

Drug allergy diagnosis work up

Drug hypersensitivity reactions are a daily worry for clinicians. The tools allowing a definitive diagnosis are few and poorly validated. They include a thorough clinical history, standardized skin tests, reliable biological test, and sometimes drug provocation tests. These tools are currently being evaluated by the European Network of Drug Allergy, under the aegis of the EAACI drug hypersensitivity group of interest.

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Introduction

Drug hypersensitivity reactions are responsible for levels of morbidity (2–3% of hospitalized patients), mortality, and health care costs which are presently under evaluated (1). Their clinical manifestations are wide ranging from maculopapular exanthema to anaphylactic shock which may be fatal. Drug allergies are adverse reactions where antibodies and/or activated T-cells are directed against the drugs. Their underlying immunologic mechanisms include all four types described by Gell and Coombs (Table 1) (2). Some reactions do not have an immunological mechanism but mimic allergic symptoms (3). They occur in only a small percentage of patients and in general cannot be predicted since they are often idiosyncratic. The etiologies of these reactions include nonspecific histamine release (e.g. opiates, radiocontrast media, and vancomycin), bradykinin accumulation (angiotensin-converting enzyme inhibitors), complement activation (radiocontrast media and protamine), induction of leukotriene synthesis (aspirin and nonsteroidal anti-inflammatory products) and bronchospasm (e.g. SO₂ released by drug preparations containing sulfites).

The diagnosis of immediate and/or delayed hypersensitivity reactions to drugs requires a knowledge of the scientific literature with, for the more recently introduced drugs, access to Medline searches and to the Committee on Safety of Medicine Reports. The lack of case studies involving a particular compound does not mean that it cannot induce allergic reactions. The diagnosis is indeed based on history, clinical manifestations, and if possible on skin tests and biological tests. The available clinical and biological tools at our disposal are few and have not all been fully evaluated.

Moreover, a definite diagnosis of such a reaction is required in order to institute proper preventive measures.

Under the aegis of the European Academy of Allergy and Clinical Immunology, the European Network of Drug Allergy (ENDA) works for the establishment of clinical tools for the daily practice.

Clinical history

Clinical history should be extremely thorough and address the symptomatology (compatible with an allergy?), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment), other medication taken (both at the time of the reaction and other drugs of the same class taken since), and the medical background of the patient (any suggestion of previous allergies whether associated with medications or not). Data should be taken in a uniform format, and to harmonize our drug hypersensitivity diagnostic procedures in Europe, members of ENDA have first developed a questionnaire (4), available into many different languages. It also includes some procedures as skin tests, provocation tests, and biological tests.

The history is in fact often not reliable since different drugs are often taken simultaneously and can account for the symptoms, it is often unprecise. Finally, the clinical picture of drug allergy is very heterogeneous, mirroring many distinct pathophysiological events. Thus, many doctors rely on history and some reference manuals for drug allergy diagnosis, without attempting to prove the relationship between drug intake and symptoms or to clarify the underlying pathomechanism

of the reaction. Such an attitude leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field. In cases where an hypersensitivity reaction is suspected, if the drug is essential and/or frequently prescribed (e.g. β -lactams, paracetamol, and nonsteroidal anti-inflammatory drugs) a certified diagnosis should be performed and tests carried out in a specialist center. Only a formal diagnosis of drug hypersensitivity reactions allows one to bring into play the measures required for prevention and treatment. For these drugs, the prudent principle of eviction may be insufficient. It would mean elimination of drugs which do not necessarily give rise to reactions and which are widely used. However, it is a valid option until a specialist consultation can be scheduled.

