

Allergic contact dermatitis due to phenylephrine hydrochloride, with an unusual patch test reaction

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2-day (2-D) closed patch tests are often used in daily clinical practice and useful for evaluating the cause of allergic contact dermatitis. However, even when 2-D closed patch tests at appropriate concentrations are performed for suspected allergic contact dermatitis based on clinical findings, positive reactions are not always obtained. Therefore, although the use of the allergen again induces similar symptoms, a definite diagnosis cannot be made in some cases. We report a case of allergic contact dermatitis due to phenylephrine hydrochloride in eyedrops, with an unusual patch test reaction. Although the results of the routine 2-D closed patch test were negative, a definite diagnosis could be made by closed scratch–patch test. In addition, long-lasting allergic patch test reactions were observed at the positive scratch–patch test site for about 3 months. We speculated that these unusual results on patch testing in our case were associated with the degree of percutaneous absorption of causative agents. Therefore, even when 2-D closed patch tests are negative, scratch–patch tests may be indicated for patients in whom clinical symptoms continue strongly to suggest contact dermatitis.

Key words: long-lasting allergic patch test reactions; patch testing technique; phenylephrine hydrochloride; scratch–patch test; unusual patch test reaction. © Blackwell Munksgaard, 2003.

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Phenylephrine hydrochloride is a sympathomimetic drug with predominantly α_1 receptor-stimulating properties and has negligible action on β receptors in the heart. It has a molecular weight of 203.67 and is freely soluble in water and ethanol but only slightly soluble in ether. Due to these properties, it is widely used not only as a mydriatic agent in ophthalmology but also as a drug that increases blood pressure, removes hyperaemia in the nasal mucosa and treats paroxysmal atrial tachycardia. When it is used as a mydriatic agent, it has a well-known sensitizing activity (1–4); two cases of long-lasting allergic patch test reaction (LLAPTR) to phenylephrine hydrochloride have also been reported (5, 6).

We report a case of allergic contact dermatitis due to phenylephrine hydrochloride in eyedrops, with an unusual patch test reaction as part of the process of definite diagnosis.

Case Report

A 70-year-old man with diabetes mellitus for 10 years had previously undergone intraocular examination uneventfully using mydriatic eyedrops. The name of the mydriatic eyedrops used

in that examination was unknown. While undergoing screening for diabetic retinopathy, mydriasis was induced with Neosynesis[®] 5% eye solution (containing 5% phenylephrine hydrochloride). A few hours after eyedrop instillation, symptoms of conjunctivitis and eruptions around eyes, accompanied by itching, developed but were improved by prescribed ophthalmic eyedrops and corticosteroid ointment. After 2 months, mydriasis was induced again with Neosynesis[®] 5% eye solution, and lacrimation and conjunctival hyperaemia developed immediately after instillation. An eruption around the eyes, accompanied by itching, developed after about 12 h. He came to our Dermatological department for investigation of contact dermatitis induced by the eyedrops.

At the initial consultation, erythema and swelling in both eyes were observed. As contact dermatitis due to eyedrops, particularly phenylephrine hydrochloride, was suspected, 2-D closed patch testing was performed.

First patch test session

Patch tests were performed with the Japanese standard series and 22 different eyedrops, including

Table 1. The results of the second patch test session

Vehicle/concentration	Routine 2-D closed patch test			Stripping 2-D closed patch test			Scratch-2-D closed patch test		
	D2	D3	D7	D2	D3	D7	D2	D3	D7
Phenylephrine hydrochloride									
5% pet.	–	–	–	–	–	–	++	++	++
2% pet.	–	–	–	–	–	–	++	++	++
1% pet.	–	–	–	–	–	–	+	+	+
0.5% pet.	–	–	–	–	–	–	+	+	+
0.1% pet.	–	–	–	–	–	–	+	+	+
Ethylenediaminetetraacetic acid (1% pet.)	–	–	–	–	–	–	–	–	–
Trisodium citrate (1% pet.)	–	–	–	–	–	–	–	–	–
Boric acid (3% pet.)	–	–	–	–	–	–	–	–	–
Chlorobutanol (5% pet.)	–	–	–	–	–	–	–	–	–
Sodium bisulfate (10% pet.)	–	–	–	–	–	–	–	–	–
Neosynesis [®] 5% eye solution as is	–	–	–	–	?+	?+	++	++	++
White pet. as is	–	–	–	–	–	–	–	–	–

