

Single doses of local betamethasone do not suppress allergic patch test reactions to nickel sulfate

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Topical corticosteroids are usually banned on test areas prior to patch testing. The previous literature on the effect of topical corticosteroids is conflicting. Patients allergic to nickel sulfate were patch tested on 4 sites with nickel on day (D) 0. Intracutaneous betamethasone was injected to test sites on D–1, D0 and D1. NaCl injection on D–1 was control. The patch test reactions were evaluated clinically and with laser Doppler. There were no differences in patch test reaction intensities on sites treated with intracutaneous betamethasone as compared to control. A single local dose of potent corticosteroid does not suppress allergic patch reactions to nickel. The current practice of avoiding topical corticosteroid use prior to patch testing should be re-evaluated.

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Topical corticosteroids are widely used in the treatment of dermatitis and other inflammatory skin diseases. It is generally believed that topical corticosteroids may suppress positive patch test reactions, and consequently patients are usually advised not to use topical corticosteroids on test areas before and during patch testing. If the patient's eczema is widespread and active, it might not be possible to avoid corticosteroid treatment even for 1 week. The aim of our study was to investigate the effect of local corticosteroid treatment on patch test responses.

Patients and Methods

The study was accepted by the ethical committee of Skin and Allergy Hospital, Helsinki University Central Hospital. Written consent to join the study was obtained from 10 patients. These patients had previously been documented by patch testing to have contact allergy to nickel, but not to topical corticosteroids. Patch test chambers with inner diameter of 7 mm (small Finn Chamber[®], Epitest, Tuusula, Finland) containing nickel sulfate [5% in petrolatum (pet.), Epikon, Helsinki, Finland] were applied to 2 test sites on the inner parts of both lower arms, a total of 4 patch tests. Betamethasone solution (0.1 ml, Betapred 4 mg/ml, Glaxo-Wellcome, London, UK) was injected intracutaneously, 1 injection each test site, 1 day before

(D–1), on same day (D0) and 1 day after (D1) nickel patch test application. Saline solution (0.1 ml, 9 mg/ml) was injected into the 4th test site (positive control site) 1 day before patch test application (D–1). The order of the betamethasone injections was randomized for each patient. Each injection created a transient oedema on site of application with a diameter of at least 10 mm. The patches were removed on D2 (48 h after application) and readings were made on D2, D5 and D7. The reactions were scored according to the International Contact Dermatitis Research Group criteria (1). All readings were recorded by a single observer who had no knowledge of which test sites had been injected with betamethasone. Patch test reactivity was also measured using laser Doppler perfusion imaging (Periflux PF3 laser Doppler perfusion monitor, Perimed, Stockholm, Sweden) by another single observer without knowledge of the order of the betamethasone and saline solution injections into test sites. Finally, betamethasone-influenced patch test responses were compared to the positive control reaction, separately for each patient. Statistical differences were evaluated by unpaired Student's *t*-test.

Results

The test results of each patient are described in Table 1. They are summarized in Table 2. A total

Table 1. Patch test results of 10 patients studied

	NaCl	B - 1	B0	B + 1
Patient 1				
D2	-	-	-	-
D5	+	+	?+	-
D7	+	+	?+	-
Patient 2				
D2	+	++	+	+
D5	++	++	++	++
D7	++	++	++	++
Patient 3				
D2	-	+	+	?+
D5	+	+	++	+
D7	+	+	+	+
Patient 4				
D2	-	-	-	-
D5	+	+	+	+
D7	+	++	+	+
Patient 5				
D2	++	+	++	+
D5	++	++	++	++
D7	++	++	++	++
Patient 6				
D2	?+	?+	-	-
D5	+	+	-	+
D7	+	+	?+	+
Patient 7				
D2	+	+	+	+
D5	+	++	++	++
D7	+	++	++	++
Patient 8				
D2	++	+	?+	+
D5	++	++	+	++
D7	+	?+	+	+
Patient 9				
D2	-	-	-	-
D5	?+	?+	+	+
D7	+	+	++	++
Patient 10				
D2	+	?+	?+	?+
D5	+	+	+	+
D7	+	+	+	+

Patients were either treated with NaCl solution injections 1 day before patch applications (NaCl), with betamethasone injections 1 day before patch applications (B-1), with betamethasone on same day as patch applications (B0) and with betamethasone 1 day after patch applications (B + 1). A total of 4 nickel sulfate patch tests were done for each patient, and patches were placed on skin for 2 days. The test results were read on day of patch removals (D2), 3 days after patch removals (D5) and 5 days after patch removals (D7).

