

# Skin Testing for IgE-Mediated Drug Allergy

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## KEYWORDS

- Drug hypersensitivity • Drug allergy • Adverse drug reaction
- Immediate reaction • Prick test • Intradermal test

Adverse drug reactions (ADRs) are a frequent problem of the daily clinical praxis. Although patients who have experienced ADRs often refer to them as drug allergies, true allergic reactions—hypersensitivities with the involvement of one or more immunologic mechanisms—represent approximately 15% of all ADRs. As a consequence, this often results in avoidance of one or more drug classes, which may lead to the prescription of less effective or more expensive alternative drugs. Therefore, an adequate diagnostic work-up is recommended and widely done in Europe, less so in the United States.<sup>1–13</sup>

Every work-up has to start with a detailed case history and accurate determination of the reaction type, followed by skin tests or, if available, in vitro tests. If this procedure remains inconclusive, drug provocation tests with the suspicious or an alternative drug could be performed by a physician experienced in the field of drug allergy.

In general, drug hypersensitivities can be classified as immediate, accelerated, or delayed, according to the time interval between intake of the drug and occurrence of the reaction. This classification was set up by Levine on the basis of his experience with penicillin allergy.<sup>14</sup> From a clinical standpoint, immediate and nonimmediate reactions differ in the time interval between drug intake and beginning of clinical manifestations. In immediate reactions, symptoms appear within 1 hour and sometimes within just a few minutes of drug intake. Main clinical manifestations are urticaria or angioedema and anaphylaxis, often due to drug-specific IgE. These ADRs are the principal indications for skin prick tests (SPTs) and intradermal tests (IDTs) in drug allergy work-up (**Box 1**).

## INDICATION FOR SKIN TESTS

A detailed history is the prerequisite for an accurate diagnosis of a drug-induced (skin) reaction. It must comprise any details of the drug administration (all active ingredients, formulation, dose, route, previous exposure to and tolerance of the drug incriminated,

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**Box 1**

**Indications for skin prick test and intradermal test in drug allergy work-up**

Erythematous eruption/flushing  
 Urticaria  
 Angioedema  
 Anaphylaxis  
 Conjunctivitis  
 Rhinitis  
 Bronchospasm/asthma

review of an anesthetic chart, and so forth) and the definite nature of the adverse reaction. Use of the European Network for Drug Allergy questionnaire may be helpful.<sup>1</sup> If an immediate allergic reaction can be stated based on the presence of a sensitization period, reaction to low drug doses, and the typical symptomatology and course of type I allergic reactions, SPTs and IDTs may be recommended depending on the drug class involved. SPTs and IDTs are read at 15 to 20 minutes and then are indicative only for an IgE-mediated drug allergic reaction.<sup>3</sup> Later readings of IDTs are used for delayed, non-IgE-mediated allergies. A list of ADRs that represent no indications or even contraindications for IDTs with immediate readings or where IDT may cause exacerbations of an allergy is given in **Box 2**.

Drugs with well-standardized test procedures are  $\beta$ -lactams (penicillins and cephalosporins), neuromuscular blocking agents, local anesthetics, iodinated contrast media, and chemotherapeutics (platinum salts).

**Box 2**

**No indications for skin prick test and intradermal tests in drug allergy work-up (sample)**

Drug-induced autoimmune diseases  
     Bullous pemphigoid  
     Pemphigus vulgaris  
     Systemic lupus erythematosus

Severe exfoliative skin reactions

    Acute generalized exanthematic pustulosis  
     Drug reaction with eosinophilia and systemic symptoms or drug hypersensitivity syndrome  
     Exfoliative dermatitis  
     Multilocalized bullous fixed drug eruption  
     Stevens-Johnson syndrome  
     Toxic epidermal necrolysis

Severe vasculitis syndromes

Late reading of intradermal tests is useful in delayed reactions but bears risk for flare-up reactions to the intradermally applied drug.

