

Diagnosis of Drug Allergic Reactions

***Daniel Vervloet,* Michel Pradal,
Denis Charpin, and Françoise Porri***

*Allergy Division, Chest Diseases Department,
Sainte-Marguerite Hospital, 13009 Marseille, France*

Introduction

Drug allergies are accounted increasingly often in every day medical practice. A recent survey done by our group (1) estimated their incidence at 14.7% of the overall adult population. Numerous mechanisms are implicated in drug allergy. We have sketchy knowledge about a few of the many mechanisms that have been implicated in drug allergy, but most remain unknown. This lack of knowledge explains the difficulty of differentiating allergy from other side-effects, assessing the incidence, risk factors, and management strategy.

Definitions

Allergic reactions to drugs are one of the most frequent pathologic processes encountered in clinical medicine. According to the World Health Organization (WHO), an adverse drug reaction (ADR) is any noxious and unintended reaction to a drug that is administered in humans in standard doses by the proper route for the purpose of prophylaxis diagnosis, therapy, or for influencing a physiological condition (2).

Some drug reactions may occur in all individuals:

1. Drug overdose: Toxic reaction linked to excess dose or impaired excretion.
2. Drug side effect: Undesirable pharmacological and unavoidable effect.
3. Drug interaction: Action of a drug on the effectiveness or toxicity of another drug.

*Author to whom all correspondence and reprint requests should be addressed.

Some other drug reactions can only occur in certain prone patients. These include:

1. Drug intolerance, which is a condition defined by a lowered threshold to the normal pharmacological action of a drug. Another meaning can be given to drug intolerance syndrome, especially when speaking about aspirin hypersensitivity (sometimes called analgesic idiosyncrasy).
2. Drug idiosyncrasy is considered a genetically determined qualitatively abnormal reaction to a drug related to metabolic or enzyme deficiency.
3. Drug allergy involves immunological mechanisms and is characterized by specificity to a given agent, transferability by antibodies or lymphocytes, and recurrence when re-exposure to the culprit drug occurs.
4. Pseudoallergic reactions show the same clinical manifestations as allergic reactions but lack the specific immune mechanism of drug allergy.

Knowledge of Main Risk Factors

Patient-Related Factors

Age

There are very few papers in the literature that deal with the role of age in drug allergy. Allergic responses are less often described in children than in adults. This may be linked to less frequent exposure to drugs, smaller doses, or as in hymenoptera allergy, a natural loss of sensitization. Most adverse reactions to drugs occur in young or middle-aged adults. For aspirin, reactions are mainly reported between 30 and 40 yr, for radiocontrast media between 20 and 50 years, and for penicillin between 20 and 50 yr. But it is not clear whether age influences the severity of the allergic response.

Sex

Few studies have looked at the possible role of sex in drug allergy. Our recent epidemiological study (1) showed that drug allergy was twice as frequent in women than in men. Interestingly, 80% of reactions to muscle relaxants occur in females; 75% of reactions to thiopental, 80% of reactions to angiotensin converting enzyme inhibitors, 66% of reactions to aprotinin, and 75% of reactions to chymopapain occur in women.

Genetic Factors

Several studies suggest that specific HLA genes are involved in reactions to certain drugs: HLA DQW₂ in patients with aspirin asthma,

HLA B₇DR₂DR₃ in insulin allergy, and HLA DRW₂/DRW₃ in D penicillinamine allergy. Other HLA genes have been linked to sulfonamide-induced toxic epidermal necrosis or to hydralazine-induced lupus. Slow-N-acetylation phenotype and oxygenated amine detoxification seem to predispose to reactions to sulfonamides and procainamide.

A familial predisposition to drug allergy has been reported recently (3): Children whose one parent was allergic to an antimicrobial drug have a 15-fold relative risk to experience an allergic reaction to an antimicrobial drug compared with children whose parent had tolerated antimicrobial drugs without allergic reaction. The class of antimicrobial drugs being different suggests a genetic propensity to react to haptens.

Atopy

The connection between atopic predisposition and drug allergy continues to be a controversial topic. A precise definition of the atopic status and its objective detection are prerequisites for further epidemiological studies as well as for an assessment of the mechanism underlying the type of drug allergy considered.

Atopy does not seem to be a risk factor for muscle relaxant, penicillin, and protamin sulfate allergy (4,5). Atopy is a risk factor for formaldehyde, ethylene oxide, and phthalic anhydride (6). Some doubt exists for chymopain allergy (7,8) and for intolerance to iodinated contrast media (9).

Acquired Immunodeficiency Disease

Adverse reactions to sulfamides (sulfamethoxazole trimethoprim, sulfadoxine), dapsone, and rifampicin occur in HIV-infected patients at rates more than 10 times the rates observed in the general population (10,11). Other drug intolerances are also frequent: pentamidine, clindamycin, amoxicillin-clavulanate, ciprofloxacin, and zidovudin (12,13).

