Skin Testing Approaches for Immediate and Delayed Hypersensitivity Reactions

Annick Barbaud, Antonino Romano

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Annick BARBAUD [1], Antonino ROMANO [2].

1- Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP.Sorbonne Université, Hôpital Tenon, Département de dermatologie et allergologie, F75020, Paris, France

2- Oasi Research Institute-IRCCS, Troina, Italy

Barbaud Annick (ORCID ID: 0000-0001-8889-1589)

Romano Antonino. (ORCID ID: 0000-0001-9742-9898)

Correspondant author: Annick Barbaud MD, PhD

AP-HP.Sorbonne Université, Hôpital Tenon, Département de dermatologie et allergologie, F75020, Paris, France

Phone : +33(0) 1 56 01 72 25
Fax : +33(0)1 56 01 72 32
Email : annick.barbaud@aphp.fr

Summary

In evaluating adverse drug reactions (ADRs), patch tests (PTs), skin prick tests (SPTs) and intradermal test (IDTs), are useful tools for identifying responsible drugs and finding safe alternatives. Their diagnostic value depends on the clinical features of the ADR and on the drug tested. PTs have a good sensitivity in assessing acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms, while their sensitivity is lower in maculopapular exanthema and toxic epidermal necrolysis. SPTs done with all drugs except opiates, are used for immediate hypersensitivity reactions. IDTs are performed by injecting 0.02 mL of the appropriately diluted suspected drug to evaluate immediate (with immediate readings) and delayed hypersensitivity reactions (with delayed readings). IDTs appears sensitive for immediate hypersensitivity reactions to beta-lactam antibiotics, iodinated contrast media, heparins, general anesthetics, and platinum salts. A negative ST does not exclude the responsibility of a drug in the occurrence of an ADR.

Key words: Diagnosis, delayed hypersensitivity, drugs, immediate hypersensitivity, intradermal tests, patch tests, prick tests, provocation tests, skin tests.

Key Points:

° Drug patch tests are well tolerated and have a good sensitivity in assessing acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms.

° SPTs are used for immediate hypersensitivity reactions and can be done with all drugs except opiates.

° IDTs are performed by injecting 0.02 mL of the appropriately diluted suspected drug to evaluate immediate (with immediate readings) and delayed hypersensitivity reactions (with delayed readings).

° For IDTs, appropriate dilutions - summarized in this paper- have to be respected in order to avoid irritant false positive reactions.

° A negative drug skin test does not exclude the responsibility of a drug in the occurrence of an ADR.

Patch tests (PTs) and skin tests (STs), namely skin prick tests (SPTs) and intradermal tests (IDTs), are useful tools for diagnosing drug hypersensitivity. They can be used to demonstrate the responsibility of a drug in the occurrence of an adverse drug reaction (ADR), as well as to assess cross-reactivity among drugs and find safe alternatives.

In performing these tests, however, there is a lack of standardized methodological approaches and particularly inconsistency with regards to the drug concentrations (1), which make comparisons between centers difficult. Moreover, there are differences between Europe and North America in the approach to the diagnosis of drug hypersensitivity reactions (2).

In this article, we considered international guidelines and relevant reviews (3-5), especially more recent ones (6,7), summarizing the data concerning the diagnostic value of both STs and PTs and providing information for their adequate indication and correct performance. In any case, the reference standard to confirm or exclude drug hypersensitivity is the drug provocation test (DPT), which consists in the controlled administration of a therapeutic dose of the suspected drug (6,8,9).

In non-severe ADRs, negative STs and/or PTs can be followed by an ingestion challenge or DPTs. There is a broad consensus on the indication of direct DPTs (i.e., not preceded by skin testing) in children with benign nonimmediate) reactions to beta-lactam antibiotics (BLs), especially in those with mild maculopapular exanthema (MPE) (10-14). Direct DPTs with BLs were also carried out in adults assessed as low risk for true BL allergy (13,15). However, this approach was not recommended in a recent review on STs (7) because it was evaluated in a limited number of patients and the indication for direct DPTs did not agree with that of the European Academy of Allergy and Clinical Immunology (EAACI) guidelines on the diagnosis of BL allergy (12). In the latter, only adults with palmar exfoliative exanthema can be candidates for direct DPTs. Regarding immediate reactions (i.e., occurring within 1 to 6 hours after the last administered dose) (16) to BLs, there is no consensus on which subjects reporting such non-anaphylactic reactions are low risk. In this connection, recently, Sabato *et al*. (7) demonstrated that urticarial reactions to BLs that appear within one 1 hour after the 1st dose and subside within 1 day (i.e., meeting the "1-1-1" criterion) are highly predictive of positive allergy testing.

