

# Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel

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A multicentre, randomized, double-blind, crossover study was designed to investigate the effects of prednisone on allergic and irritant patch test reactions. 24 subjects with known allergy to nickel were recruited and patch tested with a nickel sulfate dilution series in aqueous solution, 5% nickel sulfate in petrolatum and 2 dilution series of the irritants nonanoic acid and sodium lauryl sulfate. The subjects were tested  $\times 2$ , both during treatment with prednisone 20 mg oral daily and during placebo treatment. The total number of positive nickel patch test reactions decreased significantly in patients during prednisone treatment. The threshold concentration to elicit a patch test reaction increased and the overall degree of reactivity to nickel sulfate shifted towards weaker reactions. The effect of prednisone treatment on the response to irritants was divergent with both increased and decreased numbers of reactions, although there were no statistically significant differences compared with placebo. It is concluded that oral treatment with prednisone suppresses patch test reactivity to nickel, but not to the irritants tested.

**Key words:** allergic contact dermatitis; corticosteroids; nickel; nonanoic acid; patch test reactivity; placebo; prednisone; sodium lauryl sulfate; suppression. © Blackwell Munksgaard, 2004.

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Oral intake of, as well as topical treatment of test sites with, corticosteroids, antihistamines and immunomodulators is considered to suppress patch test reactivity (1), increasing the risk of false-negative patch test reactions in an allergic patient, who may then be left with his/her allergy(ies) undiscovered. In more recalcitrant cases of contact dermatitis, it is desirable to perform patch testing – even if the patient is still on corticosteroid therapy – to identify the cause and thereby facilitate clearance and avoid relapses. However, the threshold systemic corticosteroid dose that would not significantly reduce patch test reactivity has not been studied in the last 30 years (2–5). A review of earlier papers showed that patch testing was carried out twice, when the patients were on or without oral corticosteroids. The time interval between the test sessions was not regularly stated, and treatments as well as readings were not blinded. Allergens from the standard

series were used in 2 studies (2, 3), and in 1 (5), serial dilutions of a poison oak extract were used. In these studies, diminution and disappearance of test reactions were noted in several cases, but not regularly.

The above-mentioned reports have been interpreted as allowing patch testing patients on oral corticosteroid doses equivalent to 20 mg of prednisone daily or lower without losing the ability to detect important contact allergies. However, in the older experimental studies, the test reactions included were strong (+++), while weak (+) and doubtful (?+) reactions were not evaluated. In 1 study (2), it was stated that the reaction to the strongest concentration (that is usually used for patch testing) was approximately the same before and during cortisone thereby, namely, within a range of one plus.

The results from these past studies create uncertainty about testing patients during

corticosteroid therapy. A placebo-controlled, randomized study was therefore designed to investigate the effect of oral corticosteroids on patch test reactivity in patients hypersensitive to nickel.

## Materials and Methods

### Study design

The study was performed as a multicentre, randomized, double-blind crossover study. Participating clinics were the Department of Medicine, Occupational and Environmental Dermatology, Karolinska Institutet and Stockholm Centre for Public Health, Stockholm, Sweden, the Department of Dermatology, Odense University Hospital, University of Southern Denmark, the Department of Occupational and Environmental Dermatology, Malmö University Hospital, Malmö, Sweden, and the Department of Occupational and Environmental Dermatology, Amersham, England.

Ethical committee approvals and informed consent from participants were obtained. The study was performed from October 2001 to June 2002.

### Subjects

24 subjects, 19 females and 5 males (mean age 37 years), with previously confirmed positive patch tests to nickel sulfate in the standard series were enrolled in the study. The numbers recruited from each of the 4 clinics were as follows: Amersham ( $n = 5$ ), Malmö ( $n = 5$ ), Odense ( $n = 5$ ) and Stockholm ( $n = 9$ ).

### Test substances

Nickel sulfate was used as the allergen and sodium lauryl sulfate (SLS) (6) and nonanoic acid (NAA) (7) as the irritants.

Nickel sulfate ( $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ ) (Agros Organics, Geel, Belgium, 99% purity) was dissolved in water to 12.5% w/v. This stock solution was then further diluted in 10 steps to 0.0032% w/v (8). The nickel dilution series was supplied from the Department of Occupational and Environmental Dermatology in Malmö.