Skin tests

The diagnostic value of skin tests has not been fully evaluated and the experience in different centres has not rarely been exchanged during the last decades. Thus, reliable skin test procedures for the diagnosis of drug hypersensitivity are generally missing and test concentrations are unknown or poorly validated for most drugs. Skin tests have to be applied according to the suspected pathomechanism of the hypersensitive drug reactions. In immediate β -lactam drug reactions for example, an IgE-mediated reaction can be demonstrated by a positive skin prick and/or intradermal test after 20 min (5). On the other hand, nonimmediate reactions to β -lactams manifesting by cutaneous symptoms occurring more than 1 h after last drug intake, are often T-cell mediated and a positive patch test and/or a late-reading intradermal test is found after several hours or days (6, 7). Moreover, skin tests have the additional capability to give insights concerning the immunologic pathomechanism.

Therefore, skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism (3). They should be performed 4–6 weeks after the reaction, in a specialist environment with intensive care facilities, since the tests themselves can induce, although in rare

Table 2 β -lactam antibiotic skin tests

Reagents	Route	Serial tests (dilution)
Penicilloyl polylysine	Prick and intradermal	Undiluted (0.035 mg/ml)
Penicillin minor determinant mix	Prick and intradermal	1/10, undiluted (1.1 mg/ml)
Benzylpenicillin sodium (Pen G)	Prick and intradermal	1/10, undiluted (20–25000 U/ml)
Amoxicillin	Prick and intradermal	1/10, undiluted (20–25 mg/ml)
Other penicillins	Prick and intradermal	1/10, undiluted (20–25 mg/ml)
Cephalosporins	Prick and intradermal	1/10, undiluted (10 mg/ml)

cases only, an anaphylactic reaction (3). Their sensitivity and predictive value vary depending on the drug from excellent (penicillins, myorelaxants, heterologous sera, enzymes) through satisfactory (vaccines, hormones, protamine, opiates, thiopental) and poor or unknown (local anesthetics, paracetamol, sulfonamides, iodine radiocontrast media, quinolones, nonsteroidal anti-inflammatory drugs, cephalosporins, and other anti-infectious agents) (Table 2).

Patch tests with the suspected drug can also be used for delayed hypersensitivity reactions (8). Sometimes the drug is not available in an adequate reactive form – generally because it is a metabolic derivative which is immunogenic and provocation tests are required to confirm the diagnosis.

One of the current projects of ENDA is to develop useful test procedures for the diagnosis of drug hypersensitivity, procedures which are simple and can be used not only in centers specialized in drug allergy. As a first step, we have defined general principles for skin testing of drugs and established the optimal skin test concentrations to be used for already well-studied substances. For other substances and with collaborative studies, we will be able to provide sensitivity and specificity data for each concentration and drug (9). Specific skin test protocols are also currently being discussed thoroughly.

Provocation tests

Provocation tests have the best sensitivity, but can only be performed under the most rigorous surveillance conditions and therefore are restricted to certain specialist centres with on-site intensive care facilities. These tests are particularly needed for nonsteroidal anti-inflammatory drugs, local anesthetics, antibiotics other than penicillins or penicillins when skin tests are negative for example. They should be performed after a certain time interval has elapsed after the hypersensitivity reaction (at least 1 month) using the same drug and route of administration as in the initial case. The route of administration really depends on the suspected drug. The precise challenge procedure varies a lot from one team to another and we need to standardize our practice. Provocation tests should not be performed if

Table 1 Immunologic reactions according to Gell and Coombs (2)

Type	Effector mechanism	Clinical manifestations
I	IgE, Mast cells and basophils	Anaphylactic shock Angioedema, urticaria Bronchospasm
II	IgG, IgM, Complement and/or phagocytosis	Cytopenia Nephritis
III	Precipitins, IgM, IgG and Complement	Serum sickness Fever, urticaria Glomerulitis Vasculitis
IV	T-lymphocytes	Contact dermatitis Maculopapular rashes

the offending drug is little used, several alternatives exist or hypersensitivity reactions are associated with dermal blistering (Stevens–Johnson syndrome, toxic epidermal necrolysis) and/or organ involvements. ENDA members have set up general considerations and specific provocation protocols will soon be available.

