

Allergy testing in serious cutaneous drug reactions – harmful or beneficial?

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We report on 3 cases of adverse cutaneous drug reactions of erythema multiforme type. Despite the serious previous clinical conditions, patch tests with the possible causative drugs have been performed in all our patients, because of multiple candidate drugs and the need of the patients for further treatment with at least some of the agents. We demonstrate that patch tests are a good and safe approach to initial evaluation of the nature of a cutaneous drug reaction. In the case of a positive patch test reaction to one of the substances, re-exposure to the non-reactants in a clinical setting is recommended. If a one-side-blinded placebo-controlled challenge test is well tolerated, then the clinician should be able to reintroduce drugs previously suspected as causing the allergy.

Key words: patch testing; erythema multiforme; adverse drug reaction; scratch testing; intracutaneous testing; subcutaneous testing; intravenous challenge; oral challenge. © Munksgaard, 1997.

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Serious adverse drug reactions in the skin are characterized by bullous, pustular and/or epidermolytic appearance. Erythrodermic involvement is also considered to be severe. Several guidelines have been issued for evaluation of these events. Re-exposure to traces of possible causative drugs may induce the same (or even worse) type of skin reaction. Therefore, risk assessment of allergy testing in patients with a history of such reactions is one of the most crucial points to decide for the dermatologist.

From the start, the primary care doctors want to know which alternative drug can be given in the future, and the patient needs to know the real cause of his or her previous serious condition to exclude any risk of re-exposure in future. Moreover, there are often several drugs given together to treat a particular condition. Hence, various drugs may come under suspicion as possible causative agents, even though only 1 drug is usually responsible.

Here we report 3 cases of serious drug reactions of the erythema multiforme (EM) type, in which we decided to perform skin tests as a diagnostic tool. As our paper shows, we were able to reintroduce some of the previously suspected agents to their therapy and thereby improve our patients' quality of life.

Patients and Methods

All patients were free of skin inflammation and of specific treatments for the previous skin reaction for at least 6 weeks. Tests were done only after comprehensive information about the risks and alternatives and after signed informed consent of the patients.

Patch testing was always the initial investigation. For patch testing, tablets were pulverized and dampened with sterile water before application to intact skin on the back. Liquid drugs were used as is. Tapes remained for 2 days on the skin and recording was done using the ICDRG criteria. Positive patch test reactions were followed for at least 4 days. Negative patch tests have been followed by scratch tests and, if appropriate, by intracutaneous, subcutaneous, intravenous or oral challenge. Challenge tests were always placebo-controlled and patient-side blinded. Only 1 drug was reintroduced per day. We challenged the patients in increasing amounts of the substances, for oral challenge starting at 1/20, and finally giving 1 single entire therapeutic dose.

Case no. 1

A 37-year-old female was hospitalized in poor physical condition with generalized target-like

macules. There was exfoliative involvement of the oral mucosa and conjunctivitis. A few days earlier, she had felt some stinging on her lips, pointing in the direction of herpes-induced erythema multiforme (EM). However, 2 days earlier, she had also been given a mixture of diclofenac and lidocaine intramuscularly, as well as oral piroxicam, tetrazepam, dexamethasone and sulpiride for back pain.

For the results of the patch tests, see Table 1. After finding a +++ reaction to tetrazepam, we decided to challenge with all the other drugs that had remained negative on patch test. Lidocaine was given intra- and subcutaneously up to 2-ml final volume of the 1% preparation. Diclofenac had been reused by the primary care doctor recently, despite a warning against its use in the patient's own allergy document, and had been tolerated well, fortunately. Piroxicam was rechallenged without flare-up of the previous condition; however, after intake of 1 entire therapeutic dose, she experienced generalized pruritus without visible signs. Lifelong avoidance of both piroxicam and tetrazepam was therefore recommended. No reaction was observed to sulpiride and dexamethasone after oral challenge.

Case no. 2

A 42-year-old man had hepatic cirrhosis. He received i.v. diuretics for his hepatic ascites and had started a course of amoxycillin and omeprazole for *Helicobacter pylori* eradication against his gastric ulcer. Within a few days, he developed a macular rash, eventually becoming bullous. On arrival in hospital, he showed painful epidermolysis on skin areas overlying bones (knees, elbows, iliac crests, etc.). On treatment with prednisone and antibac-

terial dressings, his condition gradually improved. He recovered completely without scarring of skin.

Patch testing gave a strong positive reaction to amoxycillin and a questionable one to omeprazole, which was next to amoxycillin on the patch test tape. No reaction occurred to frusemide (furosemide). We decided to expose the patient to frusemide again in order to confirm tolerance to this drug. He tolerated increasing doses up to a single dose of 40 mg i.v. without side-effects. We decided against retesting omeprazole alone, despite the possibility of a negative reaction the 2nd time (the initial reaction could have been a false-positive "neighbouring" reaction), because this agent was not particularly important for the patient's future treatment. In summary, frusemide could be reintroduced into therapy, whereas the other 2 drugs still needed to be avoided.

Case no. 3

A 26-year-old woman was treated for pharyngitis with oral penicillin and had taken over-the-counter metamizol herself. At day (D) 5, she developed a macular rash, developing into generalized erythema multiforme involving the oral mucosa. Treatment with antihistamines and prednisone failed. We saw her on D11 and immediately put her on cyclosporin A, which improved the condition within a few days. The dose was tapered down and the patient recovered completely.

