Recent advances in the diagnosis of drug allergy

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Purpose of review

The present review addresses the most recent literature regarding the diagnosis of drug hypersensitivity reactions, which can be classified as immediate or nonimmediate according to the time interval between the last drug administration and the onset. Immediate reactions occur within 1 h; nonimmediate ones occur after more than 1 h.

Recent findings

Clinical and immunological studies suggest that type-I (IgE-mediated) and type-IV (cell-mediated) pathogenic mechanisms are involved in most immediate and nonimmediate reactions, respectively. New diagnostic tools, such as the basophil activation test and the lymphocyte activation test, have been developed and are under validation.

Summary

In diagnosis, the patient's history is fundamental; the allergologic examination includes in-vivo and in-vitro tests selected on the basis of the clinical features. Prick, patch, and intradermal tests are the most readily available forms of allergy testing. Determination of specific IgE levels is still the most common in-vitro method for diagnosing immediate reactions. The sensitivity of allergologic tests is not 100%; in selected cases, therefore, provocation tests are necessary. The routine use of the basophil activation test and the lymphocyte activation test could increase the sensitivity of diagnostic work-ups, thus reducing the need for drug provocation tests.

Keywords

drugs, hypersensitivity, in vitro tests, patch tests, skin tests

Curr Opin Allergy Clin Immunol 7:299–303. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2007, 7:299–303

Abbreviations

AGEP	acute generalized exanthematous pustulosis
BAT	basophil activation test
ENDA	European Network for Drug Allergy
ICM	iodinated contrast media
LAT	lymphocyte activation test
LTT	lymphocyte transformation test
MDM	minor determinant mixture
PPL	penicilloyl-polylysine
RAST	radioallergosorbent test
RIA	radioimmunoassay

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Introduction

The revised nomenclature for allergy classifies allergic reactions to drugs as IgE-mediated or non-IgE-mediated [1].

It is important, however, to distinguish between immediate and nonimmediate reactions. The former occur within the first hour after the last drug administration and are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm and anaphylactic shock. Nonimmediate reactions occur more than 1 h after last drug administration. The main nonimmediate reactions are maculopapular eruptions and delayed-appearing urticaria/angioedema. In addition, drugs can elicit fixed eruptions, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, and toxic epidermal necrolysis (TEN) [2]. Immediate allergic reactions are generally the most dangerous, are IgE-mediated, and have been extensively studied, whereas the mechanisms involved in nonimmediate reactions seem to be heterogeneous [2].

The present review addresses the most recent literature regarding the diagnosis of drug hypersensitivity reactions and often refers to the general guidelines for diagnosing such reactions devised by the European Network for Drug Allergy (ENDA)/European Academy of Allergerology and Clinical Immunology (EAACI) interest group on drug hypersensitivity.

Clinical evaluation

The clinical history should be extremely thorough and include several data, which should be collected in a uniform format. A specific questionnaire [3] has been developed by the ENDA and is available in many different languages.

Table 1 Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction	Type of test	
Immediate	*In vitro*	Specific IgE assays
		Flow cytometric basophil activation tests
	In vivo	Skin tests
		Drug provocation tests
Nonimmediate	*In vitro*	Lymphocyte transformation or activation tests
	In vivo	Delayed-reading intradermal tests
		Patch tests
		Drug provocation tests

In selecting diagnostic tests, it is important to consider whether the reaction is immediate or nonimmediate, as summarized in Table 1.