not only Neosynesis[®] 5% eye solution but also Mydrin[®] P that contains 0.5% phenylephrine

hydrochloride, both of which are used in Fujita Health University Hospital, using Finn Chambers[®] on Scanpor[®] tape (Epitest, Tuusula, Finland) applied to the back. The test patches were removed after D2, and readings were taken at D2 and D3, according to the recommendations of the International Contact Dermatitis Research Group (7). In addition, readings were also taken at D7 to detect any late-phase reactions. The results of closed patch testing were all negative.

Subsequent progress

We reported to the ophthalmologist that allergic contact dermatitis due to Neosynesis[®] 5% eye solution remained clinically suspected, although not yet confirmed. After 2 weeks, the ophthalmologist induced mydriasis again with Neosynesis[®] 5% eye solution for fluorescein angiography (FAG). Immediately after eyedrop instillation, lacrimation and conjunctival hyperaemia developed at the same sites as previously described. In addition, swelling and inflammation of the eyelids developed after about 12 h. The clinical symptoms improved after oral administration of β -methasone/D-chlorpheniramine maleate and topical application of fradiomycin sulfate methylprednisolone for 3 days. 2 days after FAG, he noticed a pruritic eruption on the back and visited our dermatological department 3 days after the development of eruptions. Comparison with photos from the previous patch tests showed that an eruption, accompanied by itching, had developed in the test site area where Neosynesis[®] 5% eye solution had previously been applied.

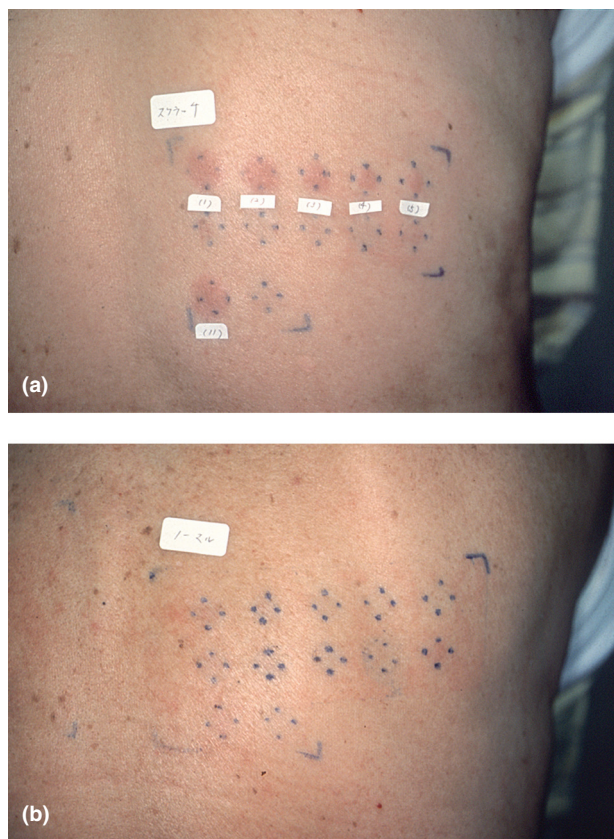


Fig. 1. D3 of the second closed patch test on the back. (a) Positive reaction is elicited at the sites of various concentrations of phenylephrine hydrochloride and eye solution using the 2-D closed scratch-patch test (1. 5%, 2. 2%, 3. 1%, 4. 0.5%, 5. 0.1%, 11 Neosynesis[®] 5% eye solution). (b) No reaction is elicited with the same concentrations of phenylephrine hydrochloride using the routine 2-D closed patch test.

