Skin Testing in Delayed Reactions to Drugs

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KEYWORDS

- Maculopapular rash
- Acute generalized exanthematous pustulosis
- Drug reaction with eosinophilia and systemic symptoms
- Toxic epidermal necrolysis (TEN) • Drug patch tests
- Intradermal tests • Antibiotics • Corticosteroids

During recent years, numerous reports have emphasized the usefulness of drug skin tests (patch tests, prick tests, intradermal tests [IDT]) for the investigation of cutaneous adverse drug reactions (CADR) caused by delayed hypersensitivity to drugs.[1–6] The following CADR are supposed to be caused totally or partially by a delayed cell-mediated hypersensitivity: maculopapular rash (MPR), photosensitivities to drugs, heparin-induced cell-mediated reactions, acute generalized exanthematous pustulosis (AGEP), drug reactions with eosinophilia and systemic symptoms (DRESS), fixed drug eruption (FDE), Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[7] Drug patch testing (or prick/IDT with delayed reading) are the logical first step in defining the relevant drug in these reactions.[1,6–12] They can also help to better understand the pathomechanism of these reactions.[1,8,13,14] However, although some drugs have been used widely and are standardized (eg, amoxicillin), many compounds are still not standardized for skin-testing and their use remains experimental. Because frequently no other possibility exists to pinpoint the relevant drug, these tests are nevertheless widely used, but they should be interpreted cautiously.

Different guidelines for performing drug skin tests (patch tests, prick tests, and IDT) with drugs in the investigation CADR have been published.[3,15] It is advised to perform drug skin tests during the 6 months following the CADR[4] because the persistence of drug allergies seem to vary substantially and cannot be predicted in the individual case. Patch tests and prick tests can be done with any commercialized form of a drug. Intradermal tests can be done only if an injectable form of the drug is commercialized. If one uses IDR in patients with severe CADR, one should be aware that skin testing may reactivate the disease.

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DRUG PATCH TESTS

Drug Concentration in Drug Patch Tests

The threshold of sensitivity for many pure substances has not been determined in drug patch tests. Therefore, a practical approach would be to use a 10% concentration in petrolatum and, if necessary, in other vehicles, although for some drugs, smaller concentrations may be sufficient.[1,3,4] Recently, standardized material to do patch test with pure molecules diluted in petrolatum has been commercialized for some drugs (Chemotechnique laboratory, Malmö, Sweden) (**Table 1**).

Using a pulverized tablet, 30% is the highest concentration possible to get a homogeneous dilution in petrolatum, in water or in alcohol.[3] When the commercialized form of the drug is used, it is advised to use a 30% concentration of the final product. It is also possible to use a concentration that leads to a final 10% concentration of the active drug, when the weight of the active drug and excipients are known in the commercialized form. With commercialized forms of the drugs, each preparation is done for only one patient. As the stability of these freshly made substances may vary, they cannot be kept more than a few hours.[1,3] Whenever possible, preservatives, coloring agents and excipients should also be tested, undiluted or diluted at 10% in petrolatum, or in the vehicles and concentrations usually proposed for testing allergic contact dermatitis. Testing with acyclovir, carbamazepine or pseudoephedrin have been reported to reinduce the CADR symptoms during patch testing (see **Table 1**).[1,2,4] Therefore, it is recommended that patch tests are performed, first diluted at 1% and, when negative, up to 10% (either with the commercialized form of the drug or the pure substance). Moreover, to avoid false positive results, some drugs have to be tested at higher dilutions. The content of capsules of celecoxib (Celebrex) should be tested at 5% or at 10% in petrolatum and not with any higher concentration.[16] Desloratadine has to be tested at 1% in petrolatum (see **Table 1**).[17] Colchicin at 10% in petrolatum induces false positive results, the threshold of specificity is unknown.[18] Captopril in commercialized forms diluted at 1% and chloroquine in commercialized forms diluted at 30% in petrolatum sometimes induce false positive results.[18] Misoprostol in commercialized forms has to be diluted at 1% in petrolatum.[18]

In investigating a photosensitivity reaction induced by a drug, both drug patch tests and drug photopatch tests with the responsible drug have 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 Joules/cm2 UVA irradiation.[3] Photoscratch patch tests are more irritating, do not have a better value than photopatch tests, and should consequently be avoided.[19]

The results of patch testing are reported according to the International Contact Dermatitis Research Group (ICDRG) criteria for patch test reading[20] with negative, doubtful or positive (+, ++, +++) results on days 2 and 4.

The best vehicle to prepare drug patch test has not yet been determined. Petrolatum seemed to be convenient in most of the cases.[1,3] Steroid hormones have to be tested diluted in alcohol because false negative results have been observed in testing estrogens diluted in water or petrolatum.[3]

Under chambers, patch tests are performed on the upper back, but it could also be of value to test on the most affected site of the initial CADR. Testing in the affected area is recommended in FDE[9] but could also be of value in other forms of CADR, as reported in TEN with co-trimoxazole[21] or with tetrazepam in a patient with MPR.[22]

Drug Patch Tests and Topical Application in Fixed Drug Eruption

In FDE, it is well known that patch tests[9] or open application tests[23–25] with the suspected drug are more positive when performed on the residual pigmented skin site