In this paper, we mainly referred to a recent review (7) on STs and PTs in the work-up of cutaneous adverse drug reactions (CADRs).

Regarding the timing of their performance, in general, it is recommended to carry out STs and PTs at least 4 weeks and within one year after the ADR (3,4). In drug reaction with

systemic symptoms (DRESS), they must be done at least 6 months after the disappearance of the CADR and in the absence of high virus replication (18). Note that IgE-mediated hypersensitivity to BLs can wane over time (19). Some studies (20,21) followed patients with such hypersensitivity prospectively over 5 years and found that more than 60% of the participants who completed the studies and were initially skin test positive reverted to skin test negative with the implicated drug. Consequently, to avoid false-negative results, it is crucial to evaluate these subjects within a few months (22). On the other hand, T-cell-mediated hypersensitivity to antibiotics, including BLs, seems to be a long-lasting condition (23).

Some drugs or ultraviolet (UV) exposure can diminish the skin reactivity to drug STs. In immediate hypersensitivity reactions (IHRs), the use of beta-blockers is considered as a relative contraindication to skin testing. However, a study by Fung *et al*. (24) demonstrated the safety of administrating SPTs to patients on beta-blocker treatment.

Topical corticosteroids should be stopped the week before on the site of any drug ST (3,4,7). Systemic corticosteroids have no inhibitory impact on SPTs, but have to be stopped one month before PTs or IDTs (25). Immunosuppressive drugs can affect the skin reactivity for any drug ST and should be stopped one month before testing if possible. Ultraviolet exposure should be avoided up to 4 weeks before STs and PTs.

In IHRs, antihistamines should be stopped 4 days (7 days for loratadine and desloratadine and tricyclic antidepressants with antihistaminic activity) before STs, but they have no impact on PT results (3,4,7). Concerning psychotropic drugs, imipramine and phenothiazines that have antihistaminic activity, but not escitalopram, fluoxetine, sertraline (25), can diminish skin reactivity to SPTs (26).

DRUG PATCH TESTS

PTs reproduce a delayed hypersensitivity reaction (DHR). PTs are applied to the upper back on unaffected and untreated skin, using IQ chambers (Chemotechnique, Velinge, Sweden) or an equivalent fixed with a ‘‘hypoallergic’’ tape. They are left for 2 days, then read on day 2 (30 minutes after removing the test material) and on day 4 or 5, and until after one week for those with corticosteroids. Reading result’s criteria are identical to those used for contact allergy (i.e., negative, irritant, + to +++) (27). At least 10 negative controls are necessary to assess the specificity of a positive PT. Negative controls have been published for PTs with many drugs (7,28). PTs are particularly useful for evaluating DHRs to noninjectable drugs

like most anticonvulsants and non-vitamin K antagonist oral anticoagulants (29,30). However, only a limited number of molecules marketed by Chemotechnique (Velinge, Sweden) or SmartPractice Canada are available as ready-to-use material, in which most drugs either the trade or reagent grade product are diluted at 10% in petrolatum. In most cases, it is necessary to prepare the test material by diluting the drugs in their marketed form provided by the patients themselves. As the stability of PT material has not been validated or established for most drugs, it should be prepared just before testing. PTs with the drug in its commercially available oral form can be prepared by diluting it at 30% (3) or 20% (4) in petrolatum. Ideally, a concentration of 10% of the active ingredient should be obtained. Brajon *et al.* (28) showed that the exact amount of the active ingredient in the PT material prepared by diluting commercial forms of the drugs concerned at 30% in petrolatum varied widely and 25% of that material had an active ingredient's concentration of less than 2%. From a practical point of view, since it is impossible to obtain a 10% active ingredient's concentration for each drug tested, we recommend that studies using PTs with drugs provide the exact concentration of active ingredient, so that the results obtained by different centers can be compared (28).

