Utility of patch testing for patients with drug eruption

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Summary

Background. Patch testing is less dangerous than oral provocation testing for identification of the causative drug for patients with drug eruption; however, its usefulness for such identification is controversial.

Aim. To clarify the rates of positive patch testing for patients with drug eruption, classified by causative drugs and clinical features.

Methods. We analysed results during the period 1990–2010 for 444 patients (151 men, 293 women; mean ± SD age 49.9 ± 18.6 years) who were tested for drug eruption. In the patient group, there were 309 people (69.1%) with maculopapular eruption and 31 (6.9%) with severe drug eruption. The test materials were applied to the back and left for 2 days under occlusion, then results were assessed by the International Contact Dermatitis Research Group (ICDRG) scoring system 3 days after application. Reactions of + to +++ were regarded as positive.

Results. Of the 444 patients, 100 (22.4%) had a positive patch test result to a suspected drug. Positive rates were 23.6% and 20.0% for maculopapular eruption and fixed drug eruption, respectively. The class of materials to which most patients reacted positively was contrast medium (n = 53; 41.1%), followed by drugs acting on the central nervous system (n = 18; 28.6%). In the latter group, 16 of the 18 patients were positive to antiepileptics.

Conclusions. Positive rates depend on the causative drug rather than the clinical features of the drug eruption. Patch testing is useful when contrast medium or antiepileptics are suspected to be the causative drugs. However, standardization of patch test materials and method of reading is needed, as well as guidelines regarding when testing should be performed. Although patch testing for drug eruption has significant potential, it requires further validation.

Introduction

The oral provocation test is a reliable method to identify causative drugs for patients with drug eruption.¹ However, it may be dangerous in some serious drug eruptions, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug-induced hypersensitivity syndrome (DIHS), as these conditions have a guarded prognosis.²,³ Patch testing is less dangerous than the oral challenge test, but its usefulness for drug eruption is controversial.⁴ To determine the utility of patch testing for patients with drug eruption, we analysed the results of patch testing for patients with drug eruption over a 20-year period.

Methods

Patients

We analysed the results for patients patch tested at the Department of Dermatology, Showa University Hospital, during the period April 1990 to March
In total, 444 patients (151 male, 293 female; mean ± SD age 49.9 ± 18.6 years, range 2–93) suspected of having drug eruption were tested (Table 1). Table 2 shows the frequency of the clinical types of drug eruptions. Of the 444 patients, 309 (69.6%) had maculopapular eruption. Because this type of eruption is often difficult to distinguish from viral infection, patients were identified on the basis of their medical history and the clinical course of the disease, as follows: (i) rash occurring up to 4 weeks after drug administration, and (ii) improvement of lesions after the suspect medication was stopped. There were 55 (12.4%) and 37 (8.3%) patients, respectively, with fixed drug eruption (FDE) and erythema multiforme (EM). A further 31 patients (7.0%) were diagnosed as having severe drug eruptions (SJS, TEN or DIHS).

Table 3 shows the number of tested patients for each class of drug: 129 were tested with contrast media, 126 with antibacterial agents and 101 with nonsteroidal anti-inflammatory drugs (NSAIDs).

Patch testing

Patch testing materials (Manufacturing Laboratory, Showa University Hospital Pharmacy) were applied to the back of each participant, and left for 2 days under occlusion. Two types of patch test unit were used: vinyl plaster (Mini-plaster or Patch Tester Torii; Torii Pharmaceutical Co, Ltd, Tokyo, Japan) for water-based materials, and Finn Chamber® (SmartPractice Co. Ltd, Yokohama, Japan) for petrolatum-based materials. In 33 of the 55 patients with FDE, patch tests were performed both on normal skin and on the affected site, while the other 22 were tested on the back because of difficulty applying the drug to the affected sites (e.g. lip, genital region). In four cases of suspected photosensitivity, photopatch testing was performed: two materials were applied to the back, then one was removed after 24 h and the area irradiated with half the minimal erythema dose of ultraviolet (UV)A/UVB (Dermaray UV; Eisai Co. Ltd, Tokyo, Japan).

All the tests were performed between 2 weeks and 4 months after onset of eruption. Results were assessed using the International Contact Dermatitis Research Group (ICDRG) scoring system 3 days after application. Reactions of + to +++ (Ph+ to Ph+++ for photopatch testing) were regarded as positive. Any results that were difficult to assess because of technical limitations were excluded.

Results

Of the 444 patients suspected of having drug eruption, 100 (22.4%; 39 men, 61 women; age 51.2 ± 17.1 years, range 17 to 86) had positive patch test results. Positive rates in cases of maculopapular eruption, FDE and EM were 23.9%, 20.0% and 8.1%, respectively (Table 2). Regarding the severe drug eruptions, positive rates in cases of SJS, TEN and DIHS were 14.3%, 0% and 56.3%, respectively (Table 2). Contrast medium was the most common source of positive patch test (n = 53; 41.1%), and the second most common (n = 18; 28.6%) was the class of drugs acting on the central nervous system (CNS) (Table 3).