of 40 patch tests were placed on the 10 subjects (30 betamethasone-treated test sites and 10 control sites). The test response in 18 test sites showed no difference in comparison to the control. The other 12 test sites showed a difference of 1 grade. 4 of the test sites showed a weaker reaction and 6 a stronger reaction than the control site. The test response would have been scored negative (-) or doubtful (?+) in 3 (3/30, 10% of all) test sites, 2 of which were located in the same patient (betamethasone injected on D0 and D1, respectively). No negative test

Table 2. The effect of betamethasone injections to test responses, as compared to control (NaCl) injections in 10 patients as assessed by test reactions at day 5 (3 days after patch removals)

	Injection time		
	Day -1	Day 0	Day 1
Stronger reaction	1/10	3/10	2/10
Weaker reaction	0/10	3/10	1/10
Equal reaction	7/10	4/10	7/10

Day -1 is 1 day before patch applications, day 0 is the day of patch applications, and day 1 is 1 day after patch applications. Results are expressed as number of patients/total number of patients.

responses were observed in any of the 10 test sites where betamethasone was injected on D-1.

Laser Doppler perfusion values correlated well with the grade of patch test reactivity. In general, the highest values were recorded on D2 and D5. Clinically, the reaction was strongest on D5 and D7. Data are presented in Figs 1-3. There were no significant differences between the betamethasone-treated test sites and the NaCl-treated control sites. The *P*-values at D2 were 0.452 (NaCl versus B - 1), 0.759 (NaCl versus B0) and 0.460 (NaCl versus B + 1). The *P*-values at D5 were 0.675 (NaCl versus B - 1), 0.547 (NaCl versus B0) and 0.790 (NaCl versus B + 1).

Discussion

Local penetration of corticosteroids through normal skin can be negligible as compared to eczematous skin (2). Therefore, for example,

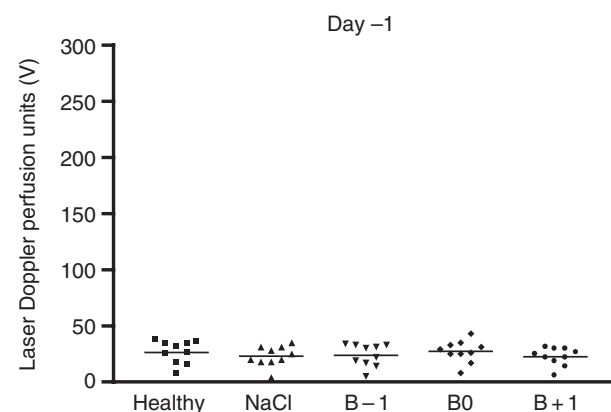


Fig. 1. Laser Doppler results obtained 1 day before application of nickel sulfate patches (day -1); the measurements were done before interventions (injections) done on same day. Healthy is untreated skin, NaCl is skin area treated with control, B - 1 is skin area treated with betamethasone 1 day before patch application, B0 is skin area treated with betamethasone on same day as patch application, and B + 1 is skin area treated with betamethasone 1 day after patch application.

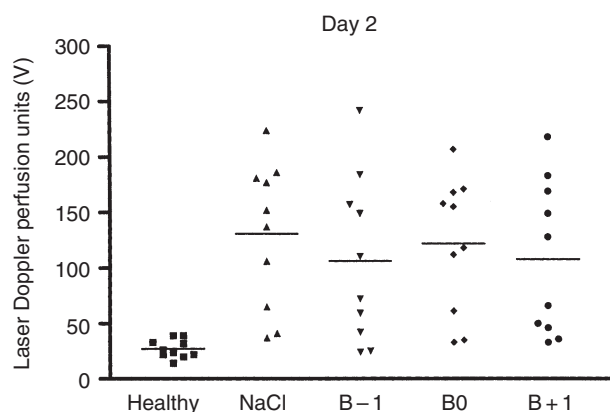


Fig. 2. Laser Doppler results obtained after removal of nickel sulfate patches (day 2). For more details see Fig. 1.