When the active ingredient is in pure form (e.g., lyophilized powder), it is recommended to dilute it at 10% in petrolatum (3).

Some drugs, such as captopril (at 1% in pet.), celecoxib (if tested >10% in pet.), chloroquine (at 30% in pet.), misoprostol (if tested > 1% in pet.), and sodium valproate (at 1% in pet.), have been reported as irritant (7). Some centers have pharmacy services that dilute drugs for patch testing. Assier *et al.* (31) demonstrated that material prepared by physicians led to results equivalent to those obtained with the ready-to-use products commercialized by Chemotechnique.

A control PT has to be done with the vehicle (e.g., petrolatum, alcohol) used to dilute the drug for the preparation of the PT material.

DRUG SKIN PRICK TESTS

SPTs can be done with any form of commercialized drug, usually, in undiluted form: pills reduced to very fine powder, capsule contents, liquid, or injectable solutions (1). In SPTs, a small drop of reagent is applied on volar forearm skin, and a standardized 1-mm-tipped lancet (pricker) is passed through the drop and perpendicularly inserted into the skin. (3,4,7,26). Reactions to SPTs are considered positive when the diameter of the wheal is at least 3 mm greater than that of the negative control and is surrounded by erythema, 20 minutes after the

prick. A positive control is done with histamine at 10 mg/mL. As a negative control, normal saline and/or any other solvent employed to dilute are used. SPTs can be performed with all drugs except opiates. If there is a global shortage of a drug (e.g., biologicals, COVID 19 vaccines), it could be possible to perform a prick-to-prick test by dipping the lancet in the drug solution residual of the vials already used and then carrying out the skin puncture with it. Non-specific degranulation is observed in SPTs with certain antibiotics or anesthetic drugs at the usual concentrations. The highest nonirritating concentrations for SPTs are reported in Table 2. SPTs are useful for evaluating IHRs. In effect, although they have a sensitivity of 6.9%, they have a very good specificity (98.8%) and a good negative predictive value (85.7%) (32).

Seldom late positive responses to SPTs have been reported in MPE, DRESS, and acute generalized exanthematous pustulosis (AGEP) (7,18). A SPT causes a delayed positive reaction when there is erythema and infiltration at the puncture site after 1 or 2 days (3,4).

SPTs with additives can be done by diluting them as follows: polyethylene glycol (PEG) 3000 at 50% water/volume, PEG 6000 at 50% water/volume, and polysorbate 80 at 20% water/volume (33).

DRUG INTRADERMAL TESTS

IDTs are performed and interpreted differently in drug allergy centers. Recently, a multi-center study standardized an IDT method that helped reduce variability, allowing for a more reliable comparison of results between physicians and centers (34). According to this study (34), the recommended volume to be injected intradermally on the volar forearm is 0.02 ml. It produces a small superficial bleb approximately 5 mm in diameter. For intradermal administrations, a tuberculin syringe is used, which contains only 0.02 ml of the reagent solution and has a flat-ended plunger.

The diameter of the injection papule (wheal) should be measured immediately after injection (Wi) and then at 20 minutes (W20). At that time, the IDT is considered positive if the diameter of the measured wheal (W20) is greater than or equal to the diameter of the Wi + 3 mm and if there is surrounding erythema that has also to be measured.

In subjects with DHRs, IDTs can be positive on delayed readings (e.g., after 1-3 days). Any late responses to IDT should be documented by the diameter of the erythema and the infiltration, as well as a morphological description. Patients are advised to return to show any positive responses appearing within 1 week after IDT, as well as to take pictures of positive or doubtful IDTs (12).

For IDTs, sterile injectable solutions are obligatory. In most cases, dilutions of reagents are done in normal saline. Performing a positive control with histamine at 1 mg/mL is not mandatory if a positive control SPT is performed. As a negative control, normal saline and/or any other solvent employed to dilute are used.