Sulfonamide intolerance is described in 60% of HIV patients with high dosage schedules. Clinical manifestations are usually late, beginning 7–14 d after treatment initiation. Fever, systemic manifestations such as cytopenias, hepatitis, and acute renal failure are frequently associated with severe bullous exanthemas.

Most of the patients are slow acetylators, which leads to rapid overrule of N-acetylation to oxidation with production of toxic hydroxylamine. Reduced glutathione levels in the liver lead to insufficient epuration (14). The B-lymphocyte hyperreactivation leads to polyclonal increase in serum immunoglobulins, which in turn produces the formation of circulating immune complexes in the presence of high and repetitive doses of antibiotics.

Drug-Related Factors

Propensity of a Drug to Induce Clinical Allergic Reaction

Macromolecular drugs (insulin, chymopapain, heterologous antisera) are, by nature, complete antigens able to induce an immune response.

Propensity of a Drug to Activate Immunologic System

The β -lactam family of antibiotics is prone to cause immediate hypersensitivity reactions. Moreover, the chemical structure of the drug may be important for binding IgE molecules to cell membranes. Muscle relaxants, such as succinylcholine, have sufficient distance between terminal determinants to act as bivalent antigens (15). Muscle relaxants with a rigid structure, such as pancuronium, provoke fewer reactions than muscle relaxants with flexible chain binding the epitopes as suxamethonium.

Route, Dose, Duration, Frequency of Administration

Each route of administration of a drug can induce allergy. In general, local administration is more likely to sensitize than parenteral administration which is more likely to sensitize than oral administration. The iv route usually leads to more severe reactions than the oral route. Single-dose antibiotics produce less sensitization than prolonged treatment.

Aggravating Factors

Treatment with β -adrenergic blocking agents increases the severity of anaphylaxis and decreases the epinephrine efficacy (16). Asthma does not increase the risk of drug allergy, but may lead to more severe reactions (17). Pregnancy has controversial effects. Histaminase, which is synthesized in placenta and arises quickly (5–6 wk after fecondation), protects the fetus against maternal anaphylaxis. On the other hand, the placenta acts as a filter against maternal IgE antibodies (18). Conversely, IgG antibodies cross the placenta and may induce severe manifestations in the fetus (dextrans).

General Diagnosis

Clinical History

The evaluation of drug allergy must begin with a precise and detailed history including clinical symptoms and their delay of onset. Immediate reactions such as anaphylactic shock, urticaria, and bronchospasm occur during the first hour after drug ingestion or injection. Other drug reactions called "accelerated," such as urticaria/angioedema, bronchospasm, or stridor, may occur during the first 3 d after drug intake. Late reactions, which are often of the mucocutaneous (rashes, exfoliative dermatitis) or hematological type (anemia, thrombopenia, neutropenia), occur more than 3 d after drug intake.

Table 1
Intrinsic Imputability (I)
from Chronological (C)
and Semiological Scores (S)^a

	S ₁	S ₂	S ₃
C ₀	I ₀	I ₀	I ₀
C ₁	I ₁	I ₁	I ₂
C ₂	I ₁	I ₂	I ₃
C ₃	I ₃	I ₃	I ₄

^aI₀, excluded; I₁, doubtful; I₂, possible; I₃, likely; I₄, very likely.

The "imputability concept" (19) leads to definite analysis of the combined data. Intrinsic imputability is related to the relationship between a drug and a clinical or biological event occurring in a patient. Extrinsic imputability concerns literature survey about the observed events. Intrinsic imputability relies on chronological (scored C₀ to C₃) and semiological criteria (scored S₁ to S₃).

Chronological Criteria

1. Latency between drug administration and occurrence of adverse event: very suggestive, incompatible, compatible;
2. Drug withdrawal: suggestive, regression of the observed event, nonconclusive; and
3. Drug readministration: positive, negative, not done.

The combination of these three criteria lead to a chronological scoring: C₀, excluded; C₁, doubtful; C₂, possible; C₃, likely.

Semiological Criteria

1. Clinical and/or biological data suggestive of allergy: yes or no;
2. Allergy promoting factors: present or absent;
3. Other explanation for the observed data: yes or no; and
4. Reliable test to confirm diagnosis: positive, negative, nonavailable.

The combination of these four criteria lead to a semiological score: S₁, doubtful; S₂, possible; S₃, likely. Intrinsic imputability (I) scores are listed in Table 1.

