact data, should be interpreted with caution. *Curr Opin Allergy Clin Immunol* 1:305–310. © 2001 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2001, 1:305–310

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1528-4050

Introduction

Drug allergies or hypersensitivities and drug pseudo-allergic reactions represent an important aspect of iatrogenic pathology, and the morbidity, mortality and cost associated with these syndromes are often underestimated [1–3]. They are a frequent, almost daily worry for prescribing physicians, and more generally are a major public health problem. However, no extensive epidemiological studies have been reported, because numerous reactions with symptoms that are suggestive of an allergy, but which do not have an allergic mechanism, are often considered to be real drug allergies [2].

In drug hypersensitivity reactions, a reliable diagnosis is particularly difficult to obtain. The history is often not reliable because different drugs are often taken simultaneously. Test reagents are neither standardized for in-vitro or for in-vivo (skin) tests, and provocation tests are cumbersome, possibly harmful to the patient, and sometimes not sufficiently sensitive because crucial cofactors may be absent during the procedure. Finally, the clinical picture of drug hypersensitivity reactions is rather heterogeneous, mirroring many distinct pathophysiological events.

The vast majority of allergic drug reactions are found to be due to immunoglobulin-E-mediated immediate-type reactions, or T-cell-mediated delayed-type reactions. Unfortunately, drug hypersensitivity reactions may not easily be differentiated from pseudo-allergic adverse reactions, belonging to intolerance or idiosyncratic reactions, or from another diagnosis, such as an infectious exanthema. In a large number of patients no allergy can be proven, which may either be due to the lack of adequate test reagents or procedures, or may indicate a nonallergic pathomechanism. Thus, many doctors (and epidemiological studies) rely on history without attempting to prove the relationship between drug intake and symptoms, or to clarify the underlying pathomechanism of the reaction. Such an approach leads to misunderstanding of both the epidemiology and the pathophysiology of this highly important group of syndromes.

Before the importance of drug allergy as a public health problem is considered, we must define what is meant by 'drug allergy' as precisely as possible.

Drug allergy and pseudo-allergy

A large number of drug reactions are presumed to be of allergic nature, but are not. Moreover, there are multiple

mechanisms of drug allergy, leading to some levels of complexity and confusion.

Confusion regarding the allergic nature of drug reactions

Almost two-thirds of patients who visit a doctor for a reaction that is diagnosed as a 'drug allergy' are not allergic (Fig. 1; unpublished data); however, this relation is reversed in anaphylactic shock. More often the clinical signs are maculopapular cutaneous eruptions, which appear during a course of antibiotics for a respiratory tract infection. The eruptions are frequently (especially in children) related to the pathogenic agent, even though the interaction of both infection and medication is still an under-evaluated issue. They can also be of a pharmacological nature (a central effect of morphinomimetics for example), a subjective symptomatology (anguish, hyperventilation syndrome during local anaesthetics) or a food allergy (medication is often taken during a meal).

Mechanisms of drug allergy

Although drugs are capable of inducing all the types of immunological reactions described by Gell *et al.* [4], they are in the vast majority immunoglobulin-E- or T-cell-mediated reactions. Very often the allergic determinants are unknown, and sometimes several allergic mechanisms and nonallergic mechanisms may be responsible (e.g. those hydroxylamines that are derived from sulfonamides or those induced by certain viruses, such as the Epstein-Barr virus [5] or the HIV virus [6]). One can categorize as 'pseudo-allergic' all those adverse reactions with symptomatology that is suggestive of allergy, but for which an immunological nature cannot be proved [3]. These reactions are often unpredictable, and often implicate the involvements of a pharmacological effect of the drug. There are numerous reactions, which may be of multiple aetiologies [3]. These include the

following: nonspecific histamine release (opiates, radiocontrast media and vancomycin), accumulation of bradykinin (converting enzyme inhibitors), complement activation (radiocontrast media, protamine), activation of leukotriene synthesis (aspirin and nonsteroidal anti-inflammatory drugs) and bronchospasm (by liberation of sulphur dioxide during treatment with agents that contain sulphites or by blockage of the β -adrenergic receptors, even when the drug is administered through the eyes).

Epidemiology of drug allergy

Drug allergies represent an important aspect of adverse reactions to drugs. These are responsible for mortality, morbidity and extra costs that are typically underestimated. Some data are available, however.