Skin tests

These are the most readily available form of allergy testing for physicians. Because of their greater sensitivity, skin tests cannot yet be replaced by in-vitro tests. A recent article by Blanca *et al.* [4] reviewed the results of skin tests in β-lactam allergy and provided evidence for their continued need. Other studies [5–7] reinforced the important concept that in patients reporting adverse reactions to β-lactams, the clinical history is not predictive of subsequent skin test results. Therefore, skin testing continues to be essential before β-lactam re-exposure. In both the ENDA position paper [8] and the American practice parameters [9], skin testing with penicilloyl-polylysine (PPL) and minor determinant mixture (MDM) represents the first-line method for diagnosing immediate hypersensitivity reactions to β-lactams. Moreover, recent studies emphasized the importance of skin testing with PPL and MDM in diagnosing β-lactam hypersensitivity [10,11]. Bousquet *et al.* [10] observed positive skin tests in 136 (16.5%) of 824 patients with histories of β-lactam hypersensitivity; 20 (14.7%) of them were positive only to PPL or MDM. Matheu *et al.* [11] diagnosed hypersensitivity in 44 (9.5%) of 463 patients with such histories; 21 (47.7%) of the sensitive patients displayed positive skin tests only to PPL or MDM. In the study by Wong *et al.* [6], 50% of the 16 patients displaying positive results to skin tests with penicillin reagents were positive only to PPL (seven patients) or MDM (one). Therefore, after Allergopharma and Hollister-Stier ceased production of PPL and MDM in 2004, there was the danger that physicians would be set back more than 25 years in managing patients with hypersensitivity reactions to β-lactams. Nevertheless, penicillin reagents (PPL and MDM) have been sold in Spain by Diater (DAP, Madrid, Spain) since 2003 as an allergen for prick and intradermal tests. In a recent study [12], we observed a good concordance between the Allergopharma reagents (Allergopen, Hamburg, Germany) and the DAP ones. In effect, Allergopen MDM and DAP MDM produced identical results in all 195 patients evaluated, 22 of whom were positive to both reagents. Results of skin testing with PPL were concordant in 190 (97.4%) of the 195 subjects. Thus, our results confirmed those of a previous study by Rodriguez-Bada *et al.* [13], which had also compared the Allergopen and DAP reagents in 22 penicillin-allergic subjects by using both in-vivo and in-vitro tests.

In evaluating subjects with immediate reactions to β-lactams, the aforesaid protocols [8,9] recommend the use of benzyl-penicillin, amoxicillin, ampicillin, and any other suspect β-lactam, in addition to PPL and MDM.

With regard to cephalosporins, recent studies have contributed to standardizing skin testing with these β-lactams and to proving that such testing is a useful tool in evaluating subjects with immediate reactions to cephalosporins [14–16]. In a study of ours [14], skin testing at a concentration of 2 mg/ml in normal saline of several injectable and noninjectable cephalosporins proved to be a very effective method for evaluating subjects who suffered immediate reactions to cephalosporins. We evaluated 76 adults with histories of immediate reactions to cephalosporins by performing skin tests and serum specific IgE assays. Some subjects with negative results underwent challenges and re-evaluations. The rate of positive responses to skin tests with responsible cephalosporins was 69.7%; it increased to 78.9% when considering also the results of the re-evaluation. A subsequent study by Antunez *et al.* [15], however, did not confirm such sensitivity of cephalosporin skin testing in 127 patients with immediate reactions. After the allergologic exam, hypersensitivity was diagnosed in 51 patients: 39 (30.7%) were skin-test positive, 2 (1.5%) were skin-test negative and specific IgE assay positive, and nine (7.1%) displayed negative results in both skin tests and specific IgE assays and reacted to challenges. Therefore, further studies should be performed in large samples of subjects with immediate reactions to cephalosporins in order to fully establish cephalosporin skin test sensitivity.

Cephalosporin skin tests are also useful in finding safe alternatives in penicillin-allergic subjects. In a study regarding 128 patients with a well established IgE-mediated allergy to penicillins, mainly to aminopenicillins [17], all 101 patients who displayed negative skin tests for cefuroxime, ceftazidime, ceftriaxone, and cefotaxime and underwent graded challenges with cefuroxime axetil and ceftriaxone tolerated them. Therefore, this study supports the advisability of performing skin tests with cephalosporins before their administration to penicillin-allergic patients who especially require a cephalosporin treatment. In the United States, nevertheless,

the current consensus recommendation [9,18] for the administration of a cephalosporin to subjects with IgE-mediated hypersensitivity to penicillins is to choose one with a different side chain and perform a graded challenge in an intensive care unit without carrying out prophylactic skin tests with the relevant cephalosporin.

Two recent studies of ours [19,20••] proved that skin testing with native carbapenems is also useful in finding safe alternatives in penicillin-allergic subjects. In effect, we found a 0.9% rate of positive responses to skin tests with imipenem/cilastatin and meropenem among 112 and 104 adults, respectively, with a well demonstrated IgE-mediated hypersensitivity to penicillins. In these two studies [19,20••], all negative subjects who agreed to undergo imipenem/cilastatin or meropenem challenges tolerated them; specifically, 42 subjects tolerated imipenem/cilastatin, 35 meropenem, and 68 both imipenem/cilastatin and meropenem.