Extrinsic imputability is illustrated by literature data analysis and stated as a score (B):

1. B0, new event never reported;
2. B1, very unusual event;
3. B2, non well-known event; and
4. B3, well-known event.

Skin Tests

Although hindered by the lack of standardized extracts, skin tests are of great value in the diagnosis of drug allergy (IgE mediated or not). They present many advantages—they are easy to perform, cheap, quick, sensitive, and reproducible. Immediate skin testing detects the mediator release of cutaneous mast cells as a result of binding of IgE antibodies against a drug to mast cells. Skin testing must be performed 4–6 wk after reaction; in the absence of drugs changing skin reactivity (H_1 receptor antagonists, anxiolytics, antidepressors) and with positive and negative controls. They may be positive for many years—22% of penicillin allergic subjects are still skin test positive after 10 years or more (20); skin test to muscle relaxants are still positive 4–29 yr after reaction (21).

Skin testing is used in two ways:

1. Prick test in which one drop is placed on the skin surface, the dermis is pricked through the drop with the tip of a lancet or a needle (drug concentration is usually one hundred fold higher than with intradermal use).
2. Intradermal test in which 0.01–0.02 mL of the drug is injected intradermally.

Immediate skin testing is valuable in the diagnosis of IgE dependent allergy to (nonexhaustive list):

1. Antibiotics: β -lactams, sulfonamides, trimethoprim, cyclines, rifampin;
2. Anesthetic drugs: muscle relaxants, thiopental, narcotics, propofol;
3. Enzymes: chymopapain, streptokinase;
4. Chemotherapeutic agents: cisplatin, cytarabine; and
5. Others: insulin, latex.

Patch tests are used in the field of delayed sensitivity to drugs, essentially involving the skin. They may lead to the diagnosis of drug-induced contact dermatitis but also drug-induced vasculitis and bullous eruptions.

Serum-Specific Measurements

Radioimmunoassays (RIA) have been developed for years in the field of detection of IgE antibodies to drugs. Historically, the radioallergosorbent test (RAST®) was the first introduced. RASTs to different drugs have since been developed: penicillin (major determinant), drugs used during general anesthesia (muscle relaxants, thiopental), and others (latex, chymopapain, protamine, insulin, trimethoprim, ethylene oxide, formaldehyde). False-negative (poor sensitivity) and false-positive tests (e.g., high total IgE levels) may occur. Enzymologic

assays (ELISA), although seldom performed, are able to detect specific IgE antibodies to certain drugs (e.g., chlorhexidine, cytarabine).

Two techniques lead in improvement in sensitivity and specificity of RIA tests:

1. The quantitative RIA-inhibition test (used in the field of muscle relaxants allergy), which allows allergenic crossreactivity study between two drugs, and states the specificity of IgE antibodies; and
2. The improvement of compounds used as solid phase or the coupling procedures (22,23).

It must be known that, apart from sensitivity and specificity values of different tests, discrepancies may exist between skin testing and RIA tests because they do not exactly measure the same things: skin testing explores *in vivo* mast cell reactivity whereas RIA shows reactivity with antibody combining sites.

Specific IgG, IgM, or IgA Antibodies

In the vast majority of cases, the measurements of IgG, IgA, or IgM antibodies to drugs are not clinically useful because they only represent an immune response to the drug without clinical disease. Exceptions exist concerning cytopenias (hemolytic anemia, leucopenia, thrombocytopenia), where IgG and IgM antibodies play an important role.

Concerning dextrans, the detection of a high level of specific IgG antibodies by hemagglutination is a major risk factor of anaphylactoid reactions (24). IgG or IgM antibodies to rifampicin have been found in patients with thrombocytopenia and systemic manifestations (acute renal failure and hemolysis). The presence of IgG antibodies to protamine in diabetic patients treated with protamine containing insulin increases the risk of anaphylactoid reactions to protamine 38-fold (25).

Complement Activation

Measurements of complement components showing decrease permit assessment of the presence and degree of complement activation (C_3 , C_4 , CH_{50}) just as the levels of anaphylatoxin levels do (C_{3a} , C_{4a} , C_{5a}).

Mediators Release

Tryptase is a neutral protease specifically released by the mast cells showing specific mast-cell activation in systemic anaphylaxis and mastocytosis (26). The long 2 h half-life of tryptase allows its plasmatic detection at least 3 h after the reaction until return to normal values (12–24 h). Tryptase levels are very low in normal individuals and do not raise after other events as septic or cardiogenic shock. On the other hand, tryptase levels may be normal in patients exhibiting acute bronchospasm as the initial symptom of anaphylaxis. Another impor-

tant point is that tryptase is a relatively stable protein that may be measured in stored serum samples. From a practical point of view, in presence of an anaphylactoid reaction, 3 or 4 serum samples must be taken during the first 12–24 h after reaction.

Methylhistamine is the main metabolite of histamine and may be measured in urine by radioimmunoassay. Levels higher than 15–20 ng/mL/mmol creatinine/L (27) are consistent with mast cell degranulation. This, combined with serum tryptase measurement is helpful to diagnose an allergic reaction after drug administration. Specific histamine release assays done in vitro have shown good correlation with skin tests and RIA methods in the field of some drug allergy (muscle relaxants, propofol, fluid gelatins [28]).

