Usefulness of Patch Testing in Dermatology

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Patch testing is the gold standard for identifying the cause of allergic contact dermatitis (ACD). It is a well-established scientific method of diagnosing a delayed type of hypersensitivity (type IV) reaction.[1] The success of valid results from the test is in fact a complicated procedure, and this test needs to be performed and interpreted properly under the supervision of trained personnel.[2] Patients who are suspected of contact dermatitis are re-exposed to the culprit allergens under controlled conditions to reproduce a mini-eczematous reaction for verifying the diagnosis. It is primarily aimed to diagnose ACD, but its field of interest has been extended to some cutaneous systemic drug eruptions.[3]

Usefulness of Patch Testing

There are various applications of patch testing. The most valuable candidates to perform a test are the patients who have clinical symptoms and signs suspected of allergic contact dermatitis.[3] Allergic contact dermatitis can also accompany other endogenous eczema, for instant, atopic dermatitis.[3] In addition, there are no definite clinical clues to distinguish between irritant contact dermatitis and allergic contact dermatitis, this thus brings about the role of patch testing.[3] Furthermore, there are numerous researches which have paid attentions to the value of patch testing in cutaneous adverse drug eruptions. Skin compatibility assessment is another purpose of patch testing cosmetic products.

Indications for patch testing

- Contact dermatitis
  - Allergic contact dermatitis
  - Photo-allergic contact dermatitis
- Contact urticaria
- Atopic dermatitis
- Drug eruptions
  - Photo-allergic drug eruption
  - Certain drug eruptions mediated by T cells
- Cosmetics testing

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Allergic Contact Dermatitis

Allergic contact dermatitis is a prototype of type IV (delayed-type) hypersensitivity reaction. The crucial clinical clue is an eczematous rash with sharply demarcated border on the area which is closely related to the suspected allergen.[4] The indications to perform patch testing are[1,3-5]

(1) dermatitis with localized or unusual distribution such as hands, feet, periorbital, or perianal distribution

(2) dermatitis that may be caused by occupations or hobbies

(3) suspected cases of contact allergy

(4) treatment-resistant dermatitis or prolonged duration of disease for more than 3 months

(5) various types of endogenous eczema that may worsen by superimposed contact allergy

The most common allergens in Thailand are composed of potassium dichromate, followed by nickel sulfate, fragrance mix, and cobalt chloride.[6] The sensitivity and specificity of patch testing in suspected contact dermatitis patients by common screening allergens are 77% and 71% respectively.[4]

Atopic dermatitis

Atopic dermatitis (AD) is a common, chronic recurrent inflammatory skin disease which has a wide range of clinical manifestations. The diagnosis is based upon various validated diagnostic criteria. The well-known criteria are Hanifin and Rajka diagnostic criteria[7], U.K. working party diagnostic criteria[8], and Kang and Tian criteria for AD in the Chinese population.[9] There are many researchers interested in finding investigative tools to help to define the diagnosis.

Clinical sub-types[10-12]

(1) Extrinsic AD is a classic IgE-mediated AD. The patients have high total serum IgE levels and specific IgE for food and environmental allergens. Most of AD patients are in this group.

(2) Intrinsic AD (Atopiform dermatitis) is AD with absence of high total serum IgE and allergen-specific IgE. The clinical features of intrinsic AD include later disease onset, milder severity, and absence of atopic diseases.

Atopy patch test (APT)

APT is a patch test with allergens known to elicit IgE-mediated reactions. This test was developed as a

diagnostic tool for patients with aeroallergen-triggered AD. The study revealed that eczematous skin lesions in the APT caused by IgE-associated activation of allergen-specific T-cells[13], supported the role of APT in AD patient.

The APT method is similar to conventional patch testing except for the result interpretation.[14] The aeroallergen used in APT includes lyophilized allergens from house dust mite *(Dermatophagoidespter onyssinus)*, cat dander, grass and birch pollen in a petrolatum vehicle.[1] Food protein APT is used mainly experimentally and still has a lack of standardized allergens. Moreover, the results of food APT are controversial. Therefore oral food challenges remain the standard test for food allergy.