Biological tests

It would be highly desirable to have discriminating biological tests available to establish the nature of the culprit agent, especially when the patient is receiving several drugs simultaneously. However, these tests are few and for the most part not fully validated. It should also be remembered that the interpretation of the results has to be done with caution. A negative tests does not exclude the responsibility of the drug whilst a positive results shows a sensitivity to the drug but does not confirm its responsibility.

The demonstration of isolated drug-specific IgE (to penicillins, myorelaxants, chymopapain or tetanus toxoid for example) does not allow one to diagnose a drug allergy, but in conjunction with clinical findings (e.g. typical symptoms of rapid onset) they allow one to pinpoint the IgE-dependent mechanism (particularly if the skin tests to the drug are also positive). They may also permit the exploration of cross-reactivities between several drugs using quantitative inhibition. The absence of specific circulating IgE does not rule out a diagnosis of allergy and indeed, this assay is not available for all drugs. The measure of drug-specific IgM or IgG is only of interest in the case of drug-induced cytopenia or allergies to dextrans. The release of histamine from total blood in the presence of the drug correlates well with skin tests and specific IgE for myorelaxants but is not reliable for many other drugs (10). Moreover, it is costly and requires a high level of technicity. Tests involving basophil degranulation are not trustworthy given the low numbers of circulating basophils. The usefulness of measuring sulfidopeptide leukotrienes still requires further validation both in the case of IgE-dependent and non-IgE-dependent hypersensitivity reactions (11). In cases of acute clinical reactions, blood measurements of histamine or tryptase and urinary measurements of methylhistamine confirm the role played by basophils and mast cells whatever the cause of the degranulation (12). The search for membrane markers of human basophils in the presence of the drug and studies involving T-lymphocytes remains the domain of a few laboratories (13). For drug-induced type II and III allergic

reactions, a Coombs' test, *in vitro* hemolysis test, determination of complement factors and circulating immune complexes can be performed.

Conclusion

The diagnosis of hypersensitivity reactions to drugs is often difficult and requires a stereotypic attitude no matter which drug is involved. It remains largely clinical since diagnostic testing is available for only a few drugs. Provocation tests have the best sensitivity, are cumbersome and may be harmful. Better care for these patients, available to all clinicians, requires new and validated biological tools for diagnosis. With this major goal, Professor Alain de Weck brought together several teams in Europe under the aegis of ENDA (European Network of Drug Allergy) (14) and a lot has been (4, 9) and will be performed.

A definite diagnosis of hypersensitivity reactions to drugs is required in order to institute proper preventive measures, since whatever the intensity of the clinical reaction, it shows a state of hypersensitivity towards the particular drug with the possibility of a more serious reaction in the future. General preventive measures include the declaration to the Committee on Safety of Medicine Reports. Individual measures include the issue of an "Allergy Card" specifying the culprit agent(s), the delivery of lists of drugs to avoid and of possible alternatives. The patient is also asked to make known his allergies prior to all prescriptions and surgical operations and to read the package insert on all drugs that he takes. The lists given can never be completely exhaustive and are only indicative and should be frequently updated. Similarly, questioning (to elicit any history of allergy) of every patient by every clinician prior to issuing a prescription is essential from both a medical and a medico-legal point of view. Preventive measures by premedication (e.g. slow injection and preparations with glucocorticosteroids and antihistamines) mainly concern non-allergic hypersensitivity reactions (for example to radiocontrast media, vancomycin, certain anesthetics and chemotherapy drugs). The possibility of desensitization should always be considered when the offending drug is essential and either no alternatives exist or they are unsatisfactory, as is the case for sulfonamides in HIV-infected patients, quinolone allergies in some cystic fibrosis patients, serious infections with allergy to penicillins, allergy to tetanus vaccine, hemochromatosis with allergy to deferoxamine, aspirin and nonsteroidal anti-inflammatory drug hypersensitivity in patients for whom the necessity for these drugs to treat either a cardiac or rheumatoid illness is clear.

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