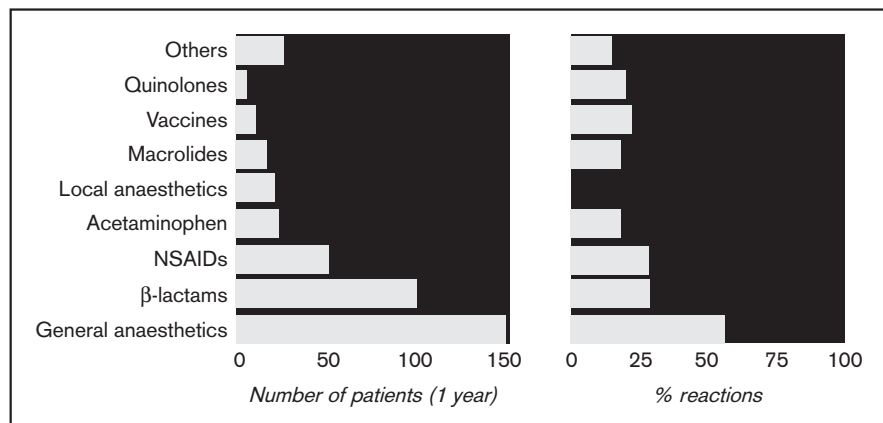
Incidence and prevalence

In the study of Bates *et al.* [7], nurses and pharmacists of the Boston Collaborative Drug Surveillance Program, USA, collected information on all adverse drug reactions in 4031 hospitalized patients during a 6-month period. A total of 247 reactions were identified (incidence of 6.1%), of which 41.7% were severe and 1.2% led to the patient's death. A number of other reactions (194) might have been related to drugs (which increased the incidence to 10.9%). The majority of these reactions were unpredictable (61.7%), and many of them might have been allergic reactions.

Classen *et al.* [8] conducted a study in 36 653 hospitalized patients over 18 months, in which pharmacists from the LDS Hospital in Salt Lake City, USA, developed and used an automatic detection system. Those investigators identified 731 reactions. The incidence was lower than that in the previous study at 1.8%, of which only 12.3% were reported by the doctors in the hospital, 13.8% were severe and 32.7% were of an allergic nature. This system detects reactions that require a biological

Figure 1. Incidence of drug-induced allergic/pseudo-allergic reactions in one consultation

Unpublished data from a 1-year drug allergy outpatient consultation. A total of 442 subjects visited our department with a clearcut history of drug-induced allergic/pseudo-allergic reactions. After a thorough diagnostic procedure (including provocation tests for drugs where skin tests are not validated), almost two-thirds of those patients were not allergic; 151/380 (40%) had proven drug allergy/pseudo-allergy, whereas 229/380 (60%) did not. Sixty-two patients are currently being tested. 'Others' includes streptogramins, heparin, insulin, nelfinavir and dihydroergotamine. Non-steroidal anti-inflammatory drugs (NSAIDs) includes aspirin and all NSAIDs.



assessment or a corrective treatment; had this system been applied in the study of Bates *et al.* [7], then the incidence in that study would have been similar to the incidence identified by Classen *et al.* [8], at 2.8%.

Lazarou *et al.* [9] recently reported a meta-analysis of 33 prospective US studies conducted from 1966 to 1996. Those investigators showed that 15.1% of hospitalized patients suffer an adverse drug reaction (of which 6.7% are severe), and that the incidence of drug-related hospital admissions ranges from 3.1 to 6.2%. A recent French survey [10*], conducted over 14 days in a representative sample of both teaching and general hospitals, support these data; 3.2% patients had been admitted to hospital because of an adverse reaction. That under-reporting of undesirable drug effects occurs is consistently indicated in studies, even at university hospitals, in which a maximum of 6–12% incidences are declared [8,11]. In general practice, the French Centres of Pharmacovigilance estimate that they are informed of less than one effect in 20 000 in general, and less than one serious effect in 6 000.

