

Usefulness of drug patch testing in cutaneous drug allergy: what is new?

Intérêt des tests épicutanés médicamenteux dans le bilan des toxidermies : quoi de neuf ?

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Abstract

Recent studies have emphasized the value of drug patch tests, in addition to, prick and intradermal tests to determine the molecule responsible for cutaneous adverse drug reactions (CADR), also known as drug eruptions. The value of drug patch tests depends on the clinical features of the CADR, and they are valuable in the investigation of drug reactions, such as generalized eczema, systemic contact dermatitis, maculopapular rashes, toxic epidermal necrolysis, and fixed drug eruptions. Their sensitivity also depends on the particular drug involved. Guidelines for performing prick, ID and patch tests, published in 2001, are analyzed in the present article. We also report on the information published more recently on how to perform the tests, how to interpret them, new drugs reported to yield positive reactions and, finally, how to define the relevance and the specificity of drug patch tests in the workup of cutaneous drug allergies.

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Résumé

Des publications récentes ont souligné l'intérêt des tests épicutanés médicamenteux en plus des prick tests et tests intradermiques (IDR) pour déterminer la molécule en cause dans le déclenchement d'un accident cutané médicamenteux appelé aussi toxidermie. La sensibilité des tests épicutanés médicamenteux dépend des caractéristiques cliniques, sémiologique de la toxidermie. Ces tests sont intéressants dans le bilan des toxidermies de type eczéma généralisé, dermatose de contact systémique, exanthème maculo-papuleux, pustulose exanthématique aiguë généralisée ou érythème pigmenté fixe. La sensibilité de ces tests dépend aussi du médicament en cause. Un guide de bonne pratique des tests cutanés médicamenteux (prick tests, IDR mais aussi tests épicutanés) dans le bilan des toxidermies a été publié en 2001. Ce guide est analysé dans cet article et des informations émanant de publications plus récentes sont également étudiées pour donner l'état actuel de nos connaissances sur comment réaliser ces tests, comment les lire, quels médicaments ont été signalés comme pouvant donner des résultats positifs et enfin discuter de la pertinence et de la spécificité des tests épicutanés dans le bilan des toxidermies.

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1. Introduction

Drug patch can be of value in the investigation of cutaneous adverse drug reactions (CADR) to determine the responsible drug. Following the recently published guidelines for

performing these tests, it is time now to improve our knowledge concerning how to perform drug patch tests, to determine their value, their specificity, and their relevance according to the encountered CADR or the drug involved.

Guidelines for performing skin tests (patch tests, prick tests and intradermal tests (IDT)) with drugs in the investigation of CADR have recently been published with the synthesis of the experiences of dermatologists, who belong to the

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working party of the European Society of Contact Dermatitis for the study of skin testing in the investigation of CADR and from a review of literature [1]. The mechanisms involved in inducing CADR are not well elucidated. The results of the drug skin tests (patch tests, prick tests and IDT) depend both on the involved drug and their mechanisms i.e. the clinical features of the CADR. A review concerning the value of drug skin tests, according to the pathophysiology of the CADR, has recently been published [2].

2. What to test and which concentration to choose?

It is advised to perform drug patch tests during the 6 months following the CADR, as we do not know whether positive results will persist or not, many years later in all patients and with all drugs.

Due to the possibility that a low concentration might yield false negative results, drug patch tests have to be performed with high concentrations of the commercialized form of the drug. Using a pulverized tablet, 30% is the highest concentration possible to get a homogeneous dilution in petrolatum (pet.), in water or in alcohol [1].

When testing with pure substances, as the threshold of sensitivity for each drug is not yet determined, it is advised to use a 10% concentration in pet. and if necessary in other vehicles, although for some drugs smaller concentrations may be sufficient.

It is possible to test with the commercialized form of the drug, possibly responsible for the CADR. Pills must have their coating removed, then reduced to a very fine powder. This powder can be tested as is (optional), but has to be incorporated at 30% in white pet. and also diluted at 30% in water. According to recent results, to avoid false positive reactions Celebrex® capsules have to be tested at 5% or 10% in pet. and not with higher concentrations [3].

The powder contained in capsules is tested, diluted at 30% in pet. and at 30% in water. The gel jacket portion of the capsules is moistened and tested as is. Liquid preparations are tested both as is and diluted at 30% in water. With commercialized forms of the drugs, each preparation is done for only one patient and kept not more than 24 h. The name of the chemical form of the molecule (salt, molecule base) has to be given.

To avoid any relapse of severe CADR in patients, who have developed drug rash with eosinophilia and systemic symptoms (DRESS), Stevens Johnson syndrome, Lyell's syndrome, generalized urticaria, angioedema and especially in case of anaphylactic shock or in testing with aciclovir, carbamazepine or pseudoephedrin (that have been frequently reported as reinducing the CADR during patch testing), it is recommended that patch tests are performed, either with the commercialized form of the drug or the pure substance, first diluted at 0.1% and when negative, at higher concentrations, from 1% up to 10%.

