

DRUG HYPERSENSITIVITIES: DEFINITION, EPIDEMIOLOGY AND RISK FACTORS

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SUMMARY: Drug hypersensitivity reactions are the adverse effects of drugs taken at a dose which is tolerated by normal subjects, and which clinically resemble allergy. There is few true epidemiological data on drug hypersensitivity reactions. The available information requires a cautious interpretation as they are rarely proven. Both under diagnosis and over diagnosis must be taken into account. Drug hypersensitivity reactions represent one third of adverse drug reactions, can be life threatening and motivate changes on drug prescription. They concern more than 7% of the general population, therefore being an important public health problem. A few risk factors are already pinpointed. Future progress in genetics can help the identification of populations at risk for specific reactions. This review describes currently known data on incidence, prevalence, mortality and risk factors of these reactions.

Key-words: Drug allergy - Drug hypersensitivity - Incidence - Prevalence - Risk factors.

CLASSIFICATION OF DRUG HYPERSENSITIVITY REACTIONS

Drug hypersensitivity reactions are the adverse effects of drugs taken at a dose which is tolerated by normal subjects and which clinically resemble allergy. Although they are a frequent, almost constant worry for the prescribing physicians, there is no existing extensive epidemiological study, as numerous reactions with symptoms suggestive of an allergy are often considered to be real drug allergies and they are not.

Adverse drug reactions in general are regarded as an important public health problem. They are defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in man (1). The classical pharmacological classification of Rawlins and Thompson (2) separates two major subtypes: type A reactions, which are dose dependent and predictable and type B unpredictable reactions non-dose dependent. Type B reactions include hypersensitivity reactions. According to the new EAACI nomenclature the designation of drug allergy should be applied only

when a definite immunological mechanism, either IgE dependent or T-cell mediated, is demonstrated (3). Reactions that clinically resemble an allergy but where an immunological process is not proven should be classified as non-immune hypersensitivity reactions (3).

Schematically, several criteria characterise an allergic reaction:

- The reaction is not an expected pharmacologic effect.
- A period of sensitization precedes the reaction.
- The reaction may occur at a dose much lower than that required for a pharmacologic effect.
- The clinical symptoms are characteristic of an allergic reaction.
- Resolution occurs within an expected interval, usually days, after discontinuation of the offending agent.
- Chemical cross-reactivity may occur.

Non-immune drug hypersensitivity reactions assume most of the criteria cited above (2-6). There are of multiple etiologies, including: a non-specific histamine release (opiates, radiocontrast media and vancomycin), an accumulation of bradykinin (angiotensin converting enzyme inhibitors), a complement activation (radiocontrast media, protamine), an activation of leukotriene synthesis (aspirin and non-steroidal anti-inflammatory drugs), a bronchospasm by liberation of sulphur dioxide (during treatments containing sulphites) or by blockage of the β -adrenergic receptors (even when the β -blocker is administered through the eyes).

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PREVALENCE AND INCIDENCE OF DRUG HYPERSENSITIVITY REACTIONS

Data on hospitalized patients

The Boston Collaborative Drug Surveillance Program collected information on all adverse drug reactions in 4,031 hospitalized patients during a six-month period. 247 reactions were declared (an incidence of 6.1%), of which 41.7% were severe and 1.2% led to the patient's death (4). The majority of these reactions were unpredictable (61.7%) and therefore possibly allergic reactions, although this is not stated in the paper. Lazarou *et al.* (5) showed in a meta-analysis of 33 prospective US studies from 1966-1996, that 15.1% of hospitalized patients suffer an adverse drug reaction (6.7% severe) and that, the incidence of drug-related hospital admissions ranges in between 3.1 to 6.2%. In the prospective French pharmacovigilance study by Olivier *et al.* (6), data from 671 patients admitted to an emergency department during a 4 week period lead to the identification of 44 adverse drug reactions involving 41 patients resulting in an incidence of 6.1%. In Singapore, a two-year prospective study by Thong *et al.* (7) using a network-based electronic notification system detected 366 cases of reported drug allergy from a total of 90,910 inpatients. After review, 210 were classified as drug allergy. Cutaneous manifestations were the most common clinical presentation (95.7%), systemic manifestations occurred in 30% of the cases and serious adverse reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis occurred in 11 patients (5.2%). Antibiotics and anti-epileptic drugs accounted for 75% of the reactions. They concluded that the incidence of drug allergy in hospitalized patients was 0.42%. In a 20-day observational prospective study in an Italian University hospital, among 171 inpatients undergoing antibiotic treatment, 7 patients experienced an adverse drug reaction (4%), 2 of them (28%) could have been allergic reactions (angioedema to piperacillin; skin eruption following ceftriaxone) (8). A recent retrospective case control study in Singapore by Kidon *et al.* (9) using the hospital inpatient electronic medical record found 222 (2.6%) patients reporting a previous adverse drug reaction among 8,437 hospitalized children. Almost 70% of them involved the use of antibiotics (β -lactams 45%) and non steroidal anti-inflammatory drugs (18.5%). 98% of the reactions were mostly cutaneous and could have been allergic in nature.