One other way to approach allergic or pseudoallergic reactions to drugs is to study the production of sulfido-leukotrienes (LTC_4 , LTD_4 , LTE_4) by leukocytes on challenge with allergens or anti-IgE antibody. This enzyme-linked immunosorbent assay (ELISA) called CAST® (cellular allergen stimulation test) could be interesting in IgE-dependent allergies but also in non-IgE related mechanisms where histamine and leukotrienes are released. Promising results have been obtained with patients presenting penicillin allergy and aspirin intolerance (29), but must be confirmed by other studies.

Lymphocyte Transformation Tests

Lymphocyte transformation tests show production of lymphokines by sensitized lymphocytes in the presence of the drug resulting in a proliferative response. Much controversy exists regarding the value of this test in the field of drug allergy. Many false-negative and false-positive results have been reported. One possible improvement could be the preincubation of cells with murine liver microsomes (30).

Provocation Tests

Although it could be considered as the “gold standard,” oral provocation tests are seldom performed. When absolutely necessary (aspirin, for example), the tests should be administered under strict medical supervision with emergency equipment at hand. Another way to use it is to ensure that the patient tolerates other drugs in different groups.

Predictive Value of a Diagnostic Test

For a diagnostic test to have good sensitivity and a good specificity is not sufficient. In order to be efficient, a test must have both a high positive and negative predictive value. Given a valid test, a high predictive value will be obtained if the prevalence of the disease in the

population under study is high enough. In order to identify such a population at higher risk, we need to know risk factors. As an example, for MR allergy, female gender is the only known risk factor (31). The role of atopy is controversial. A previous general anesthesia using MR is not always found in patients who had anaphylactoid reactions to MR. Anaphylactoid reactions to MR occur at first exposure in 1/3 of cases. Relative risk of anaphylactic reactions in women, compared to men, is 1 in 4. Considering an incidence rate of anaphylactic reactions to MR around 1/6250 anesthetics in the population at large, it would be roughly equal to 4/6250, i.e., 1/1560 in females. If the screening test (skin test or RAST) had a 99% specificity, a screening program involving 1560 females would lead to 15.6 false-positive tests for only one true positive test. In other words, 93% of the positive tests would correspond to false-positive reactions. Such a screening program cannot be run. Considering latex allergy, the issue is quite different because the risk factors are well known. In high risk subjects (particularly spina bifida children), the prevalence of sensitization can be as high as 60% (32). Even in nurses where the prevalence rate of sensitization is around 5–10%, a systematic preoperative screening could be efficient, leading to a positive predictive value equal to 63 or 90%, if the specificity of the test was equal to 95 or 99%, respectively. To identify latex allergic subjects, skin test to latex would have to be performed because symptoms have a low positive predictive value for predicting true late sensitization (33). It should also be kept in mind that the predicting value of latex sensitization for the occurrence of preoperative anaphylactic reactions is unclear.

Diagnosis of Some Specific Drug Allergies

Muscle Relaxants

Skin Tests

Following intradermal injection of the suspected allergen, an immediate reaction characterized by the appearance of wheal and flare is highly predictive of sensitization. A number of studies have demonstrated the usefulness of skin tests to retrospectively confirm allergy to muscle relaxants (34). The concentrations needed to conclusively prove muscle relaxants allergy have been rigorously defined (34). A good correlation was found to exist between intradermal tests and prick tests (35). However, it should be stated that, in a few cases, positive intradermal tests have been observed for vecuronium and pancuronium only at 400 and 200 $\mu\text{g/mL}$, respectively. In these cases, prick tests using commercially available solutions at 4 and 2 mg/mL may be negative. Thus, if only prick tests were performed, it may be wrongly concluded

that the patient is not allergic to muscle relaxants. Conversely, intradermal tests with atracurium must be performed at a maximal concentration of 10 $\mu\text{g}/\text{mL}$. Prick tests performed using commercially available solution at 10 mg/mL lead to false-positive reactions. Debate about the value of systematic preoperative skin tests to predict muscle relaxant allergy has been stressed a few years ago. Before accepting to do it, the following questions should be answered: Is the test valid? What is its predictive value? Which population should be tested? Is screening feasible?

In order to be valid, a screening test must be cheap, reproducible, sensitive, and specific. Prick tests have been advocated, because they are easy to perform, safe, sensitive, and specific. However, sensitivity and specificity of prick tests are not the same whether they are performed by anesthetists or by allergists, because performing and reading skin tests is not so easy (36). In order to be efficient, a test must have both a higher positive and negative predictive value. Given a valid test, a high predictive value will be obtained if the prevalence of the disease in the studied population is high enough. In order to identify such a population at higher risk, we need to know what the risk factors are. A good negative predictive value has been demonstrated when the skin tests were performed by an allergist (37).