In the latter group, 16 of 18 (41.0%) reacted to antiepileptics and 12 of the 16 had positive reactions to carbamazepine (Table 3). Of 101 patients tested with NSAIDs, 11 (10.9%) had a positive reaction (Table 3), while of 126 patients tested with antibacterial or antifungal agents, 9 (7.1%) tested positive (Table 3). Rates of positive reactions to drugs acting on the respiratory system, to cold remedies, and to traditional Chinese medicines were 5.9%, 3.1% and 14.3%, respectively (Table 3). No patients reacted to drugs acting on the cardiovascular system or the immune response, or to any vitamins (Table 3).

| Clinical features/condition | Patients, n | Positive reaction, n | Positive rate, % |
|----------------------------|-------------|---------------------|-----------------|
| Maculopapular eruption      | 305         | 73                  | 23.9            |
| FDE                         | 55          | 11                  | 20              |
| EM                          | 37          | 3                   | 8.1             |
| Photosensitivity             | 4           | 2                   | 50              |
| AGEP                        | 3           | 0                   | 0               |
| Severe reactions            |             |                     |                 |
| SJS                         | 7           | 1                   | 14.3            |
| TEN                         | 8           | 0                   | 0               |
| DIHS                        | 16          | 9                   | 56.3            |
| Others                      | 9           | 1                   | 11.1            |
| Total                       | 444         | 100                 | 22.5            |

AGEP, acute generalized exanthemeatous pustulosis; DIHS, drug-induced hypersensitivity syndrome; EM, erythema multiforme; FDE, fixed drug eruption; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
In this study, the positive response rate to suspected drugs in our cohort of 444 patients was 22.4%, but positive rates in patients with photosensitivity or DIHS were > 50% (Table 2). The drug to which most patients reacted was contrast medium (Table 3). Numerous drug eruptions were reported in Japan shortly after the introduction of nonionic iodinated contrast media, with the main clinical feature being papulomacular eruption, particularly oedematous erythema and papules, mainly on the trunk. We suggest two reasons for the numerous cases of drug eruption caused by contrast media in Japan. First, deficiency of aldehyde dehydrogenase (ALDH), a migrating isoenzyme of liver acetaldehyde dehydrogenase, which occurs in around 50% of Japanese (i.e. they have a low Michaelis constant and $K_m$ for acetaldehyde) may play a role. Second, until 2000, the rate of annual exposure to contrast medium was higher, as it included pretesting performed with a small amount of contrast medium, as it was thought that this pretesting might predict those patients likely to have adverse reactions. The discontinuation of this pretesting procedure might be the reason for the decrease in the positive rates and numbers of patients affected: 43.4% (46/106) during the period April 1990 to March 2000, and 30.4% (7/23) in the period April 2000 to March 2010.

Drugs acting on the CNS made up the second largest group of positive tests, with 18 patients reacting to them (Table 3): 16 reacted to antiepileptics and 12 to carbamazepine. Regarding DIHS, 9 of 16 tested patients with DIHS (56.3%) had positive results (Table 2); this high positive rate was not due to DIHS itself, but rather to the causative drugs, as 8 of the 9 patients reacted to carbamazepine. It is well known that carbamazepine results in high positive rates in patch testing. Indeed, a limitation of patch testing for drug eruption lies in differentiating between systemic and cutaneous metabolism of drugs. We speculate that this difference might be less for carbamazepine than for other drugs because this drug has a uniform distribution through the body and cases of flare-up phenomena during patch testing with carbamazepine have been reported. Our data therefore suggest that the positive rates may depend on the causative drug rather than on the clinical features of the drug eruptions. However, the positive rate for FDE might have been affected by the negative reactions occurring in 22 patients who had the materials applied to the back, as positive results are more likely when materials are applied to the involved skin.