The initial dilution of the IDT reagents depends on the severity of the index reaction. In IHRs, IDTs should be performed after ensuring the negativity of SPTs. As in the diagnosis of IHRs to BLs (12), the suggested sequence of STs is as follows: (a) SPT (1/10 and the highest nonirritating concentrations) at intervals of 20 minutes, and if SPTs are negative (b) IDTs (1/100 of the highest nonirritating concentration, 1/10, and the highest nonirritating concentration) at intervals of 20 minutes. The procedure is stopped when a positive ST is found. In evaluating subjects who suffered severe anaphylactic reactions, starting concentrations of ST reagents should be at least 10^{-3} of the highest nonirritating ones to avoid systemic reactions (2). In any case, it is advisable to perform IDTs in a hospital setting.

In low-risk patients, the work-up can be simplified by performing SPTs and IDTs directly with the highest nonirritating concentrations.

IDTs can induce false-positive results mainly due to irritating reagent concentrations. An EAACI position paper provided information on drug concentrations for skin testing (5). Table 2 shows the highest nonirritating concentrations for drug prick and intradermal testing recommended in this and other EAACI position papers (5,12,35), as well as in practice parameters (36) and relevant reviews (7). Note that these concentrations were determined in studies where IDTs were performed using many different techniques. Moreover, these concentrations were defined only regarding IHRs (5). For IDTs, the highest nonirritating concentration of many drugs might not be similar to that which evokes a T-cell response after 6 to 24 hours. This is particularly true for drugs such as fluoroquinolones and vancomycin, which intrinsically cause direct release of histamine and in which the sensitivity of IDTs using the lowest concentrations to avoid non-IgE-mediated mast-cell activation by IDTs is very poor ().

Regarding STs with the main drugs, amoxicillin, amoxicillin-clavulanic acid, and ampicillin can be tested at concentrations up to 20 mg/mL, like other semisynthetic penicillins, aztreonam, and all cephalosporins except cefepime (12,37,38). Macrolides (39,40), rifampicin (39) or quinolones (39,41) can be very irritant. IDTs with diluted solutions are of interest with glycopeptides (42). They could be of value in IHRs to proton pump inhibitors (43).

IHRs to iodinated contrast media (ICM) can be assessed by SPTs with undiluted products and by IDTs with dilutions 1:10 (36,44,45). In DHRs, PTs can be useful and delayed-reading

IDTs can be done with undiluted ICM (36). For STs with gadolinium derivatives, dilutions 1:10 (46) or undiluted products (47) can be used.

Heparin and heparinoids can be tested diluted 1:10 or undiluted (48). Nevertheless, STs are contraindicated in subjects with an index reaction of necrosis at the site of heparin injection. As the positive reaction is often delayed, readings should also be performed after 72 hours or later.

Corticosteroids can be tested diluted 1:10 (49-51). STs with corticosteroids at high concentrations, mainly with those with long-lasting effects, can induce skin atrophy (49). Allergy to excipients, mainly carboxymethylcellulose or polysorbate, should be considered and investigated. Carboxymethylcellulose can be tested by SPTs and IDTs at a concentration of 10 mcg/mL (52,53). Insulins are tested diluted at 1:10 (54). Immediate-reading IDTs with platinum salts at concentrations from 0.1 to 1 mg/mL, depending on the salt, are specific (55); however, a non-specific erythematous infiltration can occur at 24 hours with these IDTs. Therefore, their delayed readings do not appear to be specific, as published with carboplatin at 1 mg/mL (56) and observed with oxaliplatin (7).

IDTs with biologicals and cytokines are of little use (57). For STs with anti-tumor necrosis factors, specificity thresholds have been reported at the following concentrations: infliximab $\leq$ 2 mg/mL, adalimumab $\leq$ 50 mg mL, and etanercept $\leq$ 5 mg/mL (7). Some articles have reported studies in which IDTs were performed with rituximab (57,58) or tocilizumab (57,59,60). IDTs with interferons were thought to be non-specific, but they appear to be interesting, with good positive and negative predictive value (NPV) (61) in evaluating generalized exanthemas due to these molecules. The thresholds for the specificity of IDTs are reported in Table 2.