Patients with severe anaphylaxis or rapid chronology after a β-lactam administration should be carefully skin tested. Indeed, in one study [21] 147 patients had positive skin tests and 13 (8.8%) of them experienced a systemic reaction. The 13 reactors were compared to the nonreactors (135 patients who had positive skin tests without systemic reactions). The presence of anaphylaxis (69%) and a chronology (that is, the time interval between the last drug administration and the reaction) of less than 1 h (91%) were significantly more frequent in reactors than in nonreactors (35% and 43%, respectively).

Skin tests continue to be regularly used in order to evaluate patients with immediate reactions during general anaesthesia, as well as to reduce the risk of such reactions by identifying patients sensitized to anaesthetic drugs or other compounds to be administered during the procedure and providing safe alternatives to them. In this regard, the guidelines devised by the Société Française d'Anesthésie et de Réanimation and endorsed by the ENDA are available [22].

With regard to compounds other than β-lactams and muscle relaxants, the literature data suggest that immediate and delayed-reading skin tests with iodinated contrast media (ICM) are indicated in patients with severe immediate hypersensitivity reactions and in those with nonimmediate skin reactions following administration of ICM, respectively [23,24]. Kanny *et al.* [25] diagnosed a cell-mediated hypersensitivity in 12 patients with nonimmediate reactions to ICM, mostly maculopapular eruptions, on the basis of positive responses to delayed-reading skin tests or patch tests, as well as to in-vitro tests. In a study by Kvedariene *et al.* [26], which assessed 44 consecutive patients with histories of ICM hypersensitivity by skin tests, 10 patients (23%) displayed positive responses: one had a positive skin prick test, seven had immediate-reading positive intradermal tests, and two had delayed-reading positive ones. Skin tests were more often positive in patients with immediate reactions (nine of 32) as compared with those with nonimmediate ones (one of 11). The sensitivity, specificity, and predictive value of ICM skin testing, however, are not yet fully established and are being addressed in a multicenter ENDA study.

In a review by Bircher *et al.* [27•] concerning hypersensitivity reactions to anticoagulant drugs, skin tests with immediate and delayed readings, together with provocation tests, are indicated as the most reliable diagnostic tools for evaluating subjects with heparin or hirudins-induced urticaria/anaphylaxis or heparin-induced delayed plaques. Skin testing is useless in anaphylactic reactions caused by dextrans or hydroxymethyl starch, however, and it is contraindicated if necrosis from heparins or coumarins is suspected.

Biological tests

Serum specific IgE assays (radioallergosorbent tests, RASTs and immunoenzymatic assays, or enzyme-linked immunosorbent assays) are still the most common in-vitro methods for evaluating immediate reactions. These tests are available only for a few drugs, such as some β-lactams, muscle relaxants, and insulin. Studies comparing skin tests and specific IgE assays indicate that the two methods are not totally equivalent. Although these in-vitro tests appear to be less sensitive than skin testing, we recommend them at least in cases with the most severe reactions in order to avoid provocation tests, because there are patients with immediate reactions displaying skin-test negativity and specific-IgE-assay positivity. Fontaine *et al.* [28], in collaboration with Blanca's group, used the CAP-FEIA system (Phadia; Uppsala, Sweden) and a homemade RAST in evaluating three well defined groups of 15 patients each (total number 45): one with histories of immediate reactions to β-lactams (penicillins or cephalosporins), negative skin tests and positive challenges; another with positive histories and positive skin tests; and a third consisting of tolerant subjects. The specificity of CAP-FEIA ranged from 83.3 to 100% and sensitivity from 0 to 25% depending on the initial clinical manifestations. The specificity of RAST ranged from 66.7 to 83.3% and sensitivity from 42.9 to 75%. In the subgroup of patients who had suffered an anaphylactic shock and presented negative skin tests, the sensitivity and specificity of RAST were 75%. These results confirm that, although the specificity of β-lactam-specific IgE assays is good, sensitivity is low.