In addition, SPTs can be performed with other drugs and IDTs, if sterilized solutions used for parenteral applications are available (subject to investigator experience).<sup>5</sup> Some indications for nonirritative concentrations can be obtained from published case reports. These experimental tests have to be interpreted cautiously, however, as many drugs may cause wheal and flare reactions spontaneously; the sensitivity for such reactions may differ individually and positive controls often are missing.

Additionally, (immediate) skin tests are of educational value, because they provide a visual illustration that may reinforce the verbal advice given to patients.<sup>4</sup>

### TIMING FOR SKIN TEST PERFORMANCE

A few guidelines have been published for performing SPTs and IDTs with drugs in the investigation of ADRs.<sup>2-4</sup> Generally, it is advised to perform the tests 6 weeks to 6 months after the hypersensitivity reaction because it is not known whether or not positive results will persist and whether or not some drug reactivities last longer.<sup>2,5,6</sup> Ideally, immediate skin testing should be performed after an interval that allows resolution of clinical symptoms and clearance of a suspected drug.

It is important to avoid antihistamines (up to 7 days) before testing. Higher doses of systemic corticosteroids and other immunosuppressive therapy and antidepressants with antihistamine side effects also may interfere and hamper the interpretation of a negative result; hence, these drugs should be stopped for 3 days to 1 month before testing (Table 1).<sup>2,3,7</sup>

### WORKFLOW AND PERFORMANCE

Patients preferably should be in good condition and give informed verbal or (preferably) written consent.<sup>8</sup>

Finding a suitable test reagent may be a problem as most drugs have low molecular weight and are not immunogenic, and, furthermore, drug metabolites may have caused the adverse reaction. Moreover, investigators must be aware of appropriate starting dilutions and the concentrations likely to induce irritant, nonallergic skin responses. Unfortunately, for the vast majority of drugs, commercial test preparations are not available, and if adequate test concentrations for a suspected drug are not known, it is recommended to test the drug at concentrations comparable to that of a related drug for which data already are published.

| Medication                        | Route                      | Free Interval |
|-----------------------------------|----------------------------|---------------|
| H1-antihistamines, phenothiazines | Oral, intravenous          | 5 days        |
| β-Adrenergic drugs                | Oral, intravenous          | 5 days        |
| <b>Glucocorticosteroids</b>       |                            |               |
| Long-term                         | Oral, intravenous          | 3 weeks       |
| Short-term, high-dose             | Oral, intravenous          | 1 week        |
| Short-term, <50 mg prednisolone   | Oral, intravenous          | 3 days        |
| Topical corticosteroids           | Topical (at the test site) | >2 weeks      |

Data from Barbaud A, Goncalo M, Bruynzeel D, et al. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Derm* 2001;45:321-8 and Brockow K, Romano A, Blanca M, et al. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.

Because it is a safe and easy way to perform test, prick testing should be done initially. It is performed by pricking the skin percutaneously with a prick test needle (lancet) through the test (drug) solution. The drug is, if necessary, appropriately diluted (eg, 1:10 or sometimes 1:1000) with normal saline (0.9% NaCl). Whenever possible, the pure drug and excipients should be tested as is, but in patients who have developed anaphylaxis, sequential solutions ( $10^{-3}$  to  $10^{-1}$ ) should be tested.<sup>2</sup> An additional application of a positive control (histamine) and negative control (normal saline, diluent) is essential for correct interpretation of the test results. Reading is done after 15 minutes,<sup>3,4,7</sup> but some investigators propose 20 minutes<sup>2,3,5,6</sup> or even 30 minutes<sup>9</sup> after application of the test solution to skin. The SPT is considered positive in cases of a wheal with a diameter larger than that of the negative control and larger than 3 mm, typically surrounded by a red flare.<sup>3</sup> For the purpose of comparison, a morphologic description or, even better, a morphologic score also should be applied.