On the basis of the data presented above [7–9,10*,11], hypersensitivity drug reactions represent up to one-third of adverse drug reactions, which can affect 10–15% of hospitalized patients and are, in most cases, not reported. However, as a precise diagnosis is rarely made, and on the strength of our unpublished results described above (Fig. 1), these reactions may be overestimated, even though the work of the Comprehensive Hospital Drug Monitoring Program of Bern and Saint Gallen in Switzerland [12] found that 2.7% of cutaneous allergic

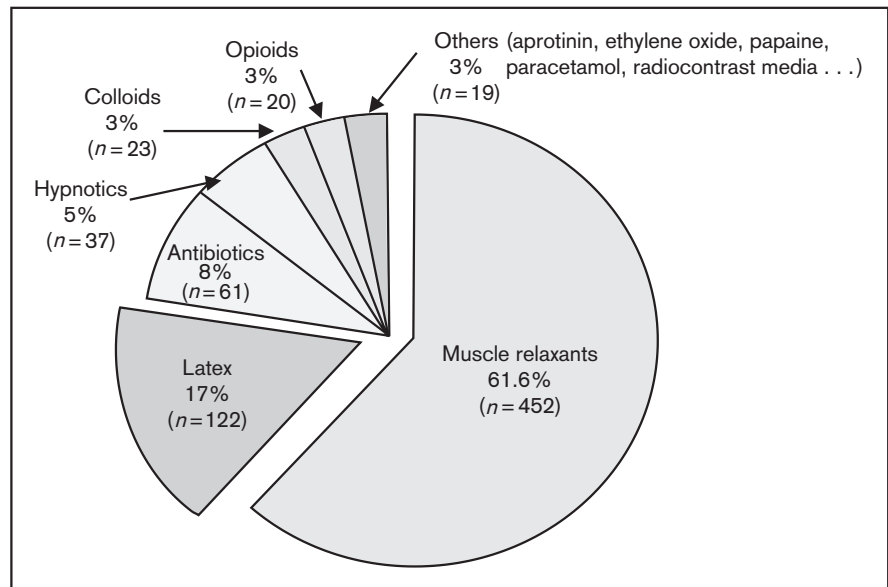
reactions were documented by a dermatologist in 48 005 patients hospitalized over a 20-year period. Again, the diagnosis was a diagnosis of probability, without subsequent firm allergology diagnosis.

This figure was confirmed by another survey conducted in the Boston Collaborative Drug Surveillance Program [13]. In that survey, Bigby *et al.* provided important data on the incidence of allergic drug reactions that are regularly cited in the literature. They analyzed the incidence of cutaneous drug reactions in 15 438 hospitalized patients over a 7-year period. A total of 358 reactions were identified and confirmed by a dermatologist. For each of the 51 drugs studied, the number of reactions over the number of administrations was reported with a global incidence of 2.3%, and 5.1% for amoxicillin, 3.4% for cotrimoxazole, 3.3% for ampicillin, 2.2% for blood derivatives, 2.1% for cephalosporins, 2% for erythromycin, 1.8% for penicillin G and 0.4% for gentamycin. A more recent prospective study [14] in patients receiving monthly injections of penicillin G (for rheumatic fever) found similar data, with 57 reactions in 1790 patients (incidence of 3.2% of patients and 0.19% of injections). Another example is that of the French registry of adverse reactions during general anaesthesia. The fourth recently published survey by that group (Fig. 2) [15] identified 1303 cases (692 anaphylactic and 611 anaphylactoid reactions), giving an incidence of such reactions of 1/13 000 in general anaesthesia and 1/6500 for myorelaxant injection.

The incidence of these reactions in nonhospitalized persons, or even in the general population, is largely

Figure 2. Anaphylaxis during general anaesthesia

Results of the fourth French survey of anaphylaxis during general anaesthesia [15]. From July 1994 to December 1996, 1303 cases were reported (692 anaphylactic and 611 anaphylactoid reactions), and the drugs involved are as shown.



unknown. In a review of almost 6000 records in a private group pediatric practice in northern Virginia [16•], cutaneous eruptions occurred in 7.3% of children who were given the common oral antibiotics: 12.3% for cefaclor, 8.5% for sulfonamides, 7.4% for penicillins, and 2.6% for other cephalosporins. In another study [17], three out of 3200 students treated with ciprofloxacin to prevent meningococcal carriage suffered an anaphylactic reaction. In a study of Katayama *et al.* [18] of 337 647 injections of radiocontrast media in Japan, the incidence of adverse reactions was 12.6% (0.22% of severe reactions for ionic products and 0.04% for non-ionic products). Other useful information is the incidence of such reactions in exposed subjects during clinical trials. However, drug monographs do not always reflect the safety profile of the drug once it is commercially available, especially because some drugs (anti-HIV drugs, for example) are more rapidly launched.