Whenever possible, preservatives, coloring agents and excipients are also tested, as is or diluted at 10% in pet., or in

the vehicles and concentrations usually proposed for testing allergic contact dermatitis.

To investigate a photosensitivity reaction induced by a drug, both drug patch tests and drug photopatch tests with the responsible drug are to be performed. The irradiation for drug photopatch tests is performed on day 1, or for practical reasons can be performed on day 2, with a 5 J/cm² UVA irradiation [1].

3. Which vehicle to use [1]?

To prepare drug patch tests, it is proposed to use different vehicles, at least pet. and water, to avoid false negative results due to a low penetration of the drug into the epidermis. False negative results can occur when antibiotics are diluted in water, whereas patch tests with the same drug diluted in pet. yield positive results [1]. Steroid hormones have to be tested diluted in alcohol as false negative results have been observed in testing estrogens diluted in water or pet. [1]. In a recently published case, patch tests were positive with ganciclovir diluted at 20% in water but negative with the drug diluted at 20% in pet. [4].

4. Where to test [1]?

Patch tests are performed on the upper back, but it could be of value to test on the most affected site of the initial CADR. In fixed drug eruption (FDE), patch tests or repeated application tests with the suspected drug are positive, only when performed on the residual pigmented skin site of the CADR, but not when applied on the non-previously affected skin of the back.

Patch tests could also be of value in other dermatitis, such as toxic epidermal necrolysis. In a woman, who twice developed a maculopapular rash due to tetrazepam with bullous lesions on the elbows, patch tests were negative when performed with this drug on the back but had positive results when tested on the elbows, the most highly affected skin sites. No cross-reactions were observed with diazepam that has a chemical structure close to that of tetrazepam [5].

5. When to perform the readings [1]?

The results of patch testing are reported according to the International Contact Dermatitis Research Group (ICDRG) criteria for patch test reading.

As drug patch tests can induce immediate positive reactions, especially with betalactam antibiotics, these tests have to be read at 20 min, especially in patients who have developed urticaria or anaphylactoid shock. Because most of the CADR are related to a delayed cellular hypersensitivity, it is absolutely necessary to do delayed readings at 48 h, 96 h and, if negative, on day 7. Patch tests can be negative when read on day 2 but positive on day 4 [1].

6. What is the value of drug patch tests?

According to literature, drug patch tests are positive in 31.7–50% of patients, who have developed CADR [1]. When they are negative, it is absolutely necessary to perform prick tests and if these are negative, IDT are performed with immediate readings in urticaria but with delayed readings in other CADR.

The usefulness of drug patch tests depends on the clinical features of the CADR. Patch tests are of value in determining the responsible drug in generalized eczema, systemic contact dermatitis, Baboon syndrome, maculopapular rash, acute generalized exanthematous pustulosis, lichenoid rash, and FDE. They also seem of value in DRESS. Photopatch tests may be useful in studying drug photosensitivity [1].

On the other hand, they are of less value in investigating urticaria, Stevens–Johnson or Lyell's syndromes, pruritus or vasculitis [1].

The usefulness of drug patch tests also depends on the tested drug. The most frequent reports of positive drug patch tests are related to the following drugs [1]: betalactam antibiotics especially amoxicillin [6], cotrimoxazole, corticosteroids, heparin derivatives, pristinamycin, carbamazepine, diltiazem, diazepam, hydroxyzine, pseudoephedrine or tetrazepam [1]. Some recent reports confirmed the usefulness of drug patch tests and IDT in the investigation of CADR due to corticosteroids [7], heparins [8] or amoxicillin [6,9].

It is interesting, now, to report on drugs which have not been, or rarely been published as valuable in investigating patients, who have developed CADR with them. Recently, other drugs have been reported to yield CADR with positive drug patch tests.

Drug patch tests with codeine diluted at 1% and 5% in pet. (two negative controls) were positive in a patient, who had had a maculopapular rash while taking codeine and paracetamol. Cross-reactions were obtained on patch testing with morphine chloride (5% in pet.), but not with other opioids (pentazocine and tramadol both tested at 5% in pet.) [10].

An eighth case of FDE, due to an analgesic called allylisopropylacetylurea, confirmed by a positive oral provocation test was published, but was skin tested for the first time. Patch tests with allylisopropylacetylurea (concentration and vehicle: unknown) were negative on normal skin, but had positive results on lesional skin. In this case, no cross-reactions were observed in patch testing or orally administered bromovalerylurea belonging to the same chemical class of the mononeuroid molecules as allylisopropylacetylurea [11]. But two out of six cross-reactions have been found in previous publications.