If SPT is negative, IDTs are done with serial dilutions of the suspected drug, usually starting with 1/100 of the concentration used for SPT. The skin of the volar forearm is injected intradermally with 0.02 to 0.05 mL of the lowest concentration (1:10,000 to 1:100, depending on the drug and patient history), resulting in a wheal of 4 to 6 mm in diameter. If no reaction can be elicited, the test solution is injected again in a concentration increased in logarithmic steps ( $\times 10$ ). In the literature it is recommended to prepare dilutions (in an optimal way under laminar flow) no more than 2 hours before administration.<sup>2,5</sup> As with SPT, negative (0.9% NaCl) and positive (histamine, 1 mg/mL) control testing are strongly recommended. IDT readings are recommended at 15,<sup>3,7</sup> 20,<sup>3,10</sup> or 30<sup>2</sup> minutes in cases of evaluating immediate-type ADR and at 24 hours if a delayed-type reaction is evaluated (IDT then is performed in addition to or instead of patch testing). IDT is considered positive when the diameter of the reaction is enlarged by a minimum 3-mm diameter, is found twice the diameter of the injection papula, or is a wheal larger than 8 mm (summarized by Barbaud<sup>5</sup>). The painfulness of IDT may limit its use in (young) children. IDTs in patients who have severe reactions, such as drug reaction with eosinophilia and systemic symptoms, and possibly also in patients who have Stevens-Johnson syndrome/toxic epidermal necrolysis (see **Box 2**), may cause a (mostly mild) flare up of the reaction (**Table 2**).

REASONS FOR FALSE-POSITIVE RESULTS

False-positive results are those in which the skin test response to the tested drug is interpreted as positive, but a patient does not develop adequate symptoms if re-exposed to the drug. Common causes include the following:

- 1. Patient is sensitized and may have (low-affinity) drug/hapten-specific IgE antibodies but does not react clinically

| Table 2<br>Maximum concentrations recommended for prick and intradermal testing with $\beta$ -lactams |                           |
|-------------------------------------------------------------------------------------------------------|---------------------------|
| Allergen/Hapten                                                                                       | Dose/Units                |
| BPO                                                                                                   | $5 \times 10^{-5}$ mmol/L |
| MDM                                                                                                   | $2 \times 10^{-2}$ mmol/L |
| Amoxicillin                                                                                           | 20–25 mg/mL               |
| Ampicillin                                                                                            | 20–25 mg/mL               |

Data from Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;58:961–72.

2. Drug may cause spontaneous mast cell degranulation (eg, opiates or quinolones)
3. Test dilution is too highly concentrated, thus producing an immediate reaction on the basis of nonspecific irritation of mast cells
4. Physical trauma of skin testing in patients who have dermatographism or urticaria (factitia)
5. Reaction to the diluent, preservative (phenol, glycerol, and so forth), or contaminants<sup>15</sup>
6. Improper interpretation of results, reading erythema rather than wheals
7. Lack of negative and positive skin test controls; because individuals react differently to drugs, at least 20 controls also should be analyzed

Even when correct technique and proper drug dilution are used, a positive skin test result does not necessarily validate the diagnosis. The diagnostic value of skin test positivity depends on the demonstration, by drug re-exposure, that clinical symptoms of the ADR are elicited by exposure to the drug allergen that induced the skin test reaction.