Mortality

Lazarou *et al.* [9] analyzed 33 prospective US studies from 1966 to 1996, and showed that 0.32% of hospitalized patients died from adverse drug reactions, resulting in an estimated 106 000 deaths for the year 1994 – the fourth cause of death in the USA! The proportion of allergic reactions in this study was not evaluated, but was estimated to be 23.8% (of all severities).

Anaphylactic shock is an immunoglobulin-E-mediated reaction and is the most frightening and potentially lethal adverse drug reaction, although non-immunoglobulin-E-related anaphylactoid shocks can also be drug related. Although these events are rare, the extremely rapid onset of the symptoms and the possibility of death render them a major threat. They are not the only causes of mortality due to allergic drug reactions; toxic epidermic necrolysis (30% mortality), Stevens–Johnson syndrome (5%), hypersensitivity syndrome (10%), and other vasculitides or liver, lung or kidney involvements can also be deadly.

Anaphylactic shock has been specifically studied in some cohorts. In particular, Yocum and Khan [19] found that drug anaphylaxis represented 12.8% of 179 anaphylactic reactions identified at the Mayo Clinic, USA, over a 3-year period. Also, Van der Klauw *et al.* [20] identified 345 cases of probable anaphylactic drug reactions and 485 possible cases during the period from 1974–1994 in The Netherlands. Glafenin was responsible for 326 cases (in which there were two deaths), followed by nonsteroidal anti-inflammatory drugs (101 cases), sulfonamides (23 cases), dextran (20 cases, among which there were three deaths), floctafenin (12 cases), allergens (12 cases, among which there were two deaths) and amoxicillin (11 cases). The mortality

associated with anaphylaxis was 2.5% in that study (21 cases out of 830).

During the period 1968–1990, the Danish Drug Administration [21] identified 30 cases of fatal anaphylactic shock, of which eight were caused by radiocontrast media, six by penicillins, five by allergen extracts, two by nonsteroidal anti-inflammatory drugs and one by myorelaxants (incidence of 0.3 cases per million inhabitants/year). A recent survey conducted in the UK [22•] identified an almost twofold increase between 1991 (56 per million) and 1995 (102 per million) in hospital admissions for acute anaphylaxis. Where the aetiology was recorded (51%), the most common causes were therapeutic drugs (62%). In the UK, a registry of all fatal anaphylactic reactions has been established since 1992. The latest report [23•] detailed 164 fatalities during the period 1992–1998, with drug anaphylaxis representing 39% of the cases (27 cases for anaesthetics, 16 for antibiotics and eight for radiocontrast media).

For certain drugs, such as general anaesthetics, penicillins or radiocontrast media, the statistics are more well known. In a study in patients receiving weekly injections of penicillin G (in the case of rheumatic fever) [14], four anaphylactic reactions (incidence of 0.2% of patients, and 0.01% of injections) and one death (incidence 0.05% of patients and 0.003% of injections) were described. In the study of Katayama *et al.* [18] of 337 647 injections of radiocontrast media in Japan, two deaths were reported (incidence of 0.0006%).

Drug-related risk factors

In order to be immunogenic in its native state, a substance must have a sufficient molecular weight (>1000 Da), which is the case with heterologic sera and certain enzymes (e.g. chymopapaine) and hormones (e.g. insulin). Most other drugs have an insufficient molecular weight, but can react as haptens, coupled with a carrier protein (which is more often autologous, such as plasma albumin), to induce a specific immune response [3]. The dose of the drug and the mode of administration influence the incidence of reactions. In case of an allergy to penicillin or insulin, intermittent and repeated administrations have a greater sensitizing effect than does uninterrupted treatment. Sensitized patients react to minimal doses. The parenteral route is the most immunogenic, but topical administration (ointments, creams, eye drops) can also be very immunogenic, and can result in sensitization and reactions (probably due to a local inflammation).

Host-related risk factors

Most studies show that women are more often affected than men (65–70% versus 30–35%) [24–26], and it is often reported that children are less affected than adults.

This is also our experience, but systematic and thorough studies are still lacking. Atopic patients do not appear to be predisposed [25–27], but their reactions can be more severe. However, this notion is regularly debated and atopy could play a role in certain drugs, such as nonsteroidal anti-inflammatory drugs [28*] and chymopapaine [29].