In an aforementioned study of ours [14], we performed sepharose-radioimmunoassays (RIAs) with cefaclor and the responsible cephalosporins in 70 of 76 patients who

had suffered immediate reactions, mostly anaphylactic shocks. Considering the positivity of at least one of the two sepharose-RIAs, specific IgEs were detected in 47 (67.1%) of these 70 patients; five of them were skin-test negative and were not challenged.

Manfredi *et al.* [29] performed a sepharose-RIA in 55 patients with immediate reactions to quinolones, detecting serum specific IgE in 54.5% of cases.

In patients with immediate reactions, a flow cytometric basophil activation test (BAT) to detect specific surface markers with monoclonal antibodies can also be performed. At present, the most commonly used antigens in BATs are CD63 and CD203c.

There is evidence that the BAT can contribute to the diagnosis of anaphylactic reactions from several drugs, particularly muscle relaxants, β-lactams, and nonsteroidal anti-inflammatory drugs [30,31]. In a study by Ebo *et al.* [30], which evaluated 14 patients who had suffered a perioperative anaphylaxis and were positive to rocuronium, as well as eight subjects who tolerated rocuronium and were skin-test negative, BAT sensitivity was 91.7% and specificity 100%. In this study, the BAT also allowed different potential cross-reactive muscle relaxants to be assessed and safe alternative ones to be found.

As far as β-lactams are concerned, in two studies [32,33] evaluating, respectively, 58 and 70 patients with immediate reactions to these antibiotics, BAT sensitivity was about 50% and specificity over 90%. Unlike the study by Sanz *et al.* [32], however, the one by Torres *et al.* [33] assessed not only patients with positive histories and positive skin tests or CAP-FEIA, but also patients negative to both these tests and positive to challenges. It is interesting to note that one of the seven patients of the latter group was BAT positive; in this study, moreover, the BAT for the responsible cephalosporins was positive in 77.7% of cases.

Additional comprehensive studies in large samples are required in order to further validate the technique and provide a definitive assessment of its sensitivity.

A cellular response involving drug-related T-cell activity may be assessed *in vitro* by the lymphocyte transformation test (LTT). The LTT is both sensitive and specific; it can be frequently positive in maculopapular exanthems, bullous disorders, AGEP, and DRESS induced by drugs like aminopenicillins and anticonvulsants [34,35,36•]. In a study by Schmid *et al.* [37], the LTT was positive to responsible quinolones (ciprofloxacin, norfloxacin, or moxifloxacin) in all six patients who had experienced exanthems or AGEP, while patch tests were positive in only three of them.

According to Merck's group [38,39], LTT sensitivity could be improved to 92% by the measurement of IL-5 in culture supernatants taken after 5 days. The LTT is frequently negative, however, in patients with TEN, fixed drug eruptions, and vasculitis [35].

In the aforementioned study by Kanny *et al.* [25], patients with nonimmediate hypersensitivity reactions to ICM were assessed not only by the LTT (three of four were positive), but also by a new in-vitro method, the lymphocyte activation test (LAT). The LAT measured by means of cell-cycle analysis through DNA content was positive to the responsible ICM in one patient; the LAT measured by means of upregulation of the activation marker CD69 was positive to the culprit ICM in another one, and negative in a third patient. These results require confirmation in a larger sample of subjects.

Drug provocation tests

These remain the gold standard for the identification of an eliciting drug when allergologic tests are negative, not available, or not validated. They can only be performed, however, under the most rigorous surveillance conditions and are therefore restricted to certain specialist centers with on-site intensive care facilities [40]. Recent studies, which performed drug provocation tests [6,41], have confirmed the data of Messaad *et al.* [42], not only allowing drug hypersensitivity to be diagnosed, but also excluding it in more than 80% of reactions suffered by patients displaying negative results in skin tests or in-vitro tests.

Conclusion

The diagnosis of drug hypersensitivity often relies on clinical histories, skin tests, and a few validated in-vitro tests, such as serum specific IgE assays, which are available only for a few drugs. The sensitivity of these tests is not 100%; in selected cases, therefore, provocation tests are necessary. New diagnostic tools, however, such as the BAT and the LAT, have been developed and are under validation. Their routine use could increase the sensitivity of diagnostic work-ups, thus reducing the need for drug provocation tests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 360).

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