### REASONS FOR FALSE-NEGATIVE RESULTS

Skin tests may be interpreted incorrectly as “negative” in individuals for various, mainly technical, reasons:

1. Application of too little antigen because of inappropriate dilution, loss of potency during storage, and so forth
2. Insufficient penetration of the antigen to the dermal mast cells, improper introduction of antigen (eg, poor technique), or exclusive use of a relatively insensitive method (eg, scratch test)
3. Blocking effect by medications, such as antihistamines, and, less often, tricyclic antidepressants or theophylline
4. Improper reading of reactions or inadequate scoring systems

In addition, there are some important, nontechnical reasons that may cause a lack of skin test reactivity:<sup>9</sup>

1. Cofactors of critical importance at the time of ADR manifestation, such as viral infections or drug-drug interactions, may be absent when performing SPT and IDT
2. Reaction requires metabolism, which cannot occur within 20 minutes to the intradermally applied drug or it happens only in the liver
3. The presentation of the relevant antigen or hapten to the immune system may be different after epicutaneous, oral, or otherwise parenteral challenge
4. SPT or IDT is performed in a time period when the mast cells have degranulated and are not yet restored

### ADVERSE REACTIONS INDUCED BY SKIN PRICK TESTS OR INTRADERMAL TESTS

SPT is a safe diagnostic approach. IDTs, however, also are safe, but several fatal or near-fatal reactions have been reported.<sup>16–19</sup> Urticaria and, rarely, anaphylaxis are described after intradermal testings, in particular with  $\beta$ -lactams.<sup>17–19</sup> In general, patients who have previous anaphylaxis or complicating conditions, such as systemic mastocytosis, may be considered at higher risk (ie, they may react more readily to the minute amounts applied).

As a consequence, it is prudent and recommended to perform SPT first, followed by IDT, in severe immediate reactions. For practical purposes, most tests are done

simultaneously (**Fig. 1**). In addition, adequate equipment and a specialist environment to treat anaphylaxis must be available.<sup>16</sup>

### VALUE OF IMMEDIATE SKIN TESTS ACCORDING TO SELECTED DRUGS

Unfortunately, the usefulness of SPT and IDT in determining the cause of cutaneous ADRs has not been evaluated as much as that of drug patch tests, except for the  $\beta$ -lactams.<sup>9</sup> Even at the beginning of the current millennium, it had to be stated that the sensitivity and predictive value of immediate skin tests vary from excellent (penicillins, neuromuscular blocking agents, heterologous sera, and enzymes) to satisfactory (vaccines, hormones, opiates, and thiopental) and poor or unknown (local anesthetics, nonsteroidal anti-inflammatory drugs, iodine radiocontrast media, quinolones, and other anti-infectious drugs).<sup>6</sup> In recent years, however, some projects in Europe (mainly under the auspices of European Network for Drug Allergy) and some United States investigators have improved this situation considerably for selected drug groups.

### $\beta$ -LACTAMS AND OTHER ANTIBIOTICS

Allergic reactions to  $\beta$ -lactams (eg, penicillins, cephalosporins, imipenem, and monobactam) are the most common cause of ADRs mediated by immunologic mechanisms.<sup>20–26</sup> The  $\beta$ -lactams all possess a characteristic  $\beta$ -lactam ring structure. When the ring is fused to a 5-membered thiazolidine ring (penam), the drug is classified as a penicillin; when fused to a 6-membered dihydrothiazine ring (cephem), it is classified as a cephalosporin. Penicillins and cephalosporins may incorporate different salt forms at the ester-binding site, but penicillins have only one side chain (6 position)



**Fig. 1.** Positive reactions in the SPT and IDT with the major and minor determinants of penicillin.

whereas cephalosporins have two side chains (3 and 7 positions). These chains differentiate the activity and metabolic parameters of each drug within each class, and this is recognized as the major source of cross reactivity (called structural activity relationship), replacing the concept of a class effect.<sup>23</sup>

Unlike many diagnostic tests for drug allergies, the positive and negative predictive values of skin tests using penicillin reagents have been well studied.<sup>24</sup> For immediate skin testing purpose, the antigenic determinant benzylpenicilloyl (BPO) has been conjugated to a carrier molecule, polylysine (PPL), which results in BPO-PPL. This compound is well suited to cross-link neighboring IgE molecules bound to high-affinity crystallizable fragment-IgE receptors. Other  $\beta$ -lactam antigens, such as the minor determinant mixture (MDM; composed of benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid), amoxicillin, or some cephalosporins are applied in uncoupled form<sup>22,27</sup> and nevertheless are able to cause mast cell degranulation, if specific IgE is present. How IgE is cross-linked by these small haptens is unknown. Perhaps rapid *in vivo* haptenization of proteins occurs during the skin testing, allowing cross-linking of IgEs by the larger, hapten-modified molecule.