Nickel sulfate 5.0% w/v in petrolatum (pet.) (from the standard series) was also used in Odense, Malmö and Stockholm.

SLS (Sigma-Aldrich Co, Steinheim, Germany, purity >99%) was dissolved in water to 2% w/v and then diluted to 1.0, 0.5 and 0.25% in Stockholm, Malmö and Odense. In Odense, the stock solution was further diluted in 3 steps to 0.03125%. In Amersham, the concentration of the SLS stock solution was 5.0% in water. This stock solution was then further diluted in 7 steps to 0.039%.

For NAA (Sigma-Aldrich Co, purity >97%), isopropanol was used as vehicle. The stock solution (80.0% w/v) was then further diluted 3 times, each by a factor of 2–10.0% in Odense, Malmö, Stockholm and Amersham. In Odense, the solution was further diluted down to 5.0%.

### Oral prednisone and placebo

All 24 subjects were supplied with capsules of prednisone and placebo from the Apoteket Production and Laboratories (APL, Stockholm, Sweden). The capsules contained either prednisone 5 mg and lactose 150 mg (active substance) or lactose 150 mg (placebo). The codes were provided in a sealed envelope. The test subjects were randomized in 2 cohorts. Cohort 1 was given prednisone for the 1st patch testing session followed by placebo for the 2nd patch testing session. Cohort 2 had placebo for the 1st patch testing followed by prednisone for the 2nd. Both cohorts started their treatment 2 days prior to patch testing. The dose of prednisone used was 20 mg,  $\times 1$  a day, for 10 days and then tapered off over a week. Placebo was administered in the same way.

The level of B-glucose was measured before and during the test periods.

### Patch testing

Finn Chambers<sup>®</sup> (8 mm Ø, Epitest Oy, Tuusula, Finland) (9) on Scanpor<sup>®</sup> tape (Norgesplaster A/S, Vennesla, Norway) were used for the patch tests. The patches were placed at random either on the left or right side of the upper back in the 1st test session. In the 2nd test session, the tests were placed on the contralateral side of the upper back. The interval between the test sessions was 4–8 weeks.

The patches were applied for 2 days, and reading was taken on days 2, 3 and 7 after application in Malmö, Stockholm and Amersham. In Odense, the reading was taken on days 3 and 7.

The evaluation of the nickel patch test reactions was done according to the International Contact Dermatitis Research Group (ICDRG) criteria (1), while the evaluation of irritant reactions to SLS and NAA was scored according to the degree of erythema and erosion, with or without oedema.

### Statistical evaluation

Sign test was used for the analysis of reactivity comparing prednisone versus placebo.

## Results

All 24 subjects completed the study. No side effects related to the prednisone or placebo treatment were reported.

Table 1. Total number of positive test reactions: the sum of reactions at all test concentrations and readings on days 2, 3 and 7

| Test substances                        | Number of subjects | Total number of positive reactions |                         |
|----------------------------------------|--------------------|------------------------------------|-------------------------|
|                                        |                    | On placebo treatment               | On prednisone treatment |
| Nickel dilution series*                | 21                 | 171                                | 63                      |
| Nickel 5% in petrolatum                | 15                 | 36                                 | 27                      |
| Nonanoic acid dilution series*         | 24                 | 106                                | 96                      |
| Sodium lauryl sulfate dilution series† | 24                 | 141                                | 124                     |

\*12.0–0.0032% in aqua.

†For concentrations, see text.

### Nickel dilution series

3 subjects had negative patch test reactions to the nickel dilution series in both arms of the study and were therefore excluded. These subjects also had negative tests with nickel 5% in pet.

The total number of positive reactions to nickel (+, ++, +++ sum of all reactions and all readings) decreased from 171 when given placebo to 63 when given prednisone (Table 1).

When looking at the degree of reactivity to nickel sulfate (number of +, ++, +++ and ?+) the number of +++ reactions decreased and the number of ?+ reactions increased when the subjects were on prednisone treatment (Fig. 1).

The individual reactivity pattern showed a decreased number of reactions in 19 of 21 subjects when on prednisone ( $P < 0.05$ ; Sign test) (Table 2). In only 2 subjects was there an increase in the number of positive reactions when on prednisone.

