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Review Article

Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions

Proposed by the Working party of the ESCD for the study of skin testing in investigating cutaneous adverse drug reactions

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Skin testing with a suspected drug has been reported to be helpful in determining the cause of cutaneous adverse drug reactions (CADR). Many isolated reports of positive drug skin tests are published, but without detailed information concerning the clinical features of the CADR and the method used in performing drug skin tests, such data are not very informative. A working party of the European Society of Contact Dermatitis (ESCD) for the study of skin testing in investigating cutaneous adverse drug reactions, has proposed the herein-reported guidelines for performing skin testing in CADR in order to standardize these procedures. In each reported case, the imputability of each drug taken at the onset of the CADR and a highly detailed description and characterization of the dermatitis need to be given. Drug skin tests are performed 6 weeks to 6 months after complete healing of the CADR. Drug patch tests are performed according to the methods used in patch testing in studying contact dermatitis. The commercialized form of the drug used by the patient is tested diluted at 30% pet. (pet.) and/or water (aq.). The pure drug is tested diluted at 10% in pet. or aq. In severe CADR, drug patch tests are performed at lower concentrations. It is also of value to test on the most affected site of the initial CADR. Drug prick tests are performed on the volar forearm skin with the commercialized form of the drug, but with sequential dilutions in cases of urticaria. Intradermal tests (IDT) are performed with sterile sequential dilutions (10–4, 10–3, 10–2, 10–1) of a pure sterile or an injectable form of the suspected drug with a small volume of 0.04 ml. Drug skin tests need to be read at 20 min and also later at D2 and D4 for patch tests, at D1 for prick tests and IDT. All these tests also need to be read at 1 week. The success of skin tests varies with the drug tested, with a high % of positive results, for example, with betalactam antibiotics, pristinamycin, carbamazepine and tetrazepam on patch testing, or with betalactam antibiotics and heparins on delayed readings of IDT. The results of drug skin tests also depend on the clinical features of the CADR. The use of appropriate control patients is necessary to avoid false-positive results.

Key words: cutaneous adverse drug reactions; patch testing; prick testing; intradermal testing; guidelines. © Munksgaard, 2001.

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Cutaneous adverse drug reactions (CADRs) are a frequent problem in dermatology, especially in cases which concern drug imputability, because patients are often on multiple drug regimes. Besides clinical and chronological parameters, there is no widely usable complementary test to help establishing the definite cause of the CADR.

Skin testing (patch testing and also prick and intradermal (IDT) testing), with the suspected compound, has been reported to be helpful in determining the cause of a CADR (1–5) and in studying the pathophysiological mechanisms involved in these reactions. According to previous data, the results of drug skin tests mainly depend on the drug tested and the clinical features of the initial CADR (1, 2, 4–6), but there are, at present, a few extensive studies that determine the sensitivity and specificity of these drug skin tests as a complementary tool for drug imputability in CADR. Too many isolated reports of positive drug skin tests in investigating CADR are published, but without detailed information concerning the clinical features of the CADR, the imputability of the suspected drug, the methods used in performing drug skin tests, namely the concentrations and vehicles used for testing the suspected drugs, this data is not always very informative. Moreover, there are undoubtedly many negative results that are not published, which make it still more difficult to ascertain the sensitivity and specificity of such tests in the study of CADR.

Therefore, the aim of a working party of the ESCD for the study of skin testing in investigating cutaneous adverse drug reactions was to promote a prospective multicentre study devoted to the usefulness of skin testing in CADRs and, also, to propose guidelines for performing skin testing in CADRs, in order to help standardize this procedure in the investigation of CADR and to assess their sensitivity and specificity, namely which concern the suspected drug and the clinico-evolutive features of the CADR.

Guidelines in Skin Testing

In order to validate the results collected individually in different centres, skin tests should be performed according to common guidelines, such as those proposed. Furthermore, it is highly recommended that several aspects are considered in each case, namely concerning data on the patient, on the drugs taken, drug imputability score, clinico-evolutive characterization of the CADR and, eventually, additional data that can be useful in establishing a more strictly defined diagnosis of the CADR.

Patient Data

Besides age, sex and accessory diseases, personal or family history of adverse drug reactions, especially with the suspected drug or chemically related drugs, have to be noted.