Indication, sensitivity and specificity of APT

APT reactions in healthy controls and respiratory atopy patients have less frequency and intensity of positivity than in AD patients.[15] The studies of APT with aeroallergen have shown that patients with dermatitis in their exposed parts have a higher frequency of positive APT.[16] Furthermore, positivity of grass pollen APT is found to be higher in patients with seasonal flare of AD when compared to patients without this history.[17]

Although previous studies showed the overall sensitivity of APT is lower than in the classic tests of IgE-mediated hypersensitivity, skin prick test and specific IgE measurement by radioallergosorbent test (RAST), the specificity is higher in APT.[17-18] From these points of view, classical tests have a value in screening and APT increases the specificity. However, the lack of clinical relevance in APT-positive patients and the discordant result of APT with skin prick test and RAST have made the test controversial. The current indications of APT are[19]

- Suspicion of aeroallergen symptoms without proof of positive specific IgE and/ or a positive skin prick test
- Severe and/ or persistent atopic eczema with unknown trigger
- Multiple IgE sensitizations without proven clinical relevance in patients with eczema

Appropriate allergen-specific avoidance is recommended in patients showing positive APT reactions.[20]

Drug patch testing in drug eruptions

One of the most important problems in the management of drug allergy is to identify the culprit drugs. There are several in vitro and in vivo methods used to reveal the cause of such reactions, which depended upon the pathomechanism of each reaction pattern. The in vivo method for cutaneous adverse drug eruptions which involves a T-cells mediated (delayed-type hypersensitivity) mechanism is patch testing. The clinical forms of drug eruptions in which PT has been reported to be beneficial in the literature include maculopapular eruption, eczematous drug eruption, acute generalized exanthematous pustulosis (AGEP), drug hypersensitivity syndrome, fixed drug eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis, and photosensitive drug reaction.[1,21]

The frequency of positive tests varies from 7.5 to 54%[1,22] which depends on the reaction pattern and the culprit drug. Patch tests are more frequently positive in maculopapular eruptions, fixed-drug eruptions, and AGEP.[1] The most frequent positive drugs are aromatic anticonvulsants.[23] On the other hand, in the case of fixed-drug eruption, the most often positive drugs are non-steroidal anti-inflammatory drugs (NSAIDs).[24] Drug patch testing does not work well with all kinds of drugs. There are many factors which contribute to patch test results in drug eruptions. Firstly, the poor penetration of drugs into the epidermis is one considerable factor. Hence, choosing the appropriate vehicle for each drug such as petrolatum, alcohol, or water is essential. Secondly, the allergen in some cutaneous adverse drug eruptions is a drug metabolite and not the drug itself.[25] Moreover, the concomitant systemic factors, for example, viral infections, are no longer present at the time of PT.[21] Therefore, the rates of false-negative results are quite high. Even if the sensitivity of patch testing in adverse drug eruptions is lower than in allergic contact dermatitis, the positive test results can be very useful to confirm the causative drug.[22]

Drug patch test technique

The proper duration for which to perform patch testing is 6 weeks to 6 months after the onset of drug eruptions.[21] Patch tests are done on the upper back, except for fixed-drug eruptions, in which the yields of positive results are higher on residual pigmentation of the previous fixed-drug lesion.[24] With regard to the drug concentration used in the test, pure substances or commercial preparations of allergen should be tested at concentrations up to 10%. However, the powder obtained from tablets or capsule should be tested at concentration up to 30% in both petrolatum and water. In the case of liquid preparations, 30% dilution in water should be used.[21]

Cosmetic testing

When new cosmetic products are launched into the market, the ingredients and the finished products need to pass irritation testing to confirm that they are safe and have no potential side effects. The animal testing of cosmetic products has been banned since the year 2000. In addition, in vitro testing for acute chemical skin irritation lacks validation[26], so that human testing is required.

COLIPA, the European Cosmetic, Toiletry and Perfumery Association, developed the guidelines for skin compatibility testing. The definition of skin compatibility is the absence of skin irritation under normal usage. An example of the testing is the 24/48 hour single application closed patch test under occlusion or semi-occlusion.[27] The results are read at 1 hour, 24 and 48 hours after patch test removal. The purpose of this method is to assess one or more materials simultaneously in the same individual.