Figure 2 shows the minimum nickel concentration required to produce a positive patch test reaction. A higher test concentration was needed to elicit a positive test reaction in the subjects when treated with prednisone compared to placebo.

### Nickel 5% in pet.

The standard patch test with nickel was performed in 19 subjects of whom 4 did not react and therefore were excluded from the analysis. The total number of test reactions (sum of all reactions and all readings) was reduced from 36 when given placebo to 27 when given prednisone (Table 1). The strong +++ patch test reactions decreased from 21 when given placebo to 7 when given prednisone (Fig. 3), while + and ?+ reactions increased. Looking at individual reactivity, the strongest patch test reaction (all readings) was decreased in 8 subjects and remained unchanged in 7 ( $P < 0.05$ ) (Table 2). 3 persons tested positive on placebo were tested negative during prednisone treatment.

### Irritants

The total number of patch test reactions to NAA (sum of all concentrations and all readings) was 106 when given placebo compared to 96 when given prednisone (Table 1). In 11 of the 24 subjects, the number of reactions was higher when treated with placebo; in 7, it was higher when on

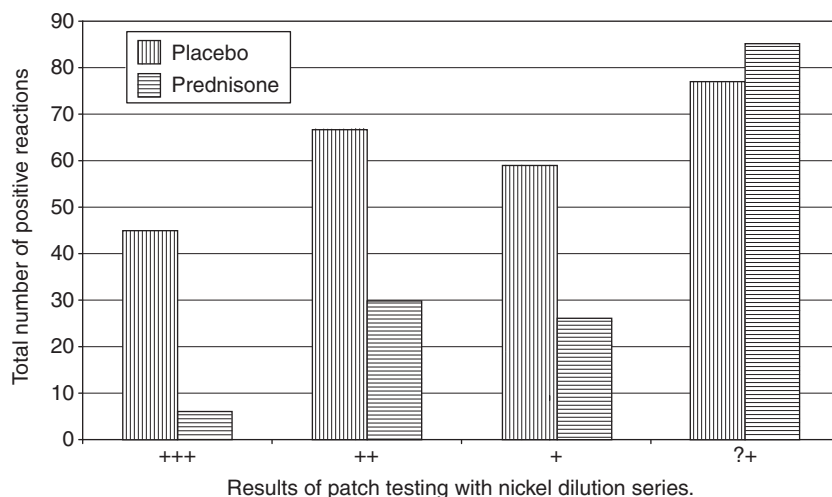


Fig. 1. The total number of test reactions (+, ++, +++ and ?+) to the nickel sulfate dilution series (0.0032–12.5%). The sum of all test concentrations and readings on days 2, 3 and 7.

Table 2. Shift in patch test reactivity in the individual subject comparing testing during prednisone treatment to testing during placebo treatment

|                                                | Nickel dilution series | 5% nickel in petrolatum | Nonanoic acid   | Sodium lauryl sulfate |
|------------------------------------------------|------------------------|-------------------------|-----------------|-----------------------|
| Total number of subjects                       | 21                     | 15                      | 24              | 24                    |
| More reactivity on placebo than on prednisone  | 19                     | 8                       | 11              | 11                    |
| More reactivity on prednisone than on placebo  | 2                      | 0                       | 7               | 9                     |
| No change                                      | 0                      | 7                       | 6               | 4                     |
| Sign test; placebo versus prednisone treatment | $P < 0.05$             | $P < 0.05$              | Not significant | Not significant       |

prednisone; and in 6 subjects, the number of reactions was equal on both test occasions (Table 2). No significant differences in the number or strength of reactions were observed when placebo and prednisone treatments were compared.

The total number of reactions (all concentrations and readings) to SLS was 141 when given placebo compared to 124 when treated with prednisone (Table 1). In 11 of the 24 subjects, the number of reactions was higher when treated with placebo; in 9, it was higher when treated with prednisone; and in 4 subjects, the number of reactions was equal on both test occasions (Table 2). No significant difference comparing placebo and prednisone treatment was observed.

### Discussion

Prednisone 20 mg oral daily had a suppressive effect on nickel patch test reactivity. A higher patch test concentration of nickel was required to elicit a test reaction when given prednisone compared to placebo. Stronger nickel patch test reactions shifted towards weaker reactions under the influence of prednisone 20 mg.