Haddi *et al.* [25] showed that the percentage of individuals with serum immunoglobulin E [globally evaluated by the positivity of Phadiatop[®] (Pharmacia Upjohn, Uppsala, Sweden)] a history of allergic reactions to drugs (17.6%) than in 1764 persons without such a history. A familial concentration of cases is sometimes reported in the literature, and certain HLA haplotypes appear to be implicated in delayed hypersensitivity reactions to aminopenicillins [30] and pyrazolone [31], but not to anti-convulsivants [32]. Genetic control of cytochrome P450 enzymes and *N*-acetyl-transferases (which ensured the biotransformation of drugs) and glutathione-S-transferases (which are detoxification enzymes of cytochrome P450-derived reactive metabolites) may also be causal, and studies in the sulfonamides are ongoing.

A case–control study [33] suggested that patients with systemic lupus erythematosus suffer from reactions two to five times more frequently than those without lupus; these reactions are (principally) cutaneous after absorption of β -lactams, sulfonamides and erythromycin. A syndrome of multiple drug hypersensitivities (which is immunoglobulin E dependent in those individuals who are allergic to penicillins) has been described [26,34] and challenged [35]. These hypersensitivities suggest involvement of genetic factors described above, but should not be mistaken for reactions to diverse drugs of an identical structure (cross-reactivities).

Patients with AIDS suffer more than others from cutaneous reactions to drugs, and are 10–50 times more likely to suffer an adverse reaction to cotrimoxazole [36]. This can be explained by a slow acetylation profile, and the deficiency in glutathione that is frequently observed in these patients [36,37]. A large number of these reactions are certainly not of an immunologic nature [6], and therefore are pseudo-allergic reactions. However, thorough diagnostic procedures, including provocation tests and analysis of the exact mechanisms, are still rarely performed.

β -Blockers aggravate all allergic and pseudo-allergic reactions, and make treatment with adrenaline (epinephrine) difficult. Consumption of β -blockers, in the same way as the presence of asthma, is a risk factor for pseudo-allergic reactions during radiocontrast media injections, multiplying the risk by 2.5 (β -blockers) and 4.5 (asthma) [38].

Enzymatic polymorphisms may participate in the pathophysiology of some pseudo-allergic drug reactions. Recently, overexpression of the key enzyme in cysteinyl-leukotriene biosynthesis was reported in bronchial biopsies of aspirin-intolerant patients [39], and this phenomenon might, at least partly, be explained by a genetic polymorphism in the leukotriene C₄ synthase.

Socioeconomic impact

The socioeconomic impact of drug allergies has never been precisely evaluated. For this, one must take into account not only the direct costs (treatment of these reactions, hospitalizations, and prolongations of hospitalization), but also the indirect costs (sick leave, invalidity, and excessive cost of the choice of alternatives, which are not always medically satisfactory). For example, Preston *et al.* [40] questioned 97 patients with a clinical history of allergy to penicillins, who required treatment with antibiotics for a classic infection that was treated first with penicillins. Less than 10% were tested for this allergy, and more than 50% had been given an alternative, but more expensive antibiotic; in addition, more than 10% had used penicillins since their incident without any problems.

Data obtained from national cross-sectional incidence studies on hospital admissions caused by adverse drug reactions [1,9,10*] can be extrapolated to the country as a whole, and the extra cost calculated (if we know the duration of the hospitalization of the patient). In the meta-analysis of 33 prospective studies conducted during 1966–1996 reported by Lazarou *et al.* [9], 4.7% of hospitalizations were made for adverse drug reactions, resulting in 1 547 000 hospitalizations for the year 1994 in the USA. It was not possible to calculate the percentage of drug allergies, but this was estimated at 23.8% of adverse reactions in hospitalized patients. In another case–control study reported by Classen *et al.* [41], 1580 patients who suffered adverse drug reactions that occurred during hospitalization were compared with 20 197 control individuals. The patients were hospitalized for 1.91 days longer than were the control individuals, incurring additional costs of US\$2262 per patient. The role of drug allergy was not evaluated with precision.

Conclusion

Epidemiological data for allergic/pseudo-allergic drug reactions are imprecise, as they are both under- and over-diagnosed. They are globally presented as adverse drug reactions, and rarely individualized and confirmed. A better understanding of the frequency of such reactions, as well as testing to establish a firm diagnosis, should allow us to improve our knowledge of this subject, and to improve the diagnosis, treatment and management of patients. This, in turn, should allow us to reduce morbidity, mortality and health care costs.

Acknowledgements

The authors thank Dr Dominique Hillaire-Buys (Department of Pharmacovigilance, Hôpital Saint-Charles, University Hospital of Montpellier – Professor Blayac) for sharing data with us.

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