Most studies performed in recent decades, mainly in the United States, have shown that PPL in combination with MDM is adequate (sensitivity up to 70% and high specificity reaching 97% to 100%) to evaluate patients by SPT and IDT with immediate-type allergies to  $\beta$ -lactams (see [Fig. 1](#)).<sup>20,21</sup> Unfortunately, in 2004, Hollister-Stier removed BPO-PPL (Pre-Pen) from the United States market, and Allergopharma in 2005 ceased production of PPL and MDM in Europe, so that the diagnostic evaluation had been hampered.<sup>25,28</sup> PPL and MDM now are on the market again, commercialized (with a substantially higher price) by Diater Laboratories (Madrid, Spain), and recent studies in Europe and Australia indicate that they are equivalent to those from Allergopharma.<sup>22,29</sup> Moreover, a new United States company (AllerQuest, Plainville, Connecticut) has the patent rights to produce Pre-Pen, so that this diagnostic gap should be closed in the near future.<sup>26</sup> If PPL and MDM are not available, SPT and IDT with benzylpenicillin (10,000 to 25,000 IU/mL) can be considered as a compensating test procedure.<sup>25</sup>

Data from the United States suggest that in the presence of a positive history for  $\beta$ -lactam hypersensitivity and negative immediate skin tests for PPL and MDM, patients have only a 0% to 6% risk for reacting with an oral challenge and an approximately 6% risk for reacting on re-exposure.<sup>4</sup> Working groups from Europe, particularly from Spain, however, challenged this conclusion, as they showed that the sensitivity is far lower, approximately 70%.<sup>30</sup> Therefore, controlled drug provocation tests are recommended in cases of skin test negativity and a positive history.<sup>4</sup>

Cephalosporins are the second most prescribed group of  $\beta$ -lactams, and their chemical structures are more heterogenous than those of the penicillins. Immediate skin testing with cephalosporins raises several questions and problems: the tests are not widely standardized, and different test concentrations, from 2 mg/mL up to 30 mg/mL, are reported by different groups. The degradation process of the  $\beta$ -lactam ring is more rapid for cephalosporins than penicillins. Therefore (as discussed previously) the immune response in cephalosporin allergy may be directed to the side chain and individual degradation components but not the  $\beta$ -lactam ring. As a consequence, the shared  $\beta$ -lactam ring of penicillins and cephalosporins is not predictive of cross-reactivity, and penicillin testing does not reliably predict sensitization to cephalosporins unless the side chain of the penicillin or aminopenicillin reagent is similar to the individual side chain of the cephalosporin under evaluation. Thus, skin testing with penicillin determinants shows some cross-reactivity between penicillins and

first-generation cephalosporins, such as cephalothin or cephaloridine, and between amoxicillin and first-generation cephalosporins, such as cephalixin and cefadroxil, but not between penicillin/amoxicillin and later-generation cephalosporins (**Box 3**).<sup>31–34</sup>

Moreover, most oral cephalosporins are only poorly soluble.<sup>27,29,32,35</sup> In patients who have negative skin test results, drug provocation tests with the suspect cephalosporin may be performed.<sup>29</sup> SPT and IDT with cephalosporins also may help find safe alternatives. In a study enrolling 128 patients who had IgE-mediated allergy to penicillins, all 101 patients who had negative skin tests for cefuroxime, ceftazidime, ceftriaxone, and cefotaxime tolerated cefuroxime axetil and ceftriaxone in drug provocation testing.<sup>36</sup> In patients allergic to cephalosporins but who have negative immediate skin testing to penicillin determinants, penicillins may be administered safely.<sup>35</sup>