The effect of prednisone on irritant patch test reactions was more divergent. The total number of reactions to the irritants applied (SLS and NAA) was higher when given placebo compared to prednisone. However, looking at individual subjects, both increases and decreases in reactivity were found, resulting in a non-significant difference between placebo and prednisone treatment.

The results of the study are compatible with previously published data on differences in skin response to various irritants and allergens. It is well established that the mechanism in the allergic contact reaction differs from the mechanism in the irritant contact reaction in the initial stages following the provocation/application of allergens or irritants (10–12). For chemically different irritants, it has been demonstrated that the epidermal and dermal response differ depending on the properties of the irritants tested. Once the contact reaction is established, the allergic and irritant contact dermatitis responses are very similar with regard to the inflammatory cell response. A patch test can be considered as a biological provocation test and it can be postulated that, if the initial mechanisms of the

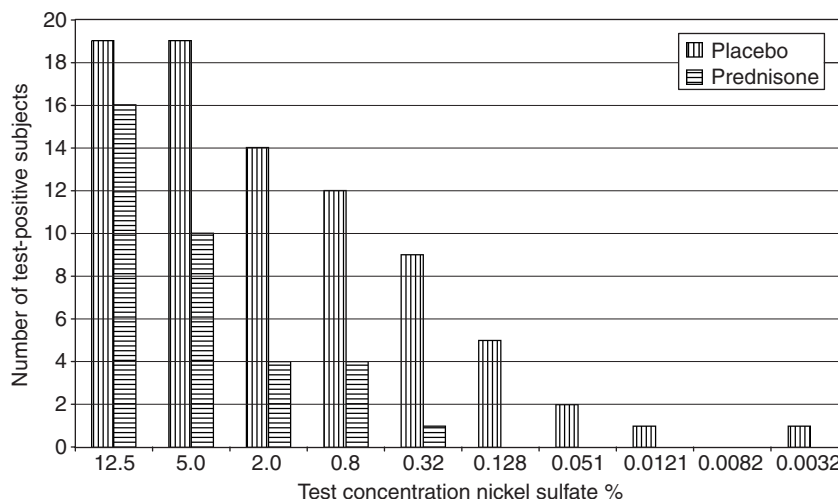


Fig. 2. The number of individuals with positive patch test reactions (+, ++ or +++) for each test concentration on at least 1 of the readings.

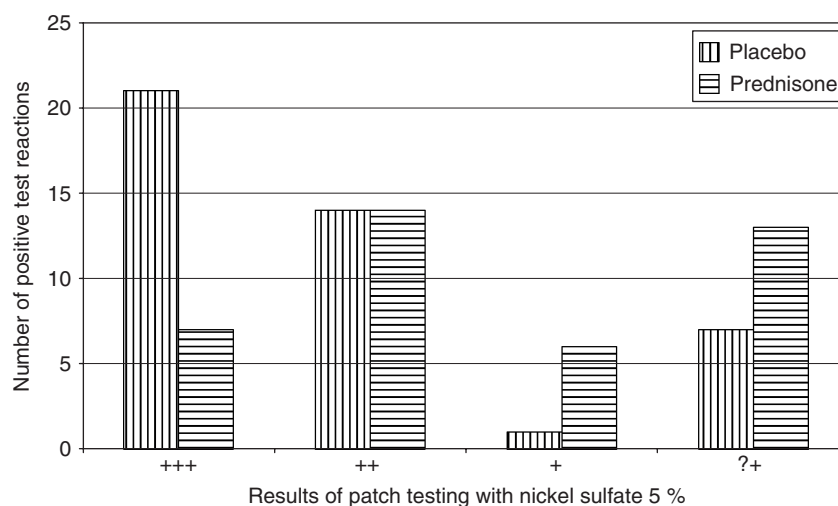


Fig. 3. The total number of patch test reactions to nickel sulfate 5% w/v in petrolatum. The sum of all readings on days 2, 3 and 7. 19 individuals were tested and 4 were negative. The results from the remaining 15 subjects are shown.

reactions differ between allergic and irritant reactions, the response to an anti-inflammatory drug might also differ.

The problems involved in multicentre patch test studies have been reviewed by Andersen (13). The present study protocol was discussed in detail in advance, and the test preparations were prepared from the same stock solutions and distributed to the participating centres. Prednisone and placebo tablets were manufactured by a Swedish pharmaceutical company (APL) and then distributed. Administration of drugs and patch testing were done according to the study protocol.

