Acta Derm Venereol (Stockh) 1994; 74: 383–385

Nickel Patch Test Reactivity and the Menstrual Cycle

ALLAN E. ROHOLD[1], LARS HALKIER-SØRENSEN[1,2], KLAUS E. ANDERSEN[1] and KRISTIAN THESTRUP-PEDERSEN[2]

Departments of Dermato-Venereology, [1]Odense University Hospital and [2]Aarhus University Hospital, Denmark

Premenstrual exacerbation of allergic contact dermatitis and varying allergic patch test responses have been reported at different points of the period. Using a dilution series of nickel sulphate, we studied the variation in patch test reactivity in nickel allergic women in relation to the menstrual cycle.

Twenty women with regular periods were tested on day 7–10 and on day 20–24. Ten nickel patch tests with different concentrations were applied using the TRUE® test assay, and the threshold concentration of nickel sulphate eliciting an erythematous reaction was determined. Half of the women were tested first on day 7–10 and the other half first on day 20–24.

There was no difference in the degree of patch test reactivity, when the results from day 7–10 and day 20–24 were compared ($p > 0.4$). However, when we compared the patch test results from the first and second test procedure, we found an increased nickel sensitivity at the second patch test ($0.02 < p < 0.05$), suggesting a booster effect from the first patch test procedure.

In conclusion, we could not demonstrate an increased sensitivity to nickel sulphate patch tests premenstrually in 20 nickel allergic women, but we found that elicitation of positive patch tests led to an increased skin reactivity towards the same allergen, when the patients were retested weeks later. ***Key words: contact dermatitis; TRUE® test.***

(Accepted March 3, 1994.)

Acta Derm-Venereol (Stockh) 1994; 74: 383–385.

K. E. Andersen, Department of Dermatology, Odense University Hospital, DK-5000 Odense, Denmark.

Variation in patch test reactivity to nickel sulphate has been reported to be related to the menstrual cycle (1). A study including 8 nickel allergic women showed that 2 of 8 had a more pronounced response in the premenstrual phase compared to the response in the mid-cycle (2). This is in agreement with observations made by some women, who complain of a premenstrual exacerbation of their eczema. Furthermore, premenstrual exacerbation has been reported in patients with atopic dermatitis and other dermatoses (3, 4). Finally, changes have been described in transepidermal water loss and cutaneous blood flow during the menstrual cycle, indicating changes in the permeability barrier function (5, 6). The varying response to patch tests at different times in relation to the menstrual cycle must be seen in the context of the reproducibility of patch test results (7, 8).

The aim of this study was to investigate the patch test reactivity in nickel allergic women at different points of the menstrual cycle by using the TRUE® test assay, which assures accurate dosing of the antigen, high bioavailability and a documented stability (9).

MATERIAL AND METHODS

Patients

Twenty women who had a previously positive nickel sulphate patch test and/or a strong clinical suspicion of nickel allergy completed the study. Their median age was 32 (range 17–44). They all had a regular menstrual cycle varying from 25–32 days. The nickel allergy was of current clinical relevance in 16 of these patients. Informed consent was obtained from all participants. The study was approved by the local ethical committees.

Patch test material

Panels of TRUE-test® patches with nickel sulphate ($NiSO_4$, $6H_2O$) in a hydroxypropyl-cellulose gel were manufactured by Pharmacia, Hillerød, Denmark, and mounted on non-woven textile acrylate tape (Scanpor®, Norgesplaster, Oslo, Norway). Each panel contained 12 patches with 10 different concentrations of nickel sulphate and 2 placebo patches arranged in 2 rows with 6 patches in each. The size of the tape was 5 by 13 cm. The square patches were 0.81 cm^2, and the distance between the patches was 1.1 cm. The nickel sulphate concentrations were 300, 100, 30, 10, 3, 1, 0.3, 0.1, 0.03 and 0.01 $\mu g/cm^2$. The sequence of the nickel content in each patch test was randomized. The nickel sulphate dilution series was placed on the upper back and left for 2 days and read at day 3 after application. The reactions were read according to the usual ranking scale developed by the International Contact Dermatitis Research Group's (ICDRG) (10). The threshold concentration was determined as the lowest concentration giving a +? response (doubtful reaction). The sequence of the various nickel concentrations was unknown to the reader, enabling blind evaluations (11).

Prior to testing patients were free from dermatitis or had slight, chronic dermatitis. The skin on the back was free from dermatitis.

Test procedure

Patch testing was performed 7–10 days and 20–24 days after the first day of a menstrual cycle. A period of 6 weeks was planned between the tests, and half of the patients were to be tested on day 7–10, and the other half on day 20–24.

Statistics

The lowest concentration to which each patient showed a positive (+, ++, +++) or a doubtful (+?) patch test reaction was used for statistical calculations. Wilcoxon's rank sum test was used for matched pairs.

RESULTS

Only one patient gave a clinical history indicating premenstrual exacerbation of eczema. Fourteen patients were tested with the scheduled interval of 6 weeks, and 6 patients were tested 8 to 30 weeks after the first test. This difference in time had no effect on the statistical evaluation of the patch test results.

All 20 participants showed positive reactions to nickel sulphate. There was no significant relationship between the point of the menstrual cycle and the degree of nickel sensitivity inferred from the threshold nickel sulphate patch test concentration ($p > 0{,}4$). The results are given in Fig. 1. Seven women showed reactivity to a lower nickel concentration in their premenstrual period compared to tests in their postmenstrual period, and 11

 ISSN 0001-5555

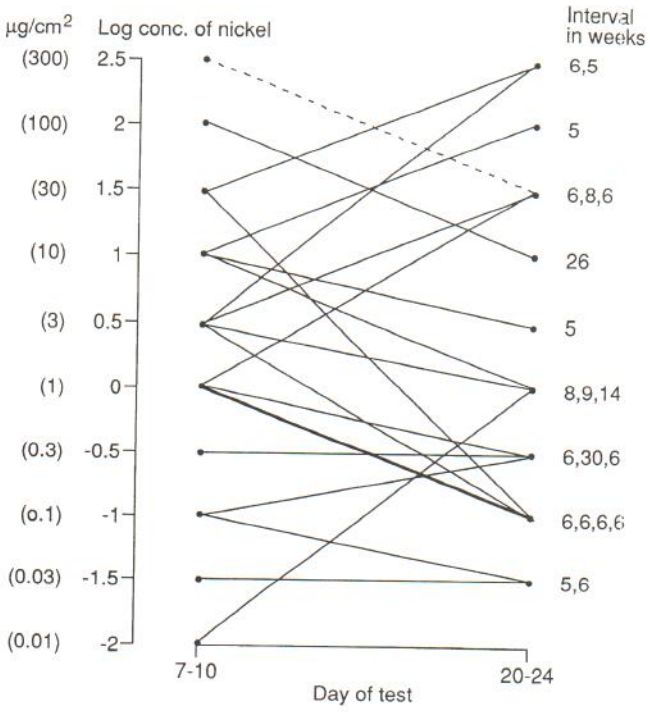

Fig. 1. The lowest concentration (Log_{10}) (µg/cm²) of nickel sulphate is given to which each woman showed a doubtful positive (+?) patch test reaction at day 7–10 and day 20–24 of the menstrual cycle ($n = 20$). There was no significant difference between the threshold concentrations for the 2 points of the menstrual cycle. The *dotted line* represents the patient who showed no reaction at the test in the postmenstrual phase. The time interval between the tests in weeks is given.