For IDTs with general anesthetics, the same method should be adopted. Some guidelines recommended an injection of 0.03 mL (62), others a volume of 0.03 mL to 0.05 mL (63) or 0.02 mL to 0.05 mL (64), but a recent EAACI position paper recommended a volume of 0.02 mL, as for other IDTs (35).

STs with some drugs are irritating and can induce false positive results. STs with vaccines are not standardized and their specificity is discussed. False positive results are frequent in delayed readings and should not be considered. In case of IHRs, SPTs or prick-to-prick tests with the undiluted vaccine and, when available, its excipients (e.g., gelatin, egg, PEG) can be done. However, IDTs with vaccines diluted 1:10 and even 1:100, mainly with influenzae vaccine, frequently induce irritative reactions (65). False positive results have also been

reported with IDTs performed with glatiramer acetate at a concentration of 200 mcg/mL, and in some cases at that of 20 mcg/mL. For STs with this molecule, the specificity threshold has not yet been determined (66). Finally, a recent practical guidance for the evaluation and management of drug hypersensitivity (6) provided information on STs with a huge number of drugs, including antivirals, antifungals, and antimalarials.

NEGATIVE PREDICTIVE VALUE OF DRUG SKIN TESTS

Since STs and DPTs are not standardized, it is difficult to compare the results regarding the NPV of STs across the literature. For BLs, the NPV of STs is around 90%, depending on the type of hypersensitivity and the method used for DPTs (12). For ICM, the NPV varies from 80% to 97.3% (36).

DRUG SKIN TESTS AND PATCH TESTS HAVE TO BE ADAPTED ACCORDING TO THE CLINICAL FEATURES AND THE DRUG INVOLVED

The diagnostic value of STs and PTs depends on the ADR clinical features and on the drug tested. STs are useful for identifying the responsible drug only in IgE- or T-cell-mediated reactions. They are not useful in some ADRs such as those to nonsteroidal anti-inflammatory drugs with a cross-reactivity pattern, bradykinin-induced angioedema due to angiotensin-converting enzyme inhibitors, and sartans, as well as reactions to dipeptidyl peptidase-4 inhibitors, as such reactions are not caused by allergic hypersensitivity. Moreover, STs have no diagnostic value in drug-induced auto-immune diseases or pruritus.

In IHRs, as for BLs (12), STs have to be adapted to the risk profile of the patient. STs have been reported as useful with many drugs but mainly with BLs, ICM, gadoterate meglumine, general anesthetics, insulins, proton pump inhibitors, corticosteroids, and platinum salts. PTs are not recommended. In case of anaphylactic shock, PTs are absolutely contraindicated as they have a poor value in IHRs, but mainly because they can re-induce the shock. Anaphylactic shocks induced by PTs have been reported with BLs, neomycin, gentamicin, bacitracin, and diclofenac (7).

Regarding DHRs, recently, ~~a~~n international consensus on their diagnosis was reached (1) and its adapted conclusions are summarized in Table 1. Drug PTs have a rather low sensibility and are of value for evaluating MPE, systemic contact dermatitis, symmetric drug-related intertriginous and flexural exanthema, or flexural exanthema, eczematous reactions at injection sites, AGEP, DRESS, and Stevens-Johnson syndrome/toxic epidermal necrolysis

(SJS/TEN) (1,7). Many drugs have been reported to have positive results when evaluated by PTs, but PTs performed with allopurinol, salazopyrin, or paracetamol are mostly or ever negative (18,67).
In MPE, delayed-reading IDTs have the highest sensitivity. Delayed positive IDT results have been reported mainly with BLs, glycopeptides, heparins, ICM, and corticosteroids.