Specific IgE

As for all allergens, a good correlation is usually observed between skin tests and specific IgE levels, but no generalization should be made in this regard. Since measurement of specific IgE is less sensitive than skin testing in most cases, discordant results with positive skin tests and negative RAST are possible. To solve this problem, a new test using a structural analog of unsolubilized choline on sepharose as a solid support has been developed (38). This support, which is called sepharose-quaternary ammonium (SQA), is used to detect the presence of specific quaternary ammonium ions in the serum based on radio-immunological method. Inhibition of specific IgE binding is systematically controlled by putting the tested sera in the presence of offending molecule in soluble form. The concordance rate with skin test is reported to be about 83%. Recently, another solid phase for detecting antiquaternary ammonium IgE using p-aminophenylphosphoryl choline immobilized on agarose beads has been proposed (39), increasing sensitivity (95%).

Some patients with IgE antibodies against quaternary ammonium ions may have positive RAST and negative skin tests especially for MR with rigid structures such as pancuronium or vecuronium (34). These drugs may not bridge two specific IgE molecules, thus preventing the mediator release.

Barbiturates

Positive immediate skin tests to thiopental have been found in patients with anaphylactic reactions (40). A radioimmunoassay for detection of thiopental reactive antibodies is available. In the sera of some patients allergic to muscle relaxants but not allergic to thiopental, such antibodies were found (41). These results suggest that IgE antibodies in the sera of muscle relaxants allergic subjects recognize determinants on both thiopental and muscle relaxants. Leukocyte histamine release to thiopental has also been shown (42). The predictive value of skin test and specific IgE antibodies to thiopental remains unknown.

Narcotics

Although opioid analgesics are among the most commonly prescribed drugs in hospitals, anaphylactoid reactions to these drugs are rare. Some narcotics (morphine, meperidine) are able to induce histamine release from mast cells, especially of the skin. Others (fentanyl) are not histamine releasers (43). Histamine releaser effects may induce pruritus, rash, or hypotension. However, some IgE-mediated anaphylactic reactions have been reported with various agents (44,45). IgE antibodies to morphine and meperidine have been detected (46). Allergenic determinants identified on morphine encompass the N-methyl group and the cyclohexenyl ring with a hydroxyl at C₆. Crossreactivity between morphine, codeine, and other narcotics has been alleged.

Local Anesthetics

The following reactions may be unrelated to the local anesthetic:

1. Psychomotor: hyperventilation;
2. Vasovagal reactions: bradycardia, sweating, pallor;
3. Sympathetic stimulation: tremor, tachycardia, hypertension; and
4. Operative trauma.

The following reactions may be toxic (iv injection):

1. Cardiovascular effects; and
2. Central nervous system effects.

The following reactions may be owing to adjuvants or injection, but not to the local anesthetic molecule itself:

1. Associated drugs: epinephrine, sulfites, parabens, antibiotics, analgesics; and
2. Traumatic subcutaneous emphysema.

The IgE-mediated type reactions (anaphylaxis, urticaria, bronchospasm) are exceptions (47).

The skin tests (scratch, prick, or intradermal tests) are usually negative or false positive (full strength intradermal injection), but are useful as a part of an incremental drug challenge. A drug challenge using the local anesthetic (usually an amide) that is to be used should be performed.

Numerous different protocols have been suggested (48). The test should be carried as follows:

1. Patient under medical supervision; and
2. Sequence of intradermal injections starting with a 1/10,000 concentration with 10-fold concentration increase at 10-min intervals until nondiluted commercial solution.

If no reaction develops, the following sequence of subcutaneous injections at 15 min interval is administered: 0.1 mL at 1/10,000, 0.1 mL at 1/1000, 0.1 mL at 1/100, 0.1 mL at 1/10, 0.1 mL stock commercial solution, and 0.5 mL stock commercial solution. Then, if no reaction develops, a 1-mL intramuscular injection is done.

Antibiotics

Skin Tests with Penicillin

Immediate wheal and flare skin tests with penicillin reagents are useful in the diagnosis of IgE-mediated reactions to penicillins (49).

Skin tests must be performed with penicillin polylysine (PPL) and a minor determinant mixture (MDM): benzylpenicillin, penicilloate, penilloate. A range of 7–63% of patients with positive histories of penicillin allergy have positive skin tests to PPM and MDM in part because of the wide range of BPO-specific IgE antibodies persistence: 10 d to >1000 d. With negative histories of penicillin allergy, the rate of positive skin tests is 2–7%:

1. 1% of patients with histories of penicillin allergy and negative skin test will develop accelerated urticarial reactions.
2. Anaphylaxis has not been reported in skin test negative patients.
3. In Europe, PPL and MDM are commercially available (Allergopen®).

