

Review article

Important questions in Allergy: 1 – drug allergy/hypersensitivity

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Magnitude of the problem

Drugs can induce several different types of immunological reactions which represent, together with nonallergic drug hypersensitivity reactions (DHRs), 15% of adverse drug reactions. Nonallergic DHRs resemble an allergy, without any proven immunological process. DHRs are a major cause of postmarketing withdrawal. They are also a daily worry for clinicians and patients. Even though urticarial and maculopapular eruptions are the most frequent manifestations, there are many other clinical forms, some of which are life-threatening, require or prolong hospitalization and entail changes in the drug prescription (1). DHRs affect more than 7% of the general population and therefore represent an important public health problem (2). Both under-diagnosis [because of under-reporting (2, 3)] and over-diagnosis [because of the over-use of the term 'allergy' (2, 4)] are potential problems. Misclassification based on the drug allergy history may have consequences on individual treatment choices and can lead to the use of more expensive and less effective drugs.

Drug hypersensitivity reactions have a significant impact on clinical practice, drug development and public health. However, epidemiological studies or research to better understand them and attempts to develop diagnostic and predictive tests have been limited. This fact

was already recognized years ago by our American colleagues, who, after losing some promising drugs as a result of severe DHRs, established a task force with representatives from the key stakeholders (research clinicians, regulatory scientists and immuno-toxicologists from the pharmaceutical industry) to identify critical data gaps and opportunities and to make recommendations on how to overcome some of the barriers to drug hypersensitivity research and address research needs (5). The situation in Europe was better, as most research was performed here, and as the interested people met already in two drug hypersensitivity meetings, the first one held in Bern in 2004, the second in Liverpool in 2006 and the third is planned in Paris, April 2008, (see <http://www.dhm3.org>). These meetings bring together people from industry and research. However, the problem is huge and much more efforts are needed to make our drugs safer.

Unresolved questions in DHRs and research needed

Clinical diagnosis of DHRs

Diagnostic tools and procedure. A large number of reactions are presumed to be drug related and of allergic nature, but closer examination reveals that they are not (2, 4). The diagnosis of DHRs relies on clinical histories,

skin tests, patch tests and a very few validated *in vitro* tests (6–10). Standardized diagnostic procedures have been published under the aegis of the European Network of Drug Allergy (ENDA) (11–17), the core group of the EAACI interest group of drug allergy and a member of GA²LEN. Validation of these clinical tests for all drugs does not exist and multicentre studies are needed to achieve this. Establishing standard operating procedures and cut-off concentrations for skin tests for most drugs is required. The diagnosis of severe cutaneous reactions, or those affecting organs, is still very poor. The development of tools for skin testing and biological diagnosis (18) is crucial for those cases where drug provocation is not possible. The establishment of multi-national, adequately resourced large DHR databases would enable all observations to be collected which would in turn facilitate epidemiologic, risk factor and pharmacovigilance analyses.

Immediate vs non immediate DHRs. Drug hypersensitivity reactions are commonly classified as immediate or nonimmediate depending on their clinical presentation (6). Immediate reactions are usually induced by an immunoglobulin E (IgE)-mediated mechanism and occur within the first hour after the last drug administration. They are usually manifested as urticaria, angioedema, rhinitis, bronchospasm or anaphylaxis. Nonimmediate reactions may occur at any time from 1 to 48 h after the last drug administration and are often induced by a delayed T-cell dependent type of allergic reaction. Maculopapular exanthema is the most common manifestation of nonimmediate reactions. A recent analysis from a large database has shown that most β -lactam DHRs can be divided into three groups: anaphylaxis and anaphylactic shock (immediate reaction); maculopapular exanthema (late reaction); and urticaria (which can occur at any time) (19). Drug-induced late-onset urticaria deserves further studies focused on its pathogenic mechanism(s).

Epidemiologic studies of DHRs

Prevalence, co-morbidities and severity. Epidemiologic risk factors for DHRs are not well characterized and may be influenced by regional/national differences in drug prescriptions. All drugs can induce DHRs, but the incidence and risk factors for individual drugs have been poorly defined. The development of a network that can increase the population size from which to capture data on DHRs would be a major advance. The development of such a network would need the concomitant development of a unique DHR database, a knowledge base developed around the collection of standardized data, the nature of which would have to be defined on the basis of expert consensus. The development of such a database would have huge benefits in defining the risk factors associated with DHRs, and would allow analysis at the level of individual patients, on a country by country basis (related to individual prescribing habits), and on an EU level to

allow longitudinal assessment of the safety of new drugs as they are launched and used on a large population basis. Such a database would be complementary to the EUDRAVIGILANCE database launched by the EMEA, and would certainly feed data into the EMEA database. However, unlike EUDRAVIGILANCE, it would try to overcome the major limitation of spontaneous reporting, i.e. under-reporting, by engaging with interested clinicians and getting them involved in the network.

Resolution over time. The natural course of DHRs is not well known. Data regarding penicillins seem to indicate that T-cell mediated reactions may be life long (10), while some patients with IgE-mediated hypersensitivity may outgrow their allergy (20). Follow-up studies regarding drugs other than penicillins are needed.