In fixed drug eruptions (FDEs), PTs are applied in duplicate on the back but also on the site of eruption (residual sometimes pigmented lesion; i.e., "*in situ* PTs") and read at day 1 or 2 (68,69). If *in situ* PTs are negative an *in situ* repeated open application test can be done (69). The preparation for the *in situ* PT is given to the patient and applied to a surface of 2 cm x 2 cm, once a day for 1 week. In case of negative STs, a DPT can be done in benign FDE, but it is absolutely contraindicated in generalized bullous FDE.

In investigating a drug-induced photosensitivity, both PTs and photo patch tests with the suspected drug have to be performed. It is recommended to test with a 1% concentration of an active ingredient, but only at 0.1% for phenothiazines (70). The irradiation for drug photo patch tests is performed at Day 2 with a 5 Joules/cm^2 UVA (70). A non-irradiated control PT is also applied. The reading is done two days after the irradiation. Criteria for positive results are identical to those used for PTs with haptens (i.e., negative, irritant, + to +++) (27).
Regarding severe DHRs, such as SJS/TEN, DRESS, AGEP, and bullous exanthemas, as stated in some European guidelines (3,4,12,71,72), PTs with the suspected drugs should be used as the first line of investigation (i.e., prior to STs). In the case of positive responses to PTs, STs should be avoided, whereas in the case of negative results, IDTs might be performed, starting with a lower concentration of the drug concerned (e.g., 1 mg/mL for semisynthetic penicillins). In some studies (Barbaud 2013, Romano 2016), this approach proved to be safe and useful not only for identifying the responsible drugs (18), but also for detecting any cross-reactivity and finding safe alternatives (73). Specifically, in the 72 patients with DRESS, 45 with AGEP, and 17 with SJS/TEN of a multicenter study (18), PT sensitivity was 64%, 58%, and 24%, respectively. Of the 11 patients with AGEP and 4 with DRESS associated with BLs who were negative to PTs, 4 and 3 were positive to delayed-reading IDTs, respectively. Nevertheless, the use of IDTs in evaluating severe DHRs to drugs remains controversial, even though recent studies on subjects with such reactions confirmed and emphasized their safety and usefulness, in particular, for exploring cross-reactivity and co-sensitization in DRESS (74-77).

For an alternative or suspected low-imputable drug, if irreplaceable and negative to STs, a graded DPT can be discussed by specialists involved in severe cutaneous ADRs (77).

IN CONCLUSION, in order to compare the results from one center to another, it is time to consider standardizing drug skin testing methods. for PTs, is essential to report results with reference to the concentration of the active ingredient. For IDTs, the only way is to work on a known allergen dose and not on injection-wheal diameters. Therefore, a controlled volume injected in IDTs seems to be the best method. We always have to keep in mind that a negative ST does not exclude the responsibility of a drug in the occurrence of a CADR.

Clinics Care Points

° In case of positive drug skin tests, in order to ensure specific results, please give 10 negative control results from your experience or literature.
° In non severe adverse reactions, drug skin tests have to be done before drug provocation tests, but can be avoided before provocation in children with non-severe delayed reactions or in adults with palmar exfoliative exanthema.

° Drug patch tests reproduce a delayed hypersensitivity reaction, use it for delayed cutaneous adverse drug reactions and not in case of anaphylaxis (not useful and able to reinduce an anaphylactic shock).
° Drug patch tests are applied on the back, but in fixed drug eruption they also have to be applied in duplicate on the site of eruption (residual sometimes pigmented lesion; i.e., “in situ patch tests”)
° In immediate hypersensitivity reactions, as for betalactam antibiotics, skin tests have to be adapted to the risk profile of the patient.
° For IDTs, sterile injectable solutions are obligatory, do not use crushed pills even with filtration of the solution.
° IDTs have to be done with a controlled volume of 0.02 mL, not based on a given diameter of the injection wheal (bleb).
° A negative drug skin test does not exclude the responsibility of a drug in the occurrence of an adverse drug reaction.