Skin tests are done 3–6 wk after reaction. Prick tests must be performed before intradermal test. The PPL tests are performed before MDM tests. Appropriate positive and negative control tests must be used. Systemic reactions occur in about 1% of the time.

According to Adkinson (50), the skin test must be done in type I reactions (urticaria-anaphylaxis). They will be negative in 85% of the cases, leading if penicillin is reused to a very low risk (10–15%) of self-limited skin allergy. When positive (15%), there is a risk of acute allergic reaction. Skin tests must be done in type II and III reactions (cytopenias, serum sickness, drug fever, interstitial nephritis) to rule

out type I allergy, and in maculopapular reactions to reassure that type I sensitivity is not present (especially if pruritus or no direct medical observation). In all other manifestations of penicillin allergy (contact dermatitis, exfoliative dermatitis, and toxic epidermal necrolysis), skin testing is not useful.

Skin Tests with Other β Lactams

CEPHALOSPORINS

Native cephalosporins have been used as skin test reagents. Concentrations must be ≤ 1 mg/mL (false-positive reactions with higher concentrations).

AMOXICILLIN

Blanca et al. (51) used 20 mg/mL concentration for intradermal testing.

CLAVULANIC ACID

Fernandez-Rivas et al. (52) found two patients with specific allergy to clavulanic acid using 1 and 10 mg/mL concentrations for prick and intradermal tests.

AZTREONAM

Intradermal tests with 2 mg/mL and 20 mg/mL were positive in the case of aztreonam-induced urticaria reported by de la Fuente-Prieto et al. (53).

Other Tests

RAST and other solid phase radioimmunoassays have been developed to detect penicilloyl determinants IgE antibodies (54). Although not commercially available, RAST detecting minor determinant specific IgE antibodies have also been developed (55). More recently, Harle and Baldo (56) using ampicillin, amoxicillin, and ticarcillin solid phase assays, showed the presence of specific IgE antibodies.

Sulfonamides

Sulfonamides are now widely used in the field of AIDS-related infections (*Pneumocystis carinii* pneumonia, cerebral toxoplasmosis). They are frequently responsible of intolerance reactions, occurring far more frequently in HIV infected patients.

Some sulfonamide reactions are IgE-mediated, since positive skin tests with sulfamethoxazole-trimethoprim have been described; IgE antibodies against sulfonamides have been detected by solid phase assays (57). The antigenic determinant appears to be N4 sulfonamidoyl. In the vast majority of cases, the mechanism of sulfonamide intolerance in HIV-infected patients is linked to the production of oxygenated metabolites of sulfonamides occurring preferentially in slow acetylators

because of the overrule of hepatic N_1 acetylation (58). Since glutathione, which usually detoxifies oxygenated metabolites, is lacking in HIV patients, haptening of these reactive metabolites is amplified.

Radio Contrast Media

High osmolar radiocontrast media induce a high rate of adverse effects, especially toxic, because of their high osmolarity. Low osmolarity products decrease pain, hemodynamic effects, and myocardial effects and have better tolerance in dehydrated patients. Conversely, third generation radiocontrast media showed less life-threatening reactions than conventional ones. Wolf et al. (59), in a prospective randomized study, compared a conventional contrast media used alone or with premedication (methylprednisolone 32 mg, 12 and 2 h before injection); with a third generation radiocontrast media. Results showed 4.4% of anaphylactoid reactions with the conventional media, 4% when premedication was adjuncted, and 0.6% with a third generation contrast media.

In another prospective study, Katayama et al. (60) compared ionic and nonionic radiocontrast media; he found 12.7% of reactions with the ionic product and 3.1% with the nonionic media. It must be stated that among all the studies, third generation radiocontrast media are compared with second generation ones whatever their osmolarity. At this time no diagnosis test is valuable.

Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Few patients with urticaria or asthma may present IgE-mediated reactions shown by ASA hapten protein conjugates (61) or specific IgE against salicyloyl and o-methylsalicyloyl disks (62), but these facts are for the moment seldom found.

Concerning patients with chronic urticaria, challenges with oral ASA or NSAIDs may be performed (63). These challenges can be single blinded: placebo + 100 mg and 200 mg of ASA the first day, and 325 and 650 mg the second day. The clinical response is measured by skin scores every 2 h, or double-blinded, which is longer (≥ 3 d).

Rhinosinusitis and Asthma (64)

It must be known that oral ASA challenges are dangerous procedures that must only be performed if absolutely necessary, i.e., ASA treatment. These oral challenges may be single blinded or double blinded. For example, on the first day, three doses of placebo; on the second day, 30, 60, and 100 mg doses at 3-h intervals; and on the third day 150, 325, and 650 mg doses at 3-h intervals.