Recent data on cross-reactivity of penicillin and carbapenems indicate a low degree of cross-reactivity in IgE-mediated reactions: of 112 patients who had immediate reactions to penicillins (mainly amoxicillin, ampicillin, piperacillin, and bacampicillin) and who had positive skin test to penicillins, only 1 of 112 reacted in skin test to imipenem. The remaining 111 were provoked with imipenem and tolerated this carbapenem.<sup>37</sup> The Romano group<sup>37</sup> also evaluated the cross-reactivity to another carbapenem (meropenem): only 1 of 104 (all who had immediate penicillin allergy and positive skin tests to penicillins) had a positive skin test to meropenem, and the 103 remaining penicillin-allergic individuals tolerated a provocation test with meropenem.<sup>38</sup> Thus, IgE-mediated cross-reactivity between penicillins and carbapenem

**Box 3**

**Cross-reactivity between penicillins and cephalosporins based on 6- and 7-position (R1) side chain similarity, respectively**

**Penicillin G**

- Cephaloridine (first generation)
- Cephalothin (first generation)

**Ampicillin**

- Amoxicillin
- Cefaclor (second generation)
- Cefadroxil (first generation)
- Cephalexin (first generation)
- Cephadrine (first generation)

**Ceftizoxime (third generation):**

- Cefepime (fourth generation)
- Cefotaxime (third generation)
- Cefpirome (fourth generation)
- Cefpodoxime (third generation)
- Ceftriaxone (third generation)

*Data from Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. Am J Med 2008;121:572–6 Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. Diagn Microbiol Infect Dis 2007;57:13s–18s.*

seems rare and skin testing with the carbapenem may exclude the few double reactors. For other non- $\beta$ -lactam antibiotics, immediate skin testing is only marginally validated. Ciprofloxacin, for example, shows a wide variance in skin test responsiveness, as quinolones cause some direct mast cell degranulation. This degranulating potency may differ among quinolones and individuals, which explains why irritating skin test concentrations differ by up to 1000-fold in several subjects on testing.<sup>39</sup> Test concentrations for cephalosporines, macrolides, aminoglycosides, and other antibiotics are given in **Table 3**.

### MYORELAXANTS AND ANESTHETICS

Perioperative anaphylaxis may be induced by a variety of agents, including local anesthetics, myorelaxants, inhaled anesthetics, induction drugs, opioids, antibiotics, and so forth.<sup>40–42</sup> Determination of the causative agent is complicated by simultaneous exposure to multimedications and other products, such as latex. Hence, a thorough work-up to identify the allergic trigger must be completed. The majority of anaphylactic reactions are induced by neuromuscular blocking agents, followed by antibiotics and latex, hypnotics, plasma substitutes, chlorhexidine, and, occasionally, opioids and colorants, such as patent blue.<sup>43</sup> Allergy to local anesthetic agents (“caines”) is believed rare (0.7%).<sup>43–45</sup>

SPT and IDT are essential diagnostic measures, because more than 50% of adverse reactions to myorelaxants seem to be IgE mediated.<sup>40–42</sup> Skin tests are performed after obtaining information on the chronology of the event documented by an anesthetist, accompanied by a (readable) copy of the anesthesia record. SPT and IDT are performed by using the commercial solutions. Usually, IDT is started with a 1/1000 dilution of the reagent, except with muscle relaxants and morphine, for