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Table 1: Use of Skin Prick Tests, Intradermal Tests, and/or Patch Tests in Immediate or Delayed Drug Reactions

	Patch tests	Prick tests	IDT	Provocation tests
Urticaria/ angioedema, anaphylaxis	Not useful, can be dangerous	Useful (immediate reading)	Useful (immediate reading)	Adapted to the low- or high-risk profile of the patient (12)
Maculopapular exanthema	Useful	Limited value (DR)	Useful (DR)	After negative skin tests with delayed readings in low-risk subjects (12) NPV of 90%.
Generalized eczema (Contact reaction)	Useful	Limited value (DR)	Useful (DR)	After negative delayed skin test with delayed readings. NPV unknown
SDRIFE	Useful (positive in 36-82%)	Limited value (DR)	Useful (DR)	After negative skin tests with delayed readings. NPV unknown
Fixed drug eruption	Useful if applied on the area of eruption (68,69)	Not useful	Not useful	At full dose when patch tests or repeated application tests are negative. NPV unknown.
Generalized bullous fixed drug eruption	Maybe useful	Contraindicated	Contraindicated	Contraindicated
Acute generalized exanthematous pustulosis (AGEP)	Useful, sensitivity up to 58% (18)	Limited value (DR)	Potentially useful (DR)	Contraindicated with suspected drugs and cross-reactive ones
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Useful, sensitivity 32-64% depending on the tested drug (18,67) Advised 6 months after disappearance of DRESS	Limited value (DR)	Delayed reading at 24 hours (18,74)	Contraindicated with highly suspected drug and cross-reactive ones (1,77)
SJS/TEN	Low sensitivity (<30%)	Unknown value (DR)	Contraindicated with the suspected drugs	Contraindicated.
Photosensitivity	Photopatch tests with a 5 Joule/cm2 UVA irradiation	No value	No value	No value without exposure to UV
Vasculitis	No value	No value	No value	Contraindicated

DR: Delayed reading (i.e., after 24 to 48 hours).
SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema.
SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

Data from Refs 1 and 7

Table 2: Highest nonirritating concentrations recommended for drug prick and intradermal testing [According to published literature, mainly form Brockow et al. (5), EAACI position papers (12,35,36) and a recent update on drug skin tests (7)].

	Intradermal tests	Skin Prick Tests*
ANTIBIOTICS		
Beta-lactams		
Amoxicillin, ampicillin and other semisynthetic penicillins	20 mg/mL	
Aztreonam	2 to 20 mg/mL	
Benzylpenicilloyl-poly-L-lysine	6 x 10^{-5} mol/L	
Benzylpenicilloyl-octa-L-lysine	8.64 x 10^{-5} mol/L	
Sodium benzylpenilloate	1.5 x 10^{-3} mol/L	
Benzylpenicillin	10,000 IU/mL	
Cefepime	2 mg/mL	
Cephalosporins other than cefepime	20 mg/mL	
Clavulanic acid	20 mg/mL	
Imipenem-cilastatin	0.5 mg/mL – 0.5 mg/mL	
Ertapenem and meropenem	1 mg/mL	
Quinolones		
Ciprofloxacin	0.006 mg/mL	
Levofloxacin	0.025 mg/mL	
Ofloxacin	0.05 mg/mL	
Pefloxacin	no IDT	0.32 mg/mL
Rifampicin	2 mcg/mL	
Macrolides		
Azithromycin	0.01 mg/mL	
Clarithromycin	0.05 mg/mL	
Erythromycin	0.01 to 0.05 mg/mL	5 mg/mL
Rovamycin	37.5 U/mL	37,500 IU/mL
Others		
Clindamycin	15 mg/mL	
Cotrimoxazole	0.8 mg/mL	
Gentamycin	4 mg/mL	
Rifampicin	0.002 mg/mL	
Tobramycin	4 mg/mL	
Vancomycin	0.005 to 0.05 mg/mL	
PERIOPERATIVE DRUGS		
Neuromuscular blocking agents		
Atracurium	0.01 mg/mL	1 mg/mL
Cisatracurium	0.02 mg/mL	2 mg/mL
Mivacurium	0.002 mg/mL	0.2 mg/mL
Pancuronium	0.02 mg/mL	2 mg/mL
Rocuronium	0.05 mg/mL	10 mg/mL
Suxamethonium	0.1 mg/mL	10 mg/mL
Vecuronium	0.04 mg/mL	4 mg/mL
Anesthetic agents		

