

Drug Allergy Testing

Background

Adverse drug reactions (ADRs) are a significant clinical concern and have been reported to account for 5% of all hospital admissions^(1,2). The term “drug allergy” is only one form of adverse drug reaction and should be reserved for situations where IgE-mediated reactions are involved. The term “drug hypersensitivity” is a more general term that implies an immunologic basis for the reaction (IgE, IgG, T- cells). In many cases it will not be possible to know the precise mechanism of a patient’s adverse drug reaction but most ADRs are not immune-mediated. The various types of reactions can be classified as follows⁽¹⁾:

Type	Examples
Toxicity from Overdose	Seizures with theophylline
Side-Effects	Sedation with antihistamines
Secondary Effects	Disturbance of bacterial flora
Drug Interactions	Bleeding-warfarin & cimetidine
Intolerance	Tinnitus with aspirin
Allergic	Penicillin
Pseudoallergic	Radiopaque contrast media

True drug allergic reactions (i.e. those involving IgE) only occur in a small percentage of patients receiving a drug. Such reactions require prior exposure for sensitization and generally develop rapidly after the second exposure to the drug. Only a small dose may be required to produce a true allergic reaction⁽¹⁾.

Factors Influencing Immune-Mediated Drug Hypersensitivity. There are numerous factors that influence the development of drug hypersensitivity and include both drug-related and patient specific factors.

<u>Drug-related</u>	<u>Patient-Specific</u>
<input type="checkbox"/> Molecular nature	<input type="checkbox"/> Age
<input type="checkbox"/> Route	<input type="checkbox"/> Gender
<input type="checkbox"/> Dose	<input type="checkbox"/> Genetics
<input type="checkbox"/> Duration of therapy	<input type="checkbox"/> Concurrent Illness
<input type="checkbox"/> Frequency of exposure	

Drug Metabolism and Immunogenicity

Since most drugs are low molecular weight (i.e. < 1000 Daltons), they are not complete antigens and must combine with a macromolecular carrier to be immunogenic. Presumably, small non-reactive drugs must undergo metabolism or “bioactivation” to a chemically reactive form⁽²⁾. Drug molecules that contain aromatic amines can be converted to unstable intermediates that may form immunogenic hapten-protein conjugates.

Penicillin Allergy. It is estimated that the prevalence of penicillin allergy is as high as 2% per course of treatment. Although most reactions are relatively mild, penicillin remains the leading cause of drug-induced anaphylaxis. Four hundred to 800 deaths per year are attributed to penicillin in the U.S. These reactions are mediated by IgE and can be evaluated by either a skin test or an in vitro test for penicillin-specific IgE. However, it should be noted that both the commercial skin test reagent and the in vitro (ImmunoCAP®) test are only useful in assessing sensitivity to the major penicillin determinants.

Cephalosporin Allergy. Although both penicillins and cephalosporins contain the β -lactam ring, the cephalosporins have a dihydrothiazine ring rather than a thiazolidine ring. There is a 5 – 10% risk of allergic reaction to cephalosporins in penicillin allergic patients. Anaphylaxis occurs less frequently to the semi-synthetic penicillins and cephalosporins than to natural penicillins. The cross-reactivity rate between the cephalosporins and the penicillins is low.

Sulfonamide Allergy. A maculopapular rash is the most common adverse reaction and is especially a problem for HIV patients. Sulfonamides are metabolized by the liver and if these oxygenated metabolites are not detoxified by glutathione reductase, they may react with tissue proteins to produce immunogenic hapten-carrier complexes⁽²⁾. The clinical utility of the in vitro test (i.e. RAST for sulfamethoxazole) has not been established.

Quinolone Allergy. ADRs to this class of drugs are rare. The most common ADRs involve GI symptoms. Fluoroquinolones have no cross-reactivity with β -lactam antibiotics. There is no evidence that IgE is involved in any of these ADRs and there are no validated laboratory tests for specific IgE.

Aspirin and NSAID Sensitivity. ADRs include GI bleeding, kidney and liver toxicity, respiratory distress and skin reactivity. Since both of these drugs inhibit the cyclooxygenase enzyme and could lead to increased synthesis of leukotrienes, they have the potential for causing acute bronchoconstriction, urticaria and angioedema. Respiratory reactions to aspirin include chronic nonallergic rhinitis, nasal polyps, sinusitis and asthma (the “aspirin tetrad”). There is no evidence that aspirin-specific IgE is involved in these adverse reactions.