The patient is closely monitored with clinical symptoms (ocular, nasal, and respiratory) and FEV₁ measures. Reactions may only be rhinitis or asthma (with a decline in FEV₁ values), but are usually nasooocular and asthmatic. Another way to perform the challenge test is to use bronchial inhalation with lysine ASA (65).

References

1. Haddi, E., Charpin, D., and Tafforeau, M. (1990), *Allergy* **45**, 1-4.
2. World Health Organization (1969), *WHO Tech. Rep. Ser.* **425**, 1-24.
3. Attaway, N. J., Jasin, H. M., and Sullivan, T. J. (1991), *J. Allergy Clin. Immunol.* **87**, 227.
4. Adkinson, N. F. Jr. and Wheeler, B. (1983), *XI International Congress of Allergology and Clinical Immunology*, Kerr, J. W. and Ganderton, M. A., eds., Mac Millan Press, London, pp. 55-59.
5. Charpin, D., Benzarti, M., and Hemon, Y. (1988), *J. Allergy Clin. Immunol.* **89**, 356-360.
6. Bousquet, J., Maurice, F., and Rivory, J. (1988), *J. Allergy Clin. Immunol.* **81**, 605-610.
7. Bernstein, D., Gallacker, J., and Ulmer, A. (1985), *J. Allergy Clin. Immunol.* **76**, 458-465.
8. Cornaille, C., Guerin, B., and Leynadier, F. (1987), *Presse Méd* **18**, 881-884.
9. Enright, T., Chua-Lim, A., and Duda, E. (1989), *Ann. Allergy* **62**, 302-305.
10. Armstrong, D., Gold, J. W. M., and Dryjanski, J. (1987), *Ann. Intern. Med.* **103**, 738.
11. Mitsuyasu, R. and Groopman, J. (1983), *N. Eng. J. Med.* **308**, 1535,1536.
12. McKinley, G. F., Mazza, D. S., and Grieco, M. H. (1990), *Lancet* **335**, 384.
13. Wurtz, R. M., Abrams, D., and Becker, S. (1989), *Lancet* **334**, 955,956.
14. Chauvin, P., Cnudde, F., Leynadier, F., and Dry, J. (1990), *Med. Hyg.* **48**, 1125-1128.
15. Vervloet, D., Arnaud, A., and Senft, M. (1985), *J. Allergy Clin. Immunol.* **76**, 222.
16. Toogood, T. H. (1988), *J. Allergy Clin. Immunol.* **81**, 1-5.
17. Van Arsdell, P. P., Jr. (1991), *Immunol. Allergy Clin. North Am.* **11**, 475-492.
18. Gallagher, J. S. (1988), *Obstet. Gynecol.* **71**, 491-493.
19. Begaud, B., Evreux, J. C., and Jouglard, J. (1985), *Thérapie* **40**, 111-118.
20. Sullivan, T. J. (1992), *Allergy Proc.* **12**, 361-364.
21. Fisher, M. and Baldo, B. (1992), *Anaesth. Intern. Care* **20**, 143-146.
22. Gueant, J. L., Mata, E., and Monin, B. (1991), *Allergy* **46**, 452-458.
23. Guilloux, L., Ricard-Blum, S., and Ville, G. (1993), *Ann. Fr. Anesth. Reanim.* **12**, 182-186.
24. Kraft, D., Hedin, H., and Richter, N. (1982), *Allergy* **37**, 481-489.
25. Weiss, M. E., Nyhan, D., and Peng, Z. (1989), *N. Engl. J. Med.* **390**, 886-892.
26. Schwartz, L. B., Metcalfe, D. D., and Miller, J. S. (1987), *N. Engl. J. Med.* **316**, 1622-1626.
27. Anderson, J. A. and Adkinson, N. F., Jr. (1987), *JAMA* **258**, 2891.
28. Guilloux, L., Ricard-Blum, S., and Ville, G. (1993), *Ann. Fr. Anesth. Reanim.* **12**, 182-186.
29. de Weck, A. L., Stadler, B. M., and Urwyler, A. (1993), *ACI News* **15/1**, 9-14.
30. Merk, H. F., Schneider, R., and Scholl, P. (1988), in *Toxicological and Immunological Aspects of Drug Metabolism and Environmental Chemical*, Estabrook, R. W., Lindenlaub, E., Oesch, F., de Weck, A. L., eds., Schatauer, Stuttgart.
31. Vervloet, D., Arnaud, A., Vellieux, P., Kaplanski, D., and Charpin, J. (1979), *J. Allergy Clin. Immunol.* **63**, 348-353.