Patch testing methodology

Patch testing should be performed on normal skin to avoid false positive reactions. Test sites have to be clear of treatment with topical corticosteroids because of false-negative reactions. Testing a patient on oral corticosteroids doses ≥ 20 mg of prednisone may miss important allergies. Interpretation of patch test results in patients treated with corticosteroids needs great caution. Repeat patch testing after discontinuation of corticosteroid treatment can be useful when in doubt.[3]

Instruments

To perform patch testing, we need a chamber filled with a proper concentration of allergens. There are multiple models of the chambers from several companies. The most popular one is the Finn Chamber® (SmartPractice, U.S.A); a round aluminum patch test device. (Fig.1) The 8 mm inner diameter provides a 50 mm^2 area and about

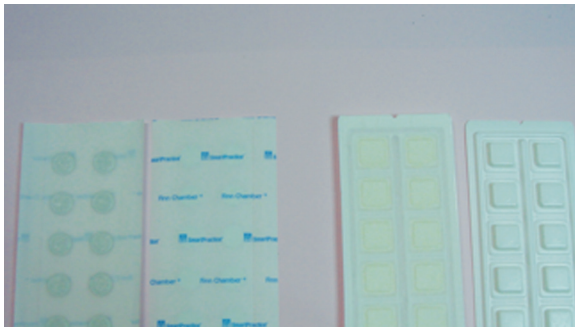

Fig 1. IQ and Finn chamber.

20 µl volume.[28] The strips of 10 chambers are practical when testing with a batch of allergens, for example, with baseline series.[3]

The other type of chamber that is available in Thailand is IQ chambers™ (Chemotechnique Diagnostic, Sweden); this is made of additive-free polyethylene plastic on a hypoallergenic acrylic-based nonwoven adhesive tape. (Fig 1) The volume of the chamber is 65 µl (81 mm^2).[1] It is more expensive than the Finn chamber® but the prepared unit can be stored in a plastic bag in a refrigerator and may be kept for a few days.[29]

Allergens

Standardized allergens should be used for patch testing to avoid irritation, avoid false positive reactions and support comparison with other patch test centers. (Fig.2) Standard patch test allergens are available on the market by several suppliers, e.g. TrolabPatch Test Allergens, Germany, Chemotechnique Diagnostics, Sweden and allerg EAZE/ SmartPractice Canada.[3]

The allergens are considered chemically pure. The majority of allergens of the standard and/ or additional series are dispersed in white petrolatum, as it is the purest inert vehicle. Some allergens cannot be dispersed in petrolatum due to their chemical instability, therefore water, acetone, ethanol 70% or olive oil is used to dissolve those allergens.[3] Petrolatum-based commercial test preparations can be applied directly into the ordinary test chambers, e.g. 8 mm. Finn chamber® with an optimal dose of 20 mg.[30] Liquid test preparations are preferably applied onto the filter paper disks with an exact dosing of 15 µl.

Fig 2. Commercially available allergen series.

Series

The mainstay series is a standard series or baseline series. European baseline series and International standard series are commercially available on the market (Table1), although, some countries have developed their own standard series to suit patients' sensitized pattern in those geographical areas.[6] These series are comprised of basic daily exposed allergens, e.g. common metal, perfume, preservatives and rubber.[31]

In the ready-to-use patch test system, all necessary materials are prepared in advance. TRUE Test is the well-known system for this kind of test, available with 29 allergens of baseline series at present, (Mekos, www.mekos.dk). The doctor must balance between the reliability, simplicity, and costs of the ready-to-use system and those of the original systems.[1]

Tests with non-commercial substances

Unknown substances or products should never be applied to human skin as complications may occur: scarring, necrosis, keloids, pigmentation, depigmentation, systemic effects following percutaneous absorption, and many other complications. If it really needs to be tested, the doctor requires a safety data sheet for each product and has to search references for the proper concentration and vehicle. For most products with intended use on normal or damaged skin (cosmetics, skin care products, soap, shampoos, detergents, topical medicaments, etc.), open tests and Use tests probably give enough information for proving the cause of the patient's dermatitis. However, there is a well-known recommendation to patch test the patients with their own products when cosmetic allergic contact dermatitis is suspected[32] and suggestions on concentrations and vehicles can be found in textbooks.[33]

Performing patch test

The correct application of patch test units onto the skin is a necessity to ensure the best reading and interpretation of patch test results. The preferred site is the upper back and, for a small number of allergens, the outer aspect of the upper arm is also acceptable. One must avoid

TABLE 1. Examples of commercially available screening series.[31]