One particularly weak point in multicentre studies is the reading and scoring of test reactions. However, the participating dermatologists were all very experienced, and it is unlikely that they altered/changed their scoring system within 1–2 months, i.e. between the 2 test occasions. The shift/change in patch test reactivity in an individual test subject is of greater significance than the pattern when comparing clinics. For this investigation, a multicentre study was required in order to recruit sufficient number of subjects for statistical analysis. For reading of the nickel reactions, the ICDRG scale was used (1). However, for the irritant reactions another approach was taken. It has been demonstrated that the clinical appearance of irritant reactions differs between chemically different irritants and the dose of the substance applied (14, 15). Therefore, for NAA and SLS, we noted the individual clinical features and used them to compare the reactivity on the 2 test occasions.

In conclusion, we found that oral treatment with 20 mg of prednisone daily suppresses patch

test reactivity to nickel in sensitized individuals, while there is no statistically significant effect on reactions to the irritants SLS and NAA. This is probably due to differences in the mechanisms initiating the 2 types of contact reactions.

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### References

1. Wahlberg J E. Patch testing. In: *Textbook of Contact Dermatitis*, Rycroft R J G, Menné T, Frosch P J, Lepoittevin J P (eds), 3rd edn. Berlin: Springer, 2001: 437–468.
2. Sulzberger M B, Witten V H, Zimmerman E H. The effects of oral cortisone acetate on patch test reactions to eczematogenous contact allergens. *Acta Derm Venereol Suppl (Stockh)* 1952; 29: 343–352.
3. O'Quinn S E, Isbell K H. Influence of oral prednisone on eczematous patch test reactions. *Arch Dermatol* 1969; 99: 380–389.
4. Feuerman E, Levy A. A study of the effect of prednisone and an antihistamine on patch test reactions. *Br J Dermatol* 1972; 86: 68–71.
5. Condie M W, Adams R M. Influence of oral prednisone on patch-test reactions to Rhus antigen. *Arch Dermatol* 1973; 107: 540–543.
6. Tupker R A, Willis C, Berardesca E, Lee C H, Fartasch M, Agner T, Serup J. Guidelines on sodium lauryl sulfate (SLS) exposure tests. A report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis* 1997; 37: 53–69.
7. Wahlberg J E, Lindberg M. Nonanoic acid – an experimental irritant. *Contact Dermatitis* 2003; 49: 117–123.
8. Hindsén M. Clinical and experimental studies in nickel allergy. *Acta Derm Venereol Suppl (Stockh)* 1999; 204: 1–22.
9. Pirilä V. Chamber test versus patch test for epicutaneous testing. *Contact Dermatitis* 1975; 1: 48–52.
10. Willis C M, Lindberg M. Understanding the irritative reaction. In: *Skin, Hair and Nails: Structure and Function*,

- Lindberg M, Forslind B (eds). New York: Marcel and Decker, 2004: 233–271.
11. Lisby S, Baadsgaard O. Mechanisms in irritant contact dermatitis. In: *Textbook of Contact Dermatitis*, Rycroft R J G, Menné T, Frosch P J, Lepoittevin J P (eds), 3rd edn. Berlin: Springer Verlag, 2001: 91–110.
  12. Rustemeyer T, van Hoogstraten I M W, von Blomberg B M E, Scheper R J. Mechanisms in allergic contact dermatitis. In: *Textbook of Contact Dermatitis*, Rycroft R J G, Menné T, Frosch P J, Lepoittevin J P (eds), 3rd edn. Berlin: Springer Verlag, 2001: 13–58.
  13. Andersen K E. Multicentre patch test studies: are they worth the effort? *Contact Dermatitis* 1998; 38: 222–223.
  14. Reiche L, Willis C M, Wilkinson J D, Shaw S, Lacharriere O. Clinical morphology of sodium lauryl sulfate (SLS) and nonanoic acid (NAA) irritant patch test reactions at 48 h and 96 h in 152 subjects. *Contact Dermatitis* 1998; 39: 240–243.
  15. Willis C M. Variability in responsiveness to irritants: thoughts on possible underlying mechanisms. *Contact Dermatitis* 2002; 47: 267–271.
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