32. Yassin, M. S., Sanyurah, S., Lierl, M. B., Fisher, T. J., Oppenheimer, S., Cross, J., O'Brien, K., Stenmetz, C., and Khoury, J. (1992), *Ann. Allergy* **69**, 207–211.
33. Lagier, F., Vervloet, D., Lhermet, I., Poyen, D., and Charpin, D. (1992), *J. Allergy Clin. Immunol.* **90**, 319–322.
34. Birnbaum, J. and Vervloet, D. (1991), *Clin. Rev. Allergy* **9**, 281–293.
35. Leynadier, F., Sansarricq, M., and Didier, J. M. (1987), *Br. J. Anaesth.* **59**, 683–689.
36. Porri, F., Pradal, M., Rud, C., Charpin, D., Alazia, M., Govin, F., and Vervloet, D. (1995), *Allergy* **50**, 374–377.
37. Leynadier, F., Calinaux, C., and Dry, J. (1989), *Ann. Fr. Anesth. Reanim.* **8**, 98–101.
38. Gueant, J. L., Mata, E., and Monin, B. (1989), in *Biologic Prospective*, Galteau, M., Siest, G., Henny, J., eds., Libbey Eurotext, Paris, pp. 737–740.
39. Guilloux, L., Ricard-Blum, S., and Ville, G. (1992), *J. Allergy Clin. Immunol.* **90**, 153–159.
40. Dolovich, J., Evans, S., and Rosenbloom, D. (1980), *Can. Med. Assoc. J.* **123**, 292.
41. Harle, D. G., Baldo, B. A., and Smal, M. A. (1986), *Clin. Allergy* **16**, 493.
42. Hirshman, C. A., Edelstein, R. A., and Ebertz, J. M. (1985), *Anesthesiology* **63**, 353.
43. Marone, G., Stellato, C., and Mastronardi, P. (1991), *Clin. Rev. Allergy* **9**, 269–280.
44. Harle, D. G., Baldo, B. A., and Coroneos, N. J. (1989), *Anesthesiology* **71**, 489–494.
45. Zucker-Pinchoff, B. and Ramanathan, S. (1989), *Anesthesiology* **71**, 599.
46. Fisher, M. M., Harle, D. G., and Baldo, B. A. (1991), *Clin. Rev. Allergy* **9**, 309–318.
47. de Shazo, R. D. and Nelson, H. S. (1989), *J. Allergy Clin. Immunol.* **63**, 387.
48. Sindel, L. J. and De Shazo, R. D. (1991), *Clin. Rev. Allergy* **9**, 379–395.
49. Weiss, M. E. and Adkinson, N. F. (1988), *Clin. Allergy* **18**, 515–540.
50. Adkinson, N. F., Jr. (1992), in *Postgraduate Education Course and Asthma Consultants Course Syllabus*, 48th Annual Meeting, Orlando, Florida, March 6–11, pp. 178–190.
51. Blanca, M., Perez, E., and Garcia, J. (1988), *Allergy* **43**, 508–510.
52. Fernandez-Rivas, M., Perez-Garral, C., and Garcia-Lazaro, M. A. (1992), *Rev. Esp. Alerg. Immuno. Clin.* **7**, 76 (S2).
53. de la Fuente Prieto, R., Armentia Medina, A., and Sanchez Palla, P. (1993), *Allergy* **48**, 634–636.
54. Adkinson, N. F., Jr. (1986), in *Manual of Clinical Immunology*, Rose, N. F. and Friedman, H., eds., Washington DC, American Society for Microbiology, pp. 692–697.
55. Edwards, R. G., Speckman, D. A., and Dewdney, J. M. (1982), *Int. Arch. Allergy Appl. Immunol.* **68**, 352–358.
56. Harle, D. G. and Baldo, B. A. (1990), *Mol. Immunol.* **27**, 1062–1071.
57. Carrington, D. M., Earl, H. S., and Sullivan, T. J. (1987), *J. Allergy Clin. Immunol.* **79**, 442.
58. Rieder, M. J., Shear, N. H., and Kanee, A. (1991), *Clin. Pharmacol. Ther.* **49**, 13–17.
59. Wolf, G. L., Arenson, R. L., and Cross, A. P. (1989), *A. J. R.* **152**, 939–944.
60. Katayama, H., Yamaguchi, K., and Kosuka, T. (1990), *Radiology* **175**, 621–628.
61. Phils, J. A. and Perlmutter, L. (1974), *Acta. Allergol.* **29**, 474.
62. Daxun, Z., Becker, W. M., and Schulz, K. H. (1993), *Invest. Allergol. Clin. Immunol.* **3**(2), 72–78.
63. Stevenson, D. D. and Mathison, D. A. (1985), *Postgrad. Med.* **78**, 111.
64. Stevenson, D. D. (1984), *J. Allergy Clin. Immunol.* **74**, 617.
65. Schmitz-Schumann, V. M., Juhl, E., and Costabel, U. (1985), *Atemn Lungenkrkh Jahrgang* **10**, 479.