Bakery Series
Corticosteroid Series
Cosmetic Series
Cutaneous Adverse Drug Reaction Series
Dental Screening
Epoxy Series
Fragrance Series
Hairdressing Series
Isocyanate Series
Leg Ulcer Series
Medicament Series
Metal Series
Acrylate Series
Oil & Cooling Fluid Series
Photographic Chemicals Series
Plant Series
Plastics & Glues Series
Rubber Additives Series
Scandinavian Photo Patch
Shoe Series
Sunscreen Series
Textile Colors & Finish

TABLE 2. Reading of patch test reactions according to ICDRG.[2]

Symbol	Interpretation
?+	Doubtful reaction, faint erythema only
+	Weak positive reaction, erythema, infiltration, possible papules
++	Strong positive reaction, eryhtema, infiltration, papules and vesicles
+++	Extreme positive reaction, intense erythema, infiltration and bullous reaction
-	Negative reaction
IR	Irritant reactions
NT	Not tested

applying patch tests on skin lesions e.g. naevi, seborrhoeic keratoses or tattoo because of the difficulty of reading them. Firstly, degreasing by gentle treatment with ethanol or other mild solvents is recommended in clinics in tropical areas like ours. The solvent must evaporate before the test strips are applied. Then the allergens strips are placed on unaffected skin (Day0), such as the upper back for 2 days, and the reactions are read on Day2, Day3, Day4 or/and D7, according to the guidelines of the International Contact Dermatitis Research Group (ICDRG) (Table 2).[2]

Interpreting of Patch test

Typically, a patch test is read 15–30 minutes after the removal of the occlusive strips to allow the transient erythema caused by the occlusive effects of allergens and plasters to subside and to avoid false-positive reaction.[2] Some allergens, especially corticosteroids, are "late reactors" for which positive reactions show on Day5 or later. The scoring system of patch testing is shown in Table 2.[2]

Clinical Relevance

The positive patch test results need to be evaluated as to whether or not the allergy is relevant to a patient's lesion. The reactions can be either primary cause or aggravating factor relevant to their present dermatitis, past dermatitis or not relevant.[2] Relevance can be considered possible, probable or certain. If a patient contacts with the material known to contain the allergen that gave a positive patch test reaction and has skin lesions, it is "possible" relevance. If a chemical component of the suspected material can be verified as the allergen, it is "probable" relevance. However, if the Use test of that material can cause dermatitis at the site of contact, then relevance is "certain".[2]

Irritation

Irritant reactions are not uncommon in practice. This is due to (i) the nature of tested substances, (ii) a too-high concentration of some allergens, above the threshold of irritation. The clinical signs of irritant patch test reactions are varied with regard to the nature and/or concentration of irritants, e.g. sharp well-delineated margins erythema, purpuric reaction, "Soap or shampoo effect" reactions red shiny and wrinkled), bullous reaction, pustular reaction or necrotic reaction.[3]

False positive

False-positive patch test reactions could be due to;[3]

- Too high a test concentration for a defined allergen
- Contaminated test substance
- Solvent is irritant
- Excess test preparation applied
- The test substance, usually as crystals, is unevenly dispersed in the vehicle.
- Current or recent dermatitis at the test site or distant skin sites
- Pressure effects of tapes, mechanical irritation of solid test materials and garments
- Adhesive tape reactions
- The patch itself has caused reactions

False negative

False-negative patch test reactions could be due to;[3]

- Insufficient penetration of the allergen, i.e., too low a test concentration, the test substance is not released from the vehicle, insufficient amount of test preparation, insufficient occlusion, duration of contact too short, or wrong site tested
- The reading is made too early, e.g., neomycin and corticosteroids are known to give delayed reactions
- The test site has been treated with corticosteroids or irradiated with ultraviolet lights
- Systemic treatment with corticosteroids or immunomodulators
- Allergen is not in active form or is degraded

Adverse reactions of patch tests

Patch testing may have possible adverse reactions such as active sensitization, flare of existing dermatitis, pigmentation and scars. Conversely, the greater risk is "negligence" in performing patch testing in the dermatitis patients and allowing these patients to experience repeated attacks of preventable contact dermatitis.[2]

Value of patch testing

Patch testing is a time consuming, inconvenient process that needs multiple patient visits (3-4 visits), and a great effort by a patient in the avoidance of identified allergens. Nevertheless, it was proven that patch tested-patients feel satisfied with the process of the test[34] and the test benefits which led to improved quality of life.[35] There are multiple factors affecting patients' awareness of the benefits of the test such as level of patient education and age, according to our study performed at the Siriraj contact dermatitis clinic.[36]

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