Patch testing is much safer than oral challenge or intracutaneous test for the identification of a causative drug in patients with drug eruption. Our results suggest that patch testing can be useful when contrast medium or antiepileptic is suspected as the causative drug, and can be relevant to patient management. However, the general opinion of patch testing for patients with drug eruption is not high, and negative reactions are not useful. To perform patch testing for drug eruptions, patient consent must be gained after they are informed as to the limitations of the testing, as described above, and the influence of the testing on their social life, e.g. avoidance of showers, sunbathing and exercise. Although some guidelines have been defined, we consider that three standardized metrics are needed to overcome the issues described above if patch testing is to be used for drug eruptions. First, the actual treatment drugs should be used as patch test allergens. There is a limited number of com-

| Drug                                           | Patients, n | Positive reaction, n | Positive rate, % |
|------------------------------------------------|-------------|----------------------|------------------|
| Contrast agent                                 | 129         | 53                   | 41.1             |
| Drugs acting on the CNS                        | 63          | 18                   | 28.6             |
| Antiepileptics                                 | 39          | 16                   | 41.0             |
| Nonsteroidal anti-inflammatory drugs           | 101         | 11                   | 10.9             |
| Antibacterial and antifungal agents            | 126         | 9                    | 7.1              |
| Drugs acting on the respiratory system         | 51          | 3                    | 5.9              |
| Cold remedies                                  | 65          | 2                    | 3.1              |
| Traditional Chinese medicine                   | 14          | 2                    | 14.3             |
| Muscle relaxants                               | 4           | 2                    | 50.0             |
| Drugs affecting metabolism and GI function    | 74          | 1                    | 1.4              |
| Metal antagonants                              | 4           | 1                    | 25.0             |
| Drugs acting on the cardiovascular system      | 48          | 0                    | 0                |
| Drugs acting on the immune response            | 34          | 0                    | 0                |
| Vitamins                                       | 10          | 0                    | 0                |
| Others                                         | 20          | 0                    | 0                |

CNS, central nervous system; GI, gastrointestinal.
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Table 4 Patch test concentration and vehicles of main causative drugs.

| Classification | Drug                | Concentration, % | Vehicle |
|----------------|---------------------|------------------|---------|
| Contrast medium | Iohexol             | As supplied (water) |         |
|                 | Iopamidol           | As supplied (water) |         |
|                 | Iomeprol            | As supplied (water) |         |
| Drugs acting on the CNS | Carbamazepine | 1 | Pet. |
|                 | Phenotoin           | 1 | Pet. |
|                 | Phenobarbital       | 1 | Pet. |
| NSAIDs | Diclofenac sodium | 10 | Pet. |
|                 | Mefenamic acid      | 10 | Pet. |
|                 | Acetoaminophen      | 10 | Pet. |
|                 | Pirroxicam          | 1 | Pet. |
| Antibacterial agents | Amoxicillin trihydrate | 10 | Pet. |
|                 | Ampicillin hydrate   | 10 | Pet. |
|                 | Minocycline hydrochloride | 10 | Pet. |
|                 | Clarithromycin      | 10 | Pet. |
|                 | Cefaclor            | 10 | Pet. |
|                 | Cefalexin           | 10 | Pet. |
| Others | Dihydrocodeine phosphate | 10 | Pet. |

CNS, central nervous system. NSAID, nonsteroidal anti-inflammatory drug. pet., petrolatum.

Commercially available drugs for patch testing, thus most are formulated by each local facility, leading to difficulties in comparing data between different facilities. Each drug also has an optimal patch test concentration that is not irritant, and optimal vehicle(s). Table 4 shows the patch test concentrations and vehicles of the main causative drugs used in this study. In addition, where possible, patch testing should also be carried out using the individual ingredients of the medicines as these ingredients may also be used in other products.

Second, assessment of patch test reactions for drug eruption needs to be standardized. The ICDRG scoring system is an established method of identifying allergens in cases of allergic contact dermatitis (ACD), but it can be difficult to interpret a reaction of ‘+’ in drug eruptions. In our study, 13 of 14 patients (92.9%) with ‘+’ reactions to contrast media had a positive reaction to intracutaneous testing. In addition, although it is recommended that for ACD, readings should be performed on day 2, day 3 or 4, and day 7 in ACD, there are no similar data for drug allergy.

Third, it is unclear when patch testing should be performed immediately after improvement of the rash or several weeks later. Bruyzeel and Maibach suggested that the latter is better than the former, but Grandhe et al. reported a longer interval occurred between the rash and evaluation in patients with negative patch test reactions than in patients with positive patch test reactions.

However, each clinical condition might have an optimal time for patch testing. Kano et al. suggested that the lymphocyte transformation test should be performed within 1 week after the onset of rash in patients with maculopapular drug eruption and SJS/TEN, but should be delayed until 5–8 weeks after rash onset in DIHS. Similar data for patch testing will be necessary to increase its usefulness.

The fact that the oral challenge test is rarely used for drug verification demonstrates that this test is also not well standardized. It is also necessary to clarify when intradermal testing should be carried out if patch testing is negative. Thus, further studies are necessary, both for patch testing and for other tests to detect the causative drug in patients with drug eruptions.

Conclusion

in terms of increased refinement of the evidence-based diagnosis of clinical relevance, patch testing for drug eruption has significant potential. However, further validation is necessary to overcome the limitations of the test and to clarify the optimal conditions for its performance.

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