**Table 3**  
Nonirritating test concentrations for commonly used antibiotic agents

| Antimicrobial Drug | Full-Strength Concentration | Nonirritating Concentration for Intradermal Tests (as dilution from Full-Strength Concentration) |
|--------------------|-----------------------------|--------------------------------------------------------------------------------------------------|
| Cefotaxime         | 100 mg/mL                   | 10 mg/mL                                                                                         |
| Cefuroxime         | 100 mg/mL                   | 10 mg/mL                                                                                         |
| Cefazolin          | 330 mg/mL                   | 33 mg/mL                                                                                         |
| Ceftazidime        | 100 mg/mL                   | 10 mg/mL                                                                                         |
| Tobramycin         | 40 mg/mL                    | 4 mg/mL                                                                                          |
| Ticarcillin        | 200 mg/mL                   | 20 mg/mL                                                                                         |
| Clindamycin        | 150 mg/mL                   | 15 mg/mL                                                                                         |
| Gentamicin         | 40 mg/mL                    | 4 mg/mL                                                                                          |
| Cotrimoxazole      | 80 mg/mL                    | 0.8 mg/mL                                                                                        |
| Levofloxacin       | 25 mg/mL                    | 0.025 mg/mL                                                                                      |
| Erythromycin       | 50 mg/mL                    | 0.05 mg/mL                                                                                       |
| Azithromycin       | 100 mg/mL                   | 0.01 mg/mL                                                                                       |
| Nafcillin          | 250 mg/mL                   | 0.025 mg/mL                                                                                      |
| Vancomycin         | 50 mg/mL                    | 0.005 mg/mL                                                                                      |

Data from Empedrad R, Darter AM, Earl HS, et al. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol* 2003;112:629–30.

which a 1/10.000 dilution is suggested (see Mertes and colleagues<sup>43</sup>). Diagnostic work-up regarding local anesthetics comprises, in addition to SPT and IDT with products free of preservatives, subcutaneous challenge tests.<sup>44–46</sup> In the majority, tests are uneventful, so that the test procedure in most cases have an educative nature.

### CHEMOTHERAPEUTICS (PLATINUM SALTS)

Platinum salts are cytotoxic agents and currently components of many chemotherapy regimens. Hypersensitivity reactions to platinum components are well described among refinery workers, who inhaled complex salts of platinum. The extensive chemotherapeutical use of carboplatin, cisplatin, and oxaliplatin has led to an increase in cases of platinum salt hypersensitivity reactions.<sup>47–50</sup> Hypersensitivity to carboplatin (12% to 30%) seems more frequent than that to cisplatin (5% to 20%) or oxaliplatin (mild reaction 10% to 12%, severe reactions <1%).<sup>49</sup> Early-onset symptoms are believed IgE mediated (rather than induced by direct histamine release). The allergy hypothesis is supported by the usually long (and uneventful) therapy intervals before onset of hypersensitivity symptoms (this may be interpreted as the sensitization phase).<sup>47,48</sup> SPTs should be performed with pure injectable drugs; for IDTs, sequentially diluted solutions (1:1000 to 1:10) are recommended with a maximum concentration of 0.1 mg/mL for oxaliplatin.<sup>49,50</sup> In total, skin testing seems safe because no serious systemic reaction has been reported, and, moreover, negative test results are helpful in identifying suitable platinum salts for the continuation of chemotherapy.<sup>49</sup> For details on desensitization see the article by Castells and colleagues elsewhere in this issue.

### CONTRAST MEDIA

Iodinated contrast media are regarded as safe but are capable of inducing immediate and nonimmediate hypersensitivity reactions in susceptible patients. Contrast media-induced reactions traditionally have been classified as nonallergic, and skin tests have been regarded as inappropriate tools.<sup>51,52</sup> In a recent prospective multicenter study, 32 of 122 patients who had immediate reactions positive skin tests were observed with the highest frequency of positive reactions in the first 6 months after the adverse event: 4 of 122 patients had positive SPT (undiluted contrast media) and 30 of 121 patients had positive IDT (10-fold diluted contrast media, reading after 20 minutes).<sup>52</sup> As the reactions were occurring mostly to the eliciting contrast medium, whereas other contrast media failed to cause a reaction, the hypersensitivity often was specific for one contrast medium, supporting the hypothesis that at least 50% of the hypersensitivity reactions to contrast media are caused by immunologic mechanism and that skin testing was rated as a useful tool.<sup>52</sup> Positive reactions by immediate skin testing were found for iobitridol, iohexol, iomeprol, iopamidol, iopentol, iopromide, ioversol, iodixanol, ioxithalamate, and ioxaglate. For details, see the article by Brockow and coworkers elsewhere in this issue.