The first case of a positive patch test with cefcapene pivoxil hydrochloride, diluted at 1% and 10% in pet. (five negative controls), was observed in a woman who had developed CADR with pruritic papules and erythema. The side chain of this third generation cephalosporin is a pivaloyloxymethyl base, present in other molecules, such as pivmecillinam, ceftam pivoxil, cefetamet pivoxil, cefditoren piv-

oxil and cefcapene pivoxil hydrochloride (not skin tested in the reported case) [12]. A case of positive drug patch tests in the investigation of an FDE, due to fluoroquinolones (norfloxacin and ciprofloxacin), was published by Rodriguez-Morales et al. [13]. Patch tests, negative on normal skin, had positive results when performed on lesional skin with ciprofloxacin diluted at 10% in pet. Patch tests were negative with norfloxacin (10% in pet.) on both sites. The oral provocation test with a first generation quinolone (pipemidic acid) was negative. Drug patch tests in other CADR due to quinolones had been previously published.

The first case of positive patch tests obtained with vancomycin at 0.005% in water was reported with cross-reactions obtained on patch tests with another glycopeptide antibiotic called teicoplanin (diluted at 4% in water). The clinical features of the itchy rash are not described. A crucial point in this case is that prick tests as well as IDT done with glycopeptide antibiotics remained negative even on delayed readings, while drug patch tests were positive with specific results (20 negative controls) [14]. This case emphasizes that delayed reactions to IDT are not sufficient to investigate CADR due to delayed hypersensitivity to drugs, but that drug patch tests have also to be performed as they can be positive while IDT remain negative.

Nystatin can be tested diluted at 10% in pet. (10 negative controls) [15]. For the first time, positive patch tests performed with metamizol have been published. In the investigation of one patient with FDE, open patch tests on lesional skin and patch tests performed on normal skin were negative. But patch tests, done on the pigmented skin with metamizol at 1% and 10% in pet. were positive, reinducing a generalized pruritus and a flare up of lesions on the sites previously involved in the FDE. The authors advise to test metamizol diluted at 1% in pet., then if negative at higher concentrations to avoid a reinduction of the initial CADR while skin testing [16].

An FDE without residual pigmentation, due to metamizol has been reported, but the patch test with the drug diluted at 10% in pet. performed on lesional non-pigmented sites, prick tests and IDT had negative results. The oral provocation test was positive [17].

Valaciclovir patch tests performed as is and also diluted at 20%, 10% and 1% in pet. and in water were positive in a patient who had developed an itchy, symmetrical exanthema on the face, trunk and extremities while taking this antiviral drug. Using aciclovir cream after the disappearance of the CADR, the patient developed vesiculobullous lesions on the site of application followed by a generalized exanthema. Cross-reactions were observed with aciclovir on patch tests done as is and diluted at 20%, 10% and 1%, and with ganciclovir (as is and 20% in water but negative at 20% in pet.). Famciclovir tested by patch tests and prick tests as is and diluted at 20% in pet and/or water had negative results, therefore an oral provocation test was done but it reinduced the CADR [4].

A patch test with isoniazide diluted at 50% in pet. had positive results (10 negative controls) in a man, who had developed a face edema accompanied by fever, pancytopenia and increased liver transaminases while taking three antituberculosis drugs. As readings of drug patch tests done with rifampicin and ethambutol were negative, they were readministered without any side effect [18].

Drug patch tests were positive with mexiletine hydrochloride diluted at 10% and 20% in pet. in a patient who had developed a widespread infiltrated erythema, with facial edema, accompanied with a liver dysfunction and hypereosinophilia, 1 month after taking this antiarrhythmia drug. The description and the evolution are compatible with DRESS [19].

A positive patch test was obtained in one case of acute generalized exanthematous pustulosis due to celecoxib, in testing with the content of one Celebrex[®] capsule (100 mg celecoxib diluted in 0.5 ml PBS, 19 negative controls) [9]. One patient developed a maculopapular rash 9 d after the beginning of a treatment with Celebrex[®]. Patch test done with Celebrex[®] diluted at 20% in pet. had positive results [20]. But according to Klienmans et al. [3], Celebrex[®] tested pure with a concentration higher than 10% in pet. can induce false positive results but with a concentration at 10% in pet. the patch tests do not induce false positive reactions.

Patch tests could be of value in the investigation of delayed exanthema occurring 24 h after an injection of non-ionic contrast medium. This was again reported in two recent cases with iohexol (dilution non-stated) in two patients, who also had cross-reactions on patch tests with iodixanol, but not with ionic contrast medium (amidotrizoate, iopanoico) [21]. We have also observed such positive patch tests with different radiocontrast media products (RCM), even though IDT with delayed readings are more frequently positive in patients suffering from delayed reactions after receiving RCM (unpublished data).