Drug imputability

All the drugs taken during the onset of the CADR, even if they have been prescribed for many months, have to be listed. Imputability for each drug taken before or during the onset of the skin reaction has to be determined according to criteria proposed by Moore et al. (7).

Clearly, it is of great value to note whether the patient has had previous exposure to the suspected drug and to know whether he has had at least 1 other episode of similar CADR after taking the culprit drug (accidental rechallenge) or if a drug provocation test has been performed. Other test results, namely positive or negative in vitro tests, such as RAST or a lymphocyte transformation test, should also be reported, as they may modify the imputability score.

Concerning the suspected drug, the history of drug intake must be reported with the dates the treatment was begun and stopped, the interval between the beginning of drug intake and the onset of the CADR, the mode of administration, the prescribed dosage, the common international nomenclature of the drug and the disease that it was prescribed for. Concurrently, the evolution of the CADR must be given.

Characterization of the CADR

Clinical and evolutive features of the cutaneous adverse reaction need to be clearly described. Additionally, when possible, the CADR should be classified according to the following: pruritus, urticaria and/or angioedema, anaphylactoid or anaphylactic shock, maculopapular and/or purpuric rash, erythroderma (exfoliative dermatitis), hypersensitivity syndrome or drug rash with eosinophilia and systemic syndrome (DRESS), pseudolymphoma, generalized or localized eczema, baboon syndrome, systemically-induced contact dermatitis, flexural cutaneous adverse drug reaction, acute generalized exanthematic pustulosis (AGEP), purpura, leucocytoclastic vasculitis, lichenoid dermatosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), fixed drug eruptions (FDE) or eczematous photosensitivity reactions.

Facultative additional data

To improve the diagnosis, the pathophysiological mechanism or to determine whether there is associated organ dysfunction, the following laboratory investigations should be carried out during the CADR: full blood count, platelet count, sedimentation rate, serum creatinine, transaminases, alkaline phosphatase, bilirubin, eosinophil cationic protein and tryptase in case of anaphylactoid reaction. Histological examination of a skin biopsy performed at the onset of the cutaneous adverse drug reaction can be of value in classifying the clinical and pathophysiological type of CADR.

In particular types of CADR, serological tests for viral infection that may interfere with the onset of the drug eruptions are welcomed, particularly tests for cytomegalovirus, Epstein-Barr virus and parvovirus B19 for patients who have developed a maculopapular rash, hepatitis B and C for patients with urticaria, Herpes simplex virus hominis type I and II for patients with erythema multiforme, and tests for mycoplasma for patients with Stevens-Johnson syndrome.

Guidelines in Drug Skin Testing

After informed patient consent, drug skin tests should be performed 6 weeks to 6 months after complete healing of the CADR, at least 1 month after discontinuation of systemic corticosteroid or immunosuppressive therapy. It is preferable, if possible, not to test during pregnancy.

Skin testing should be performed with the commercialized drug and, whenever possible, also with the pure active products and excipients. Testing with drugs with a similar chemical structure, or from the same pharmacological family, may also be of importance in understanding cross-reactions (8).

In order to avoid adverse effects, namely severe immediate reactions, skin testing should be performed according to the following sequence: patch tests with an immediate reading at 20 min, then prick tests and, if negative, delayed readings are recommended in all such procedures.

Drug Patch Testing

General procedures

Patch tests should be performed on the upper back using Finn Chambers® on Scanpor® tape (Epitest, Tuusula, Finland), Van der Bend Square Chambers (Brielle, The Netherlands) or IQ Chambers (Chemotechnique), according to the methods used in patch testing for contact dermatitis.

Patch test reactions need to be read at 20 min, day (D)2 and D4, or, if this is not possible, on D3. Whenever possible, if the patch tests are negative on D4, a reading should be performed on D7. Results of patch testing should be reported according to the International Contact Dermatitis Research Group (ICDRG) criteria (9).

In investigating a photosensitivity reaction induced by a drug, both drug patch tests and drug photopatch tests with the responsible drug need to be performed. Irradiation for drug photopatch tests should be performed on D1, or for practical reasons on D2, with 5 J/cm UVA irradiation (10).

In fixed drug eruptions (FDE), patch tests should be performed both on the normal skin of the back and on the residual pigmented site of the FDE (11–13).