When considering more specific clinical settings it is possible to find more accurate data. The French registry of anaphylaxis during general anesthesia identi-

fied 789 cases during a 2-year survey, given an incidence of such reactions of 1/13,000 general anesthesia. 518 (66%) had a demonstrated immune mechanism. Among those, the most culprit drugs were neuromuscular blocking agents (58.2%), giving a calculated incidence of 1/6,500 myorelaxant injections. Antibiotics were responsible for 15.1% of these reactions (10). They are now a rising cause of anaphylaxis during general anesthesia. In the study of Katayama *et al.* (11) of 337,647 injections of radio contrast 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) and two deaths were reported (incidence of 0.0006%).

Data on outpatients and general population

A prospective study in patients receiving monthly injections of penicillin G (for rheumatic fever), found 57 reactions in 1,790 patients (incidence of 3.2% of patients and 0.19% of injections). 4 anaphylaxis (incidence of 0.2% of patients and 0.01% of injections) and 1 fatality (incidence of 0.05% of patients and 0.003% of injections) are described (12). Apter *et al.* (13) lead a retrospective study using the UK General Practice Research Database. Records of patients who received at least 2 prescriptions for penicillin at least 60 days apart were selected and examined for hypersensitivity reactions. A penicillin prescription was given to 3,375,162 patients (all ages) and from those 6,212 (0.18%) experienced an allergic-like event. 48.5% were given a second prescription after the event and only 1.89% had another event, suggesting that most reactions resembling drug allergy are not drug related. On the other hand although the difference in incidence was small in the group with previous reaction, their risk of a second event was markedly increased. In a review of 5,923 records in a private pediatric practice group in northern Virginia, cutaneous eruptions occurred in 7.3% of the children who were given common oral antibiotics (14). Considering quinolones, 3 out of 3,200 students treated by ciprofloxacin to prevent meningococcal carriage experienced an anaphylactic reaction (15).

A cross-sectional survey of a general adult population from Porto, Portugal found a global 7.8% (181/2,309) prevalence of self-reported drug allergy; 4.5% to penicillins or other β -lactams, 1.9% to aspirin or other non steroidal anti-inflammatory drugs and 1.5% to other drugs. Most of the reported reactions were immediate (43%), occurred on the first day of treatment (78.5%) and involved the skin (63.5%) so could have been immune mediated (16).

Data on mortality

Drug hypersensitivity reactions can be serious and potentially life-threatening. In the USA, the study of Lazarou *et al.* (5) showed that 0.32% of hospitalized patients died from adverse drug reactions making 106,000 deaths estimated for the year 1994 (that would be the fourth cause of death in this country). The proportion of allergic reactions in this study has not been evaluated, but could be estimated around 23.8% (all severities). In the study of Thong *et al.* (7) referring to drug allergy, the attributable mortality was 0.09 per 1,000 hospitalizations.

Anaphylactic shock is the event currently associated with drug allergy fatalities. Non-IgE related shocks can also be drug related and equally dangerous. Based on a medical literature review to obtain prevalence estimates on anaphylaxis in the general population, Neugut *et al.* (17) calculated a rate of anaphylaxis from 0.7% to 10% for penicillins (USA population at risk would be 1.9 to 27.2 millions) and from 0.22% to 1% for radiocontrast media (USA population at risk would be 22,000 to 100,000). Matasar and Neugut reported about 1,500 annual deaths from anaphylaxis in the US (18). In the UK, the work by Pumphrey (19) on deaths by anaphylaxis (1992-2001) shows that drugs are the leading cause (88 deaths from 202) followed by food and insect stings. The recent 3-year Swiss study by Helbling *et al.* (20) led to the detection of 226 individuals diagnosed as having presented life-threatening anaphylaxis (246 episodes) and 3 deaths due to anaphylaxis. The authors calculated an annual incidence of 7.9 to 9.6 cases per 100,000 inhabitants per year and refer drugs as the second cause (18.1%) after hymenoptera stings.

Anaphylaxis is not however the only cause of mortality due to allergic drug reactions. The serious, mostly drug related, dermatological conditions Stevens Johnson Syndrome (5% mortality) and toxic epidermal necrolysis (30% mortality) with estimated incidence of 0.4 to 1.2 and 1.2 to 6 per million people/year, respectively (21) are other examples of life-threatening events. They occurred in 5.2% of the 210 drug allergic patients in the Thong *et al.* study (7). Besides, multisystem organ hypersensitivity syndrome and organ specific involvement can also contribute to drug hypersensitivity related mortality.