7. Negative results in drug patch tests may have several explanations [1]

The final responsible agent for the CADR is a drug metabolite that is not formed in the skin in which the native drug is applied; there is no immune mechanism involved in the CADR; concomitant factors that are responsible in inducing a transient oral drug intolerance, as a viral infection, are not present at the time of testing. So, if negative, a drug skin test does not exclude the responsibility of a drug [1].

The predictive value of a negative patch test is unknown. When possible, if the imputability of a drug is probable in the onset of CADR and if drug patch tests with this drug are negative, it is advised to perform drug prick tests rather than IDT with immediate and delayed readings. There are a lot of published cases of CADR with negative drug patch tests but positive delayed IDT [22]. Rifampicin had negative results when tested diluted at 30% in pet. and in water, but immedi-

ate positive results were obtained in ID testing 0.05 ml of 0.1% w/v rifampicin (no negative control) in a patient who had a morbilliform pruritic eruption while taking five antituberculosis drugs. Isoniazid, streptomycin, ethambutol and pyrazinamide were reintroduced without any adverse side effect [23]. Drug patch tests with cefotetan at 200 mg/ml diluted in 0.9% NaCl were negative, while IDT had delayed positive results in one patient who had had a maculopapular rash when taking this second-generation cephalosporin [24].

To our knowledge, the first case was reported with negative results on prick tests and IDT done with the responsible drug, negative on both immediate and delayed readings, but in the drug patch test with vancomycin had positive and specific results [14].

Therefore, it is advisable to perform first drug patch tests, then if negative, the other drug skin tests, especially in CADR related to a delayed cellular hypersensitivity. We emphasize that there is no value for the patient in performing patch tests when positive delayed reactions have been previously obtained in testing the same drug with IDT. As it has already been published in such cases, drug patch tests are always strongly positive; unfortunately such cases have appeared in publications again since 2001!

8. Interpretation of the results

8.1. Relevance and specificity of drug patch tests

The interpretation of the results of drug skin tests is a crucial point. False positive results are frequently induced while performing IDT [25]. In one recent paper, we also gave the thresholds of specificity for IDT with 20 different drugs that can induce false positive results. We also emphasized the value in determining the specificity and the relevance of drug patch tests as false positive or non-relevant results can also be obtained in drug patch testing, namely with the commercialized form of drugs containing sodium laurylsulfate in their formulation. With colchicine diluted at 10% in pet., 80% of 29 negative controls developed false positive results. When diluted at 30% in pet., Cytotec[®] containing misoprostol yielded false positive results in nine of the 10 negative controls at the day 2 reading, however, none of the controls had false positive patch tests at the day 4 reading or when Cytotec[®] was diluted at 1% in pet. [25]. False positive results have been obtained when testing with captopril, chloroquine and omeprazole [25]. Recently, Klienmans et al. [3] reported on the irritant reactions observed, while patch testing with pure Celebrex[®] (celecoxib) with concentrations higher than 10% in pet. Eight out of 10 patients with a suspected CADR due to Celebrex[®], and nine patients without any history of adverse reaction to pure Celebrex[®] had false positive results on the 48 h readings of their patch tests. In all patients, the oral provocation test with Celebrex[®] was well tolerated. At 5% or 10% in pet., patch tests with Celebrex[®] seem to be specific. These concentrations could be recommended to do patch tests with Celebrex[®] [3].

This emphasizes that it is necessary to compare all skin test results with those obtained in negative controls [1,25], 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, but in such cases with their signed informed consent [1].

A positive drug patch test may have a past relevance with a contact dermatitis due to a drug or to an excipient without any relevance to the investigation of CADR [25]. In two patients, drug patch tests were positive with a commercialized form of a drug and to one component of this product (iodine in one case, avocado oil in the second case), but the oral readministration of the drug was well tolerated. Drug patch tests were positive because the patients had previously developed a contact eczema due to antiseptics containing iodine in the first case and due to a wound-healing ointment containing avocado oil in its formulation in the second case. Two other cases were observed in testing drugs containing sodium sulfites in their formulation [25]. More recently (unpublished data), we observed non-relevant false positive results in performing patch tests with commercialized forms of heparins containing benzyl alcohol in patients who had previously developed contact allergy to benzyl alcohol but who had a good tolerance to heparins.

9. Conclusion

The value of drug patch tests depends on the clinical features of the CADR, the drug involved, the vehicle, the concentration used, and the site where they have been performed. It is time now for every allergist to follow the same guidelines to be able to compare all the published results and standardize these tests in determining their value and their specificity according to each type of CADR as soon as possible.

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