### CORTICOSTEROIDS

Although delayed-type, T-cell-mediated allergic reactions to corticosteroids are well documented, the existence of IgE-mediated allergic reactions due to systemically applied corticosteroid therapy is controversial. Immediate reactions with positive skin tests are mainly due to the content of stabilizing or suspending agents, such as carboxymethylcellulose in injectable preparations. Such reactions are well

**Table 4**  
Corticosteroid concentrations used in immediate skin tests

| Corticosteroid     | Skin Prick Test (mg/mL) | Intradermal Test (mg/mL) |
|--------------------|-------------------------|--------------------------|
| Bethamethasone     | 4                       |                          |
| Dexamethasone      | 4                       | 0.04–0.4                 |
| Hydrocortisone     | 1.00                    | 0.04–0.4                 |
| Methylprednisolone | 40                      | 1–10                     |
| Budesonide         | 0.25                    | 0.4–4                    |
| Triamcinolone      | 40                      | 0.0025–0.025             |
| Prednisone         | 30                      | 0.4–4                    |
| Prednisolone       | 13                      |                          |

Data from Venturini M, Lobera T, del Pozo, MD, et al. Immediate hypersensitivity to corticosteroids. *J Investig Allergol Clin Immunol* 2006;16:51–6.

documented by positive SPT and IDT<sup>15,53</sup> and positive basophil activation tests (see article by Hausmann and Ebo elsewhere in this issue).

In rare cases, however, a true type I allergy to steroids has been postulated with SPT and IDT as useful diagnostic tools;<sup>53,54</sup> in one study, seven patients who had immediate allergic symptoms to corticosteroids was described: the reaction was caused by the steroid molecule (triamcinolone or methylprednisolone succinate) in four patients and by the suspending agent carboxymethylcellulose in two, and the sensitized molecule was not identified in one patient.<sup>55</sup> For test concentrations see **Table 4**.

## SUMMARY

In the diagnostic work-up of immediate-type ADRs, skin testing is an important component of identifying the relevant drug. SPTs and IDTs can be regarded as bioassays that rapidly detect a biologic response to mediators released from stimulated mast cells. The mediators lead to local reactions with formation of a wheal and flare, which suggest but do not prove an IgE-mediated reaction. There is a great variability, however, of skin reactivity in individual patients, which may be related to factors, such as age, skin color, time of day, timing in relation to exposure, and placement on the body.

The diagnostic validity of SPT and intracutaneous testing has been confirmed by additional in vitro or provocation testing. Thus, skin tests provide useful confirmatory evidence for a diagnosis of specific allergy that has been made on clinical grounds. Their characteristics—simplicity, rapidity of performance, low cost, and high sensitivity (at least for some reactions)—explain their key position in allergy diagnosis.<sup>56</sup>

The main limitation of skin tests is that a positive test is more relevant than a negative test, as the sensitivity is limited. A negative test cannot absolutely exclude a drug allergy. In addition, a positive reaction does not mean that a patient is allergic, as it reflects solely a sensitization, not allergy. Although in the past, reliable skin test procedures have been defined for some drug classes ( $\beta$ -lactams, neuromuscular blocking agents, and iodinated contrast media), potency and stability of the test reagents and test concentrations have been insufficiently validated for the majority of other drugs, mostly because such events are not frequent and a sufficient number of patients to serve as positive controls in a single center is lacking. Thus, progress in this field depends on (supranational) collaboration.

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