contact allergy to corticosteroids is often more easily diagnosed by intracutaneous administration of the test substance, which ensures the penetration of the test substance into the skin, than with patch tests (3). We chose intracutaneous injections instead of epicutaneous application to make sure that the drug reached target skin tissue. Although the possibility exists that local corticosteroids have to cross stratum corneum by themselves to become active, it is unlikely to be so, as systemic corticosteroids are also effective in inflammatory skin diseases. It may be possible that intracutaneous application could have less effect on epidermal cells, including keratinocytes and Langerhans' cells crucial for initiation of allergic contact dermatitis, than epicutaneous application. Although this is a possibility, intracutaneously injected drugs should reach all water-rich phases of skin, i.e. all epidermis, except stratum corneum, and dermis, without difficulty. Although this is the case, it can be that slow diffusion of corticosteroids from the stratum corneum reservoir (lipid-rich skin phase),

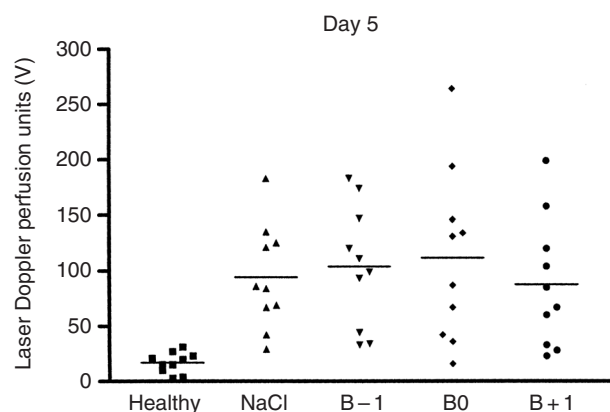


Fig. 3. Laser Doppler results obtained 3 days after removal of patches (day 5). For more details see Fig. 1.

created by topical application, to the underlying water-rich skin phase may be more effective than single injections.

This study was performed on forearm skin, as opposed to back skin which is more often used in patch tests. This was done because in our hospital, intracutaneous injections of corticosteroids as allergy tests are routinely done on the forearms (4). Although nickel tests are not as well standardized on forearm skin than on back skin, in this study, only 10% of the reactions to nickel would have been scored negative or doubtful. This was no more than what should be expected, as the reproducibility of positive patch test reactions is 56–96% (5, 6).

Studies on the effect of local corticosteroid pretreatment and simultaneous treatment on patch test reactions are rare despite their wide usage. Earlier studies have, however, suggested that topical corticosteroid pretreatment might suppress patch test reactions. Pretreatment with betamethasone valerate applied under occlusion prevented the sensitization phase of contact allergy (7). Fisher and colleagues (8) described 6 patients who had negative patch tests to Mycolog cream but positive patch tests to ethylenediamine; they concluded that the triamcinolone acetonide in Mycolog cream suppressed the elicitation of contact allergy to the ethylenediamine component. In this case, the corticosteroid remained on the skin with the allergen throughout the testing procedure. Patients were patch tested with ethylenediamine HCl 1% pet. The ethylenediamine concentration of Mycolog cream is not mentioned and might well have been lower than 1%. Clark and Rietschel (9) stated that previously applied intermediate strength topical corticosteroids may diminish patch test responses, although rarely enough to cause false-negative reactions if the corticosteroid administration is stopped prior to testing. In their study, pretreatment of the skin with triamcinolone acetonide ointment caused some false-negative patch test reactions, but so did pretreatment with vehicle alone. It is possible that not the triamcinolone acetonide itself but the vehicle was responsible for the false-negative reactions above, by diminishing penetration of the allergens from the patch test chambers.

Contrasting to studies on corticosteroid pretreatment prior to patch testing, there are several studies of repetitive topical application of corticosteroids on already-formed nickel patch test reactions. These studies show that at least potent corticosteroids suppress the reactions when used repeatedly (10–12). The reason why we saw no effect in this study may be that we used single doses of corticosteroids. Even though

we used a potent corticosteroid betamethasone, the overall pharmacological doses may have been too small to suppress the intense skin inflammation caused by nickel contact allergy. Possibly repeated applications of topical corticosteroids are needed for local efficacy. Besides, corticosteroids are also often clinically applied on large areas, and systemic effect due to percutaneous absorption may have additional suppressive effect on inflammation (2).

Conclusions

In conclusion, we saw no effect of local injections of the potent corticosteroid betamethasone on nickel patch test reactions. The practice of abstaining from topical corticosteroids prior to patch tests should possibly be re-evaluated. Also, the hypothesis that in contact allergy to corticosteroids themselves, the pharmacologic effect of corticosteroids may effectively suppress the patch test reactions to allergenic corticosteroids should be questioned. Further research should be done to obtain dose-response relationships of local corticosteroids for more evidence-based instructions on their use related to patch testing.

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