Second patch test session

A second patch test session was performed by the same method as that of the first patch test session. This time, the test was performed with not only Neosynesis[®] 5% eye solution but also its components. As a positive reaction could not previously be elicited by the routine method, the following 3 types of closed patch tests were performed: (i) closed scratch-patch test, (ii) closed, stripped patch test (stripping performed 10 times using Micropore[®]) and (iii) closed patch test (routine method). The results are summarized in Table 1. Scratch-patch tests were positive for Neosynesis[®] 5% eye solution and at all concentrations (0.1–5%) of phenylephrine hydrochloride (Fig. 1a). A positive reaction could not be elicited by the routine method (Fig. 1b). 5 healthy controls were negative. Positive reactions to the second patch test, where Neosynesis[®] 5% eye solution and phenylephrine hydrochloride (0.1–5%) were applied, persisted for 3 months.

Discussion

We describe a case of allergic contact dermatitis due to eyedrops containing 5% phenylephrine hydrochloride with an unusual patch test reaction.

2-D closed patch testing is the 'gold standard' confirmatory test in clinical practice for allergic contact dermatitis. In general, when contact dermatitis due to eyedrops is suspected, 2-D closed patch testing is performed with the eyedrops as is. However, even though allergic contact dermatitis due to eye drops is strongly suspected based on clinical symptoms, closed patch tests are sometimes negative, and the subsequent clinical use of the eyedrop can produce recurrences.

Studies have suggested that: (i) eyelid skin is thinner than that on the back as the routine site of closed patch tests (8) and (ii) drugs are percutaneously absorbed more readily on the eyelids than on the back due to frequent barrier damage in the corneal layer of the eyelids due to rubbing or pressing (9). In other words, it is possible that closed patch tests are negative due to the small amount of allergen percutaneously absorbed. In addition to (i) and (ii), the amount of percutaneous absorption of phenylephrine hydrochloride is small in normal skin due to its high solubility in water. In our case, similar reasons can be considered for the absence of positive reactions to 2-D closed patch tests with Neosynesis[®] 5% eye solution and phenylephrine hydrochloride, because 2-D scratch-patch tests were positive. Another possibility is too low a concentration of

the patch test agents (10). However, this is unlikely, because closed patch tests were performed according to previous reports.

We conclude that the degree of cutaneous absorption of the causative agent was so low during the 2-D closed patch tests that delayed-type allergic reactions could not occur. After the second eyedrop instillation, the drug absorbed via the eyelid skin and mucosa was transferred from the blood to the patch test area, resulting in a higher drug concentration. On the other hand, we did not observe a flare-up reaction at the Mydrin[®] P patch testing site. We think that the reason is the concentration of phenylephrine hydrochloride in Mydrin[®] P being only 1/10 of that in Neosynesis[®] 5% eye solution, and that therefore Mydrin[®] P may not have reached the threshold concentration to elicit a flare-up reaction.

A LLAPTR is, by definition, one in which the clinical signs of palpable erythema are still present at the site of a positive allergic patch test reaction 2 weeks or more after application of the allergen. Gold salts and nickel have both been reported to induce LLAPTR (11, 12), but only 2 previous cases of LLAPTR due to phenylephrine hydrochloride have been reported. In our patient, LLAPTR was observed for 3 months at sites positive to scratch-patch tests. However, the mechanism of development of LLAPTR has not been clarified, and further studies are necessary.

In summary, we observed a case of allergic contact dermatitis due to eyedrops, with an unusual patch test reaction that confirmed a causal relationship in suspected allergic contact dermatitis due to eyedrops. We recommend that closed scratch-patch testing may be necessary to confirm the diagnosis, when 2-D closed patch testing is negative.

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