RISK FACTORS OF DRUG HYPERSENSITIVITY REACTIONS

Drug-related factors

In order to be immunogenic or a complete allergen, a substance must have a sufficient molecular weight

(more than 1,000 daltons), so most drugs behave as haptens and have to bind to carrier proteins to induce a specific immune response. Beta-lactams are intrinsically reactive (supporting the hapten concept of the pathophysiology of drug allergy). Other drugs like sulfamethoxazole require previous conversion to a reactive intermediate (pro-hapten concept). Drug-related cytotoxicity/inflammation may also be of importance to enhance the immune response (danger concept). Some other drugs, although not reactive, can still be immunogenic by direct noncovalent binding to immune receptors such as T cell receptors and MHC peptides (pharmacological interaction concept) (22). The notion that the drug itself is an important risk factor for drug allergy even among the same therapeutic group can be illustrated by another survey of the Boston Collaborative Drug Surveillance Program (23). In this survey, the authors analyzed the incidence of cutaneous drug reactions in 15,438 hospitalized patients and provided the majority of data regularly used for the incidence of drug hypersensitivity reactions. 358 reactions were collected and confirmed by a dermatologist with a global incidence of 2.3%. The number of reactions over the number of administrations has been reported at: 5.1 % for amoxicillin, 3.4% for cotrimoxazole, 3.3% for ampicillin, 2.1% for cephalosporins, 2% for erythromycin, 1.8% for penicillin G and 0.4% for gentamycin. This great variation from one drug to another supports the statement that there are drug-related factors.

Treatment regime

Intermittent and repeated administrations can be more sensitizing than an uninterrupted treatment (24). Regarding administration, the parenteral route is considered the most immunogenic, followed by the topical administration (25, 26).

Host related factors

Most studies show that **women** are more often affected than men (65-70% against 30-35%) (27-29). Differences can however depend on the age group considered, the type of reaction and maybe also the type of drugs (9). It is often reported that **children** are less affected than adults (62), but there are controversial data available (14). The role of **atopy** is still under debate, but it does not seem to be a risk factor (28-30). The influence of atopy may however depend on the drug in question since it was reported to be a risk factor to non steroidal anti-inflammatory drug hypersensitivity (31). **Concomitant diseases** facilitate drug hypersensitivity reactions. As an example, hypersen-

sitivity to non steroidal anti-inflammatory drugs is more frequent in patients suffering from asthma (32) or nasal polyposis. The frequency of drug hypersensitivity in HIV infected patients is 10-100 higher compared to HIV negative subjects (33).

Some **ethnic groups** seem to be prone to drug hypersensitivity. African Americans have an increased risk for angiotensin-converting enzyme inhibitor induced cough (34) and angioedema (35, 36).

These could be explained by **genetic polymorphisms** that alter drug metabolism or immune responses. Indeed, individuals with angiotensin-converting enzyme inhibitor genotype II have an increased risk for cough (34) and in those who experienced angioedema an abnormality of degradation of some bradykinin metabolites has been described (37). The work of Martin *et al.* (38) demonstrates that predisposition to abacavir hypersensitivity is linked to HLA-B5701 and its combination to a haplotypic Hsp70-Hom variant is highly predictive of hypersensitivity (the authors even suggest that prospective genetic testing should be done to identify patients at risk and exclude from abacavir treatment). The TNF polymorphism -238A affects the levels of TNF production influencing the severity of abacavir reactions. (38). Another TNF polymorphism (-308TNFalpha) was associated with severe carbamazepine hypersensitivity reactions (39). The work from Bavdekar *et al.* (40) proposes that accumulation of toxic arene oxide metabolites due to a defect in epoxide hydrolase-mediated detoxification contributes to anticonvulsant hypersensitivity. In bronchial biopsies of aspirin-induced asthma patients an over expression of leukotriene C4 synthase was reported which could be partially explained by a genetic polymorphism in the promoter region of this enzyme (41). In a recent study, Qiao *et al.* (42) showed that the E237G variant of FcεRIβ may participate to the development of IgE reactions to penicillins. Time has come now to identify and analyse all relevant gene polymorphisms involved in drug hypersensitivity.

CONCLUSIONS AND PERSPECTIVES

The available information on adverse drug reactions requires a cautious interpretation as they are rarely classified and proven. Both under diagnosis, because of under declaration and over diagnosis due the common use of the term "allergy" are to be considered. Misclassification based on drug allergy history may have consequences on individual treatment choices and lead to the use of more expensive, possibly harmful and less effective drugs. A big effort is to be

made to better understand the true extent of the problem and this includes the necessity to establish a firm diagnosis. More accurate data, should also allow the implementation of better protection measures for the patients.

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