Social consequences. The socio-economic impact of DHRs has never been precisely evaluated. For this, one must take into account not only the direct costs (treatment of these reactions, hospitalizations and prolongation of hospitalization), but also the indirect costs (sick leave, invalidity, excessive cost of the choice of alternatives which are not always medically satisfactory). The development of a network and a DHR database would facilitate such an analysis.

Mechanisms of DHRs

Immunological mechanisms. Mechanistic studies need to be carried out to better understand DHRs and their risk factors – this will allow for improved therapy in clinical practice and provide lessons for drug development. Drugs are capable of inducing all the types of immunological reactions described by Gell and Coombs (21), but mostly IgE or T-cell mediated reactions. Evidence over the last 5 years suggests that not all drugs need to bind covalently to the major histocompatibility complex to induce an immune response (21). Some drugs, without undergoing the classical antigen processing and presentation pathway, may bind directly in a noncovalent fashion to T-cell receptors triggering a drug-specific immune reaction; this phenomenon has been named the pharmacological interaction with immune receptor (p-i) concept. This may explain the frequency of non-IgE mediated reactions that occur within hours of first exposure. Whether or not this mechanism is also involved in IgE-dependent reactions is not yet known. Prediction of such reactions may also be possible, but has not yet, been fully evaluated. The importance here lies in future drug development and the prediction of which molecules may be liable of leading to such reactions, and the development of congeners which retain pharmacological activity, but do not cause immune reactions.

Allergenic determinants and co-factors. For most drugs, the allergenic determinants are unknown. Pinpointing the allergenic determinants is of crucial importance; this will

allow better prediction of cross-reactivities and provide clinicians with tools for skin testing, biomarkers and biological diagnosis. Although genetic factors will be important here, we should not forget environmental factors. For instance, the role of irritant molecules and viruses acting as co-factors or danger signals is intriguing and needs further analysis.

Pharmaco/immunogenetic backgrounds. In a minority of individuals, exposure to a drug induces an immune reaction during which they become sensitized and thereafter develop an allergic reaction to each subsequent exposure to that molecule. Thus, sensitization to drugs must be regarded as 'breaking of the immune tolerance' to these molecules. Many factors, many of which are yet to be discovered, control this process, including:

- (1) the chemical structure of the molecule, which is probably the most important factor;
- (2) genetic factors including polymorphisms in genes coding for drug metabolizing enzymes and immune responses (22);
- (3) environmental factors (stress, concomitant infection, pollution); and
- (4) the characteristics of exposure (dose, duration, frequency, route of penetration).

Genetic differences can affect individual responses to drugs by influencing the way in which the drug is processed or acts in the body. Genetic variation in the activity of enzymes and carrier substances can be responsible for changes in the absorption, transport, metabolism and excretion of drugs explaining, at least partly, individual differences in drug response and drug tolerance. There is a constantly increasing number of genetic variants and polymorphisms in drug metabolizing enzymes interfering with oxidation, conjugation and hydrolysis. Polymorphism in cytochrome P450, glucuronyl transferase and glutathione S transferase genes have been found to be associated with some DHRs (22). Pharmacogenetics of the pharmacodynamic pathways, for example, drug receptors and effector proteins and of genes controlling the immune response (immunogenetics) are other emerging fields which hold a great deal of promise for the development of individual predictive tests. However, this will only be possible if we can pool resources to identify and characterize a large cohort of patients to mount studies with adequate statistical power. This will only be possible through collaboration.

Preclinical prediction of DHRs and allergovigilance

Preclinical prediction of allergenicity. Currently, DHRs are barely predictable during the different drug development phases. To date, only a few drug allergenic determinants and mechanistic pathways have been identified. Although a large amount remains to be learnt, current knowledge should be transferred to industry to better predict immunotoxicology during the drug development process. Translational multidisciplinary projects to understand the mechanisms of allergic diseases are required and these may use epidemiology, experimental models, cell biology and molecular biology techniques, as well as biobanking.

DHR in clinical trials and postmarketing surveillance. Pharmacovigilance algorithms are not accurate for the diagnosis of DHRs (23); however, optimization of the current tools may be possible using large case-control DHR databases. Identifying DHRs at an early stage of clinical trials is mandatory, but will only be possible through the development of better tools.

How current EU programmes can help

There were no opportunities for such DHR-related research projects in the first two calls of Framework Program 7. However, the new Innovative Medicines Initiative (IMI) programme is a unique public-private partnership (<http://www.imi-europe.org/>) between the pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Communities represented by the European Commission. The IMI Strategic Research Agenda (SRA) identifies four areas to focus on: predicting safety, predicting efficacy, knowledge management, education and training. The WONDA (World Network for Drug Allergy) project fits within the topic scope 'predicting safety' and has the objective of developing *in silico*, *in vitro* and *in vivo* models to predict allergenicity. It will contribute to improved predictivity of drug safety evaluation and to the safety data warehouse. Further, the project is in compliance with the chapters 'optimization of data resources and strengthening of the evidence base' and 'development and strengthening of methodologies and networks' of the IMI SRA. GA²LEN may also support the project.

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