Concentrations and vehicles

Patch testing with the commercialized drug. The drug possibly responsible for the CADR can be tested with the commercialized form used by the patient. Pills should have their coating removed, then be ground to a very fine powder. This powder needs to be tested as is (facultative) and also incorporated at 30% in white petrolatum (pet.) and diluted at 30% in water (aq.), in highly controlled concentrations.

The powder contained in capsules needs to be tested as is, diluted at 30% in pet. and/or at 30% in aq. The gel jacket portion of the capsules should be moistened and tested as is. Liquid preparations need to be tested both as is and diluted at 30% in aq. With commercialized forms of the drugs, each preparation is made for only 1 patient and kept no more than 1 D. The name of the chemical form of the molecule (salt, molecule base) needs to be given.

Patch testing with pure substances. Whenever possible, the pure drug obtained from the manufacturer should be tested diluted at 10% in pet. and, if possible also, at 10% in aq. or alcohol (alc.). Concentrations and vehicles previously considered as most adequate for certain drugs should also be chosen. For instance, for patch testing with estrogens and progesterone, we recommend, besides testing them diluted in aq. and pet., dilutions also in alc. (14).

To avoid any relapse of a severe CADR, in patients who have developed DRESS, Stevens-Johnson syndrome, Lyell's syndrome or in testing with aciclovir, carbamazepine or pseudoephedrine, we recommend that patch tests are performed, either with the commercialized form of the drug or the pure substance, first diluted at 0.1% and, if negative, at higher concentrations of 1% up to 10%.

Whenever possible, preservatives, coloring

agents and excipients should also be tested, as is or diluted at 10% in pet., or in the vehicles and concentrations usually proposed for testing in allergic contact dermatitis.

Prick Tests

Drug prick tests should be performed on the volar forearm skin, with the commercialized form of the drug thought to be responsible for inducing the CADR. Whenever possible, both the pure drug and excipients should be tested as is (in the form used for patch testing).

When testing patients who have developed urticaria, the drug needs to be tested with the same sequential solutions as those used for IDR at 10^{-3}, 10^{-2}, 10^{-1}, then pure. Reactions are considered positive when a weal with a diameter larger than 3 mm and than that of the negative control (0.9% saline) is present 20 min later. Positive controls are performed with codeine phosphate at 9% and/or with histamine (10 mg/ml). In all cases, a delayed reading needs to be done 1 D after performing prick tests.

Intradermal Tests (IDT)

Intradermal tests are performed only when prick tests give negative results 20 min after testing with the suspected drug. Intradermal tests are contraindicated in patients who have developed erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis or leucocytoclastic vasculitis on histological examination.

The following guidelines should be applied for IDT (1):

(i) Dilutions are prepared, under laminar flow, no longer than 2 h preceding administration.

(ii) All necessary precautions have to be taken in case emergency treatment should be needed. It is highly recommended, especially in investigating anaphylactoid reactions or urticaria, that patients should be tested under hospital surveillance for a minimum of 6 h following IDT. Intravenous glucose solution should be given for at least 2 h following the last IDT, when the investigation results remain negative, and for at least 6 h if the IDT is positive. Blood pressure, pulse and peak-flow should be regularly monitored.

(iii) Intradermal tests are performed using a sterile solution of the suspected drug, diluted sequentially (10^{-4}, 10^{-3}, 10^{-2} and 10^{-1}) in phenolated saline (0.5% phenol in 0.9% saline) or in 0.9% saline.

(iv) Intradermal tests are performed on the extensor surface of the arm, with a small volume (0.04 ml) that produces a weal of 4 to 6 mm in diameter. A negative control is performed with phenolated saline or saline. When read after 30 min, IDT results are considered positive if a weal of more than 10 mm in diameter is observed. The first IDT is performed with a 10^{-4} dilution. If results are negative after 30 min, subsequent IDT are performed with increasingly higher serial dilutions up to the pure solution, at 30-min intervals, as long as the test results of the previous dilution remain negative.

(v) Intradermal test result readings are performed at 30 min, 6 h and 1 D. If a delayed positive reaction is observed, the diameter of the papule is measured. When the IDT results are negative, a telephone call to the patient, 1 week later, confirming whether the results remain negative or not, or a delayed reading at 1 week, should be performed.