Patch testing, including the standard series, showed positive reactions at D2/D3 to nickel sulfate (5% pet.): +/+ + + +, cobalt sulfate (1% pet.): +/+ +, and fragrance mix (8% pet.): -/+, of no relevance to the eruption reported above. Both penicillin and the NSAID remained negative on patch testing. Scratch test with metamizol was

Table 1. Skin test and challenge test results

Drug	Patch test (2/3/4 days)	Scratch (20 min)	i.c. (20 min)	s.c.	i.v. (1 day)	Oral (1 day)
Case no. 1						
tetrazepam	+/+ + + + + +	n.d.	n.d.	n.d.	n.d.	n.d.
lidocaine	-	-	-	-	n.d.	n.d.
piroxicam	-	-	n.d.	n.d.	n.d.	(+)
sulpiride	-	-	-	n.d.	n.d.	-
dexamethasone	-	-	n.d.	n.d.	n.d.	-
Case no. 2						
amoxycillin	-/+ + + +	n.d.	n.d.	n.d.	n.d.	n.d.
omeprazole	-/-/? +	n.d.	n.d.	n.d.	n.d.	n.d.
frusemide	-	-	-	-	-	n.d.
Case no. 3						
metamizol	-	-	n.d.	n.d.	n.d.	n.d.
penicillin	-	n.d.	(+)*	n.d.	n.d.	n.d.

*Minor determinant mix of penicillin.

-: negative. (+): questionable, but regarded as positive. n.d.: not done. i.c.: intracutaneous. s.c.: subcutaneous. i.v.: intravenous.

negative, as well as specific IgE for penicillin, and prick and intracutaneous tests to penicilloyl polylysine. However, there was a positive reaction of 3/17 mm to intracutaneous undiluted minor determinant mix (MDM) of penicillin. No reaction occurred to prick and intracutaneous tests with 1:10 dilution of MDM. Upon repeated interviews, the patient, who was a nurse, finally reported a previous mild rash from metamizol 2 years ago, which had not been seen by a doctor. Taken together, we decided not to perform oral rechallenge with either the penicillin (because of the positive, even though not definite, test reaction) or the NSAID (because of the 2 possible anamnestic reactions). Both drugs needed to be excluded, therefore, from any future therapy in this patient.

Discussion

Serious adverse drug reactions of the skin, such as EM and toxic epidermal necrolysis (TEN), are generally considered to be allergic. Whereas immune deposits are common in herpes-induced EM, this is not true of drug-induced EM (8). Pathogenesis has also been explained by the decreased ability of the individual to detoxify reactive intermediate drug metabolites (4). For a comprehensive review of TEN, we commend Roujeau et al. (8). Patch testing has been proven to be a useful tool for diagnosis of allergic contact dermatitis for over 100 years. In evaluating skin reactions to systemic drugs, patch tests are one of the approaches most frequently used. The test is not suitable for investigating every type of drug reaction. In drug-induced erythema multiforme, however, patch tests may be applicable because of the strong T-cell infiltrate (7). Our results show that patch tests, in practice, can help us finding the causative agent in some patients. A high rate of positive tests occurred for intradermal tests in maculopapular, erythema multiforme and erythrodermic reactions, whereas patch tests were more reliable for eczematous-type and anticonvulsant-induced reactions (6).

Carbamazepine, aminopenicillins, sulfonamides and some NSAIDs are frequently involved in serious drug reactions (8). These agents are also good candidates for diagnostic patch testing to drugs (1). A positive patch test reaction to tetrazepam, as in our 1st case, has been reported before (3). It is clear that patch tests in serious adverse drug reactions may be beneficial for evaluation in a number of cases. However, anyone doing patch tests or any other skin test should always keep in mind that serious adverse reactions can be provoked by exposure to the test substance itself (5).

The most crucial problem is the preparation of

test substances. So far, in terms of systemic drugs, there is almost nothing commercially available for patch testing. We obtained useful results using a pulverized and dampened tablet, or powder from a capsule, whenever the original pure agent was not easily available from pharmacies or the manufacturer. In our opinion, patch testing is justified if several drugs have been used, among which there are important substances for the treatment of the patient's condition in the future. This was the case in our 1st 2 patients. The 1st patient's chronic pain condition still has decades of analgesic treatment ahead. Finding the single causative drug(s) will improve her quality of life significantly, because of the opportunity to use the other drugs in the future. The interesting point in this particular case is the possible involvement of 2 different drugs, piroxicam and tetrazepam. Rechallenge with double-blinded placebo-controlled piroxicam would probably help us to find out the true nature of this piroxicam "hypersensitivity". Nevertheless, for ethical reasons, we refused to take the risk of a severe test reaction once again.

The 2nd patient's hepatic cirrhosis will definitely require diuretics again, and so it was very helpful for the primary care doctor to acquire the opportunity for further use of frusemide.

In the 3rd case, we could not definitively explore the cause of the condition. For both drugs, some aspects pointed in the direction of relevant hypersensitivity. Challenging with related drugs (cephalosporins alternatively to penicillins) would have been helpful for optional treatments in the future, but was refused by the patient. Challenge tests should be done if a positive skin test reaction has occurred and the tolerability of non-reacting agents can be confirmed only by re-exposure. If 1 single drug is considered as the cause, we agree with Brethnach (2) that challenge tests are contraindicated (2).

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