Allergy to Local Anesthetics. Although adverse reactions have been reported, these are not believed to be immune-mediated reactions. It appears that some of these reactions may be vasovagal or anxiety-based reactions. Either the epinephrine or preservatives in the anesthetic preparations may be important in these reactions. There is no role for IgE testing.

Insulin Allergy. Most patients who receive therapeutic insulin develop IgG antibodies and a subset of these will produce IgE to the bovine or porcine forms of insulin. IgE to the recombinant human insulin are much less common. IgE testing can be helpful in evaluating these patients.

Protamine Allergy. This drug which is used to neutralize heparin during cardiopulmonary bypass surgery can cause severe reactions. The most common ADRs include flushing, urticaria, angioedema, bronchospasm, hypotension and death ⁽¹⁾. Although protamine is derived from salmon testes, allergy to fish does not increase the risk of a reaction. ADRs are also common in diabetic patients taking NPH insulin.

New Biotherapeutic Drugs. Many of the new drugs are proteins or peptides and these are all potentially capable of immunological sensitization. For example, adverse reactions to Remicade®, a biotherapeutic monoclonal antibody that blocks TNF- α , can be sensitizing and result in an ADR.

Non-IgE Immune Drug Reactions. In patients who have ADRs that are immune-based but do not involve IgE, it is possible to examine the responses of blood cells to challenge with the drug. The role of T-lymphocyte activation in adverse drug reactions is an area of intense investigation ⁽⁴⁾. IBT Laboratories has an ongoing research program to develop ex vivo drug stimulation and reactivity methods based on cytokine release from blood cell cultures. However, the clinical utility of these T-cell tests remains to be established and should be reserved for special clinical research protocols.

BasoFunction™ Test. IBT now offers an ex vivo challenge test for a number of drugs. This test uses standardized drug antigens that are mixed with whole blood and incubated in culture. The histamine released by the basophils into the culture fluid is measured with a validated and quantitative ELISA. Since the clinical utility of these tests has not been documented with prospective clinical trials, the results should be interpreted in combination with other relevant patient information. Inquire about specimen requirements and updates on new drugs that may have been added to the list of tests.

Drug specific tests currently available:

<u>Drug Name</u>	<u>Code #</u>	<u>Method*</u>
ACTH [^]	1849	CAP
Amoxicillin	236	CAP
Ampicillin	235	CAP
Cephalosporin C [^]	501351	BasoFunction
Cephalosporin [^]	87510	RAST
Chymopapain [^]	1402	CAP
Ciprofloxacin [^]	501352	BasoFunction
Chlorhexidine [^]	140810	CAP
Elastase [^]	187910	RAST
Erythromycin [^]	87710	RAST
Gelatin (bovine)	468	CAP
Gelatin (porcine) [^]	35610	RAST
Insulin (bovine) [^]	855	CAP
Insulin (human)	857	CAP
Insulin (porcine) [^]	856	CAP
Ispaghula/Psyllium	839	CAP
Lidocaine [^]	501353	BasoFunction
Penicillin (BP-PolyLys) [^]	501355	BasoFunction
Penicillin (Minor Det) [^]	501354	BasoFunction
Penicillin G	231	CAP
Penicillin V	232	CAP
Protamine [^]	1401	CAP
Remicade [^] (Infliximab)	164510	RAST
Sulfamethoxazol [^]	87610	RAST
Sulfamethoxazole [^]	501356	BasoFunction
Suxamethonium [^]	799	CAP
Suxamethonium [^]	501357	BasoFunction
Tetanus Vaccine [^]	929	CAP
Tetracycline [^]	87810	RAST
Tetracycline [^]	501358	BasoFunction

* CAP, Phadia ImmunoCAP; RAST, Conventional RAST

[^] These tests have not been cleared by FDA for in vitro diagnostic use and are not available in New York. The tests were developed and standardized by IBT Laboratories.

General Reviews

1. Yates AB and deShazo RD. Drug allergies and hypersensitivity. In Rich et al (eds) Clinical Immunology, 2nd Edition, Mosby, 2001, 54.1
2. Gruchella RS. Drug metabolism, danger signals, and drug-induced hypersensitivity. J Allergy Clin Immunol 2001; 108: 475-488.
3. Vervloet D et al. Drug Allergy. Pharmacia & Upjohn. 1999.
4. Pichler WJ. Delayed drug hypersensitivity reactions. Annals of Internal Medicine 2003; 139:683-693.

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