Etomidate	0.2 mg/mL	2 mg/mL
Ketamine	0.1 mg/mL	100 mg/mL
S-Ketamine	0.25 mg/mL	25 mg/mL¶
Midazolam	0.05 mg/mL	5 mg/mL
Propofol	1 mg/ml	10 mg/mL
Thiopental	2.5 mg/mL	25 mg/mL
Reversal agents		
Sugammadex	10 mg/mL	
Opiates		
Alfentanil	0.05 mg/mL	0.5 mg/mL
Fentanyl	0.0005 mg/mL	0.05 mg/mL
Morphine	0.005 mg/mL	1.0 mg/mL¶
Remifentanil	0.005 mg/mL	0.05 mg/mL
Sufentanil	0.0005 mg/mL	0.005 mg/mL
Local anesthetics		
Articaine	2 mg/mL	
Bupivacaine	0.25 mg/mL	
Chloroprocaine (ester derivative)	1 mg/mL	
Levobupivacaine	0.75 mg/mL	
Lidocaine	1 mg/mL	
Mepivacaine	2 mg/mL	
Prilocaine	2 mg/mL	
Ropivacaine	1 mg/mL	
CHEMOTHERAPEUTIC DRUGS		
Paclitaxel	0.03 mg/mL	
Docetaxel	0.1 mg/mL	
Platinum salts	1 mg/mL‡	
Carboplatin	1 mg/mL	
Cisplatin	0.1 mg/mL	
Cisplatin	1 mg/mL	
Oxaliplatin	0.5 mg/mL	
Oxaliplatin	1 mg/mL	
CORTICOSTEROIDS		
Betamethasone	0.4 mg/mL	
Cortivazol	2.5 mg/mL	
Dexamethasone	0.4 mg/mL	
Hydrocortisone	1 mg/mL	
Hydrocortisone hemisuccinate	5 mg/mL	
Triamcinolone	4 mg/mL	
Methylprednisolone	4 mg/mL	
Prednisolone	2.5 mg/mL	
HEPARINS	diluted 1:10	
INSULINS	diluted 1:10	
CYTOKINES, BIOLOGICAL AGENTS		
Anti-TNF		
Adalimumab	50 mg/mL	
Etanercept	5 mg / mL	

Infliximab	2 mg/mL	
Infliximab	10 mg/mL	
Omalizumab	1.25 mcg/mL	
Rituximab	10 mg/mL (7 negative controls)	
Tocilizumab	0.2 mg/mL or 20 mg/mL (10 negative controls) 1.62 mg/mL	
Interferons	undiluted	
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Diclofenac	2.5 mg/mL	
Ketoprofen	2 mg/mL	
Piroxicam	2 mg/mL	
Pyrazolones and other injectable NSAIDs	0.1 mg/mL	
CONTRAST MEDIA		
Iodinated contrast media	diluted 1:10 for immediate reactions, maybe undiluted for delayed reactions	
Gadolinium derivatives	diluted 1:10	
PROTON PUMP INHIBITORS		
Esomeprazole	0.4 or 4 mg/mL	
Omeprazole	0.4 or 4 mg/mL	
Pantoprazole	0.4 or 4 mg/mL.	
MISCELLANEOUS DRUGS, EXCIPIENTS, DYES		
Paracetamol/Acetaminophen	1 mg/mL	
Chlorhexidine	0.002 mg/mL (sterile uncolored alcohol-free solution)	
Fluorescein	diluted 1:10 (10 mg/mL in our experience)	
Carboxymethylcellulose	0.01 mg/mL	
Hydroxyethyl starch	6 mg/mL	
Methylene blue	0.1 mg/mL	
Patent blue	0.25 mg/mL	
Polyethylene glycol (PEG)/Macrogol		
PEG 300		undiluted
PEG 3000		50% water/volume
PEG 2000		50% water/volume
PEG 6000		50% water/volume
Polysorbate 80		20% water/volume

*Highest nonirritating concentrations when undiluted drugs can be irritant.

¶Possibly irritant.

‡Can induce false positive results on delayed readings (56).