Negative Control Patients for Drug Skin Testing

The most informative negative controls are patients who have presented with a dermatitis, 6 weeks to 6 months previously, after taking several drugs, including 1 of those implicated in the study. They are considered negative controls if they fail to display reactivity to 1 of these drugs, while another drug is confirmed to be responsible for the CADR with which they have presented; e.g., if a patient having taken amoxicillin and paracetamol (acetaminophen) displays a CADR due to amoxicillin but not to paracetamol, if he has had skin tests with paracetamol and if he has taken paracetamol orally again without any CADR, he/she is enrolled as a negative control for paracetamol (1).

Healthy volunteers with or without previous exposure to the drug can be used as negative controls, but this requires signed informed consent of such control patients, with approval of an ethical committee.

Comment

Following the guidelines reported herein, drug skin tests are of value in investigating CADR as positive relevant results were obtained in 43%, 24% and 67% of (photo)patch, prick and IDT drug skin tests, respectively, among 72 patients (1). Among these 3 different skin test procedures, patch testing is the one most extensively studied in CADRs. In patients with a high imputability of one drug in the onset of their CADR, drug patch tests had positive results in 43% of 72 patients (1), 50% of 108 patients (2), 43.9% of 66 patients (5), and 31.7% of 197 patients (3). Positive relevant results depend on the clinico-evolutive type of CADR, on the respon-

sible drug, on the drug concentration and vehicle used (1, 2, 5), and even on the skin sites where tests are performed (8, 11, 12, 15–17).

Due to the possibility that a low concentration might yield false-negative results, drug patch tests need to performed with high concentrations of the commercialized form of drug. After pulverizing a tablet, the highest concentration to obtain homogeneous dilution of the powder is 30% in pet., in aq. or in alc. This threshold was determined in Nancy (France) by V. Noirez (unpublished data). When testing with pure substances, as the threshold of sensitivity for each drug is not yet determined, we advise a 10% concentration in pet., and if necessary in other vehicles, although for some drugs lower concentrations may be sufficient. Nevertheless, testing with high concentrations may elicit a relapse of the initial CADR. This is a reason why patch tests need to be performed first with low concentrations in investigating DRESS, Stevens-Johnson syndrome or Lyell's syndrome (1). As we have observed (2) some differences in testing with amoxicillin base or trihydrate amoxicillin salt, the name of the chemical form of the tested drug needs also to be given (2).

We propose the use of various vehicles, at least pet. and aq., for preparing drug patch tests, so as to avoid false-negative results due to poor penetration of the drug into the epidermis. In 5 cases, we have observed false-negative results when antibiotics were diluted in aq., whereas patch tests with the same drug diluted in pet. yielded positive results (2). Gonçalo et al. (14) observed false-positive results when testing estrogens diluted in aq. or pet., but obtained positive results when steroid hormons were diluted in alc. Alcohol has been reported as a good vehicle for patch testing in investigating FDE (19). Some drugs frequently induce a relapse of the CADR during patch testing, such as aciclovir (1), carbamazepine (20) or pseudoephedrin (1, 21, 22). These drugs need to be tested at low concentrations, and if they give negative results, at higher concentrations up to 30% if necessary.

Whenever possible, it may also be of value to test on the most-affected site of the initial CADR. In fixed drug eruptions, patch tests (11) or repeated application tests (12) with the suspected drug are positive only when performed on residual pigmented skin sites of the CADR, rather than when applied on non-previously affected skin of the back. Also, in 1 case of toxic necrolysis, Klein et al. (18) obtained positive patch tests when cotrimoxazole was tested on the cutaneous sites previously affected by necrolysis, while drug patch tests performed on other less-affected skin sites remained negative. It may also be of value to test on the most highly affected skin sites in maculopapular rashes, as reported in 1 case with tetrazepam (15). As a CADR, especially urticaria, may be due to coloring agents and excipients, these components also need to be tested (23).

As drug patch tests can elicit immediate positive reactions, especially with betalactam antibiotics, these tests need to be read at 20 min. Because most CADR are related to delayed cellular hypersensitivity, it is absolutely essential to carry out delayed readings at D2, also at D4 and, if negative, on D7. We have observed negative drug patch tests when read on D2, but positive on D4, in 5 patients (2).

The usefulness of drug patch tests depends on the clinical features of the CADR. From our results (1, 2, 5, 6) and those obtained from the literature, we consider that patch tests are of value in determining the responsible drug in generalized eczema, systemic contact dermatitis, baboon syndrome, maculopapular rash (1, 2, 5, 6, 24), AGEP (25), lichenoid rash and fixed drug eruption (11), and that photopatch tests may be useful in studying drug photosensitivity (10, 26). On the other hand, they are of less value in investigating urticaria (1), Stevens-Johnson or Lyell's syndrome (25), pruritus or vasculitis (2).

The usefulness of drug patch tests also depends on the drug tested. The most frequent reports of positive drug patch tests are related to the following drugs: betalactam antibiotics, especially amoxicillin (1, 2, 4, 6, 18, 24–30), cotrimoxazole (15), corticosteroids (1, 31, 32), heparin derivatives (1, 33–36), pristinamycin (1, 36), carbamazepine (1, 2, 20, 37–44), diltiazem (1, 45, 46), diazepam (47), hydroxyzine (1, 48), pseudoephedrine (1, 21, 22) and tetrazepam (1, 16, 49–51).

Prick tests and IDT

The usefulness of prick tests and IDT in determining the cause of CADR has not been evaluated, as much as the usefulness of drug patch tests. Osawa et al. (3) obtained positive results in 89.7% of their patients, but in the absence of negative controls, the specificity of their IDT cannot be validated. We obtained positive results on prick testing in 24% of 46 cases and in 64% of the 30 patients undergoing IDT (1).

Such drug skin tests are read at 20 or 30 min, but delayed readings are also worthwhile doing after 1 D (24) or later. Immediate positive results are observed most frequently in patients who have previously developed urticaria or angioedema. Delayed positive results can be observed even with prick tests, as reported with amoxicillin (1, 24) and pseudoephedrine (1). Delayed positive results are frequent with IDT, especially in investigating maculopapular rashes due to amoxicillin (1, 24, 29). In

testing heparin derivatives, it is of value to perform more delayed readings as results can be positive only at D3 (1, 35, 36). With IDT, delayed positive results can be obtained in maculopapular rash, eczema, erythroderma or fixed drug eruption.

Most of the papers published on the usefulness of prick tests and IDT concern CADR due to betalactam antibiotics (1, 24, 29, 52–54). Prick tests and IDT have also been performed with other drugs such as diltiazem (45), heparin derivatives (33–35), insulin (45), oestradiol (1) and corticosteroids (56).

Drug skin tests can re-elicit the initial CADR. There is a risk of eliciting a relapse of the initial CADR especially when performing IDT. Among 30 IDT performed, 3 minor incidents were observed (1). Because of this risk, we suggest hospital surveillance while performing IDT. The volume of drug administered for IDT should be as low as possible, 0.04 ml being the safest quantity and the lowest volume that gives reproducible responses (1).

Interpretation of Results

Relevance and specificity of drug skin tests

A crucial point is the interpretation of results of drug skin tests, whether negative or positive. Even when performed according to reviewed guidelines, skin testing is negative in 30–50% of patients (1–3, 5). Negative results may have several explanations: the final responsible agent for the CADR is a drug metabolite that is not formed in the skin when the native drug is applied there; there is no immune mechanism involved in the CADR; or concomitant factors that are responsible in inducing a transient oral drug intolerance, such as a viral infection, are not present at the time of testing. Thus, if negative, a drug skin test does not exclude the responsibility of a drug.

On the other hand, if the test is positive, we need to determine its specificity and its relevance. We have observed many false-positive reactions when performing IDT (57). We have already determined the thresholds of specificity for many drugs, for example betalactam antibiotics, erythromycin and spiramycin (1, 57), but the thresholds of specificity still need to be determined for many drugs in IDT testing.

False-positive results have also been observed on drug patch testing, namely with commercialized forms of drugs containing sodium lauryl sulfate in their formulations, with colchicine diluted at 10% in pet., with pills containing misoprostol when diluted at 30% in pet. (59).

This emphasizes that it is necessary to compare all skin test results with those obtained in negative controls (58), namely patients who have taken the drug within the last 6 months without adverse effects, or even patients who have never had contact with the culprit drug. To collect such negative controls and to enlarge studies that may help to determine the sensitivity and specificity of drug skin tests in investigating CADR, it is necessary to organize multicentre studies using the same guidelines.

Another point to be kept in mind, when assessing the relevance of drug patch tests, is that a positive drug patch test may have past relevance to contact dermatitis due to a drug, or to an excipient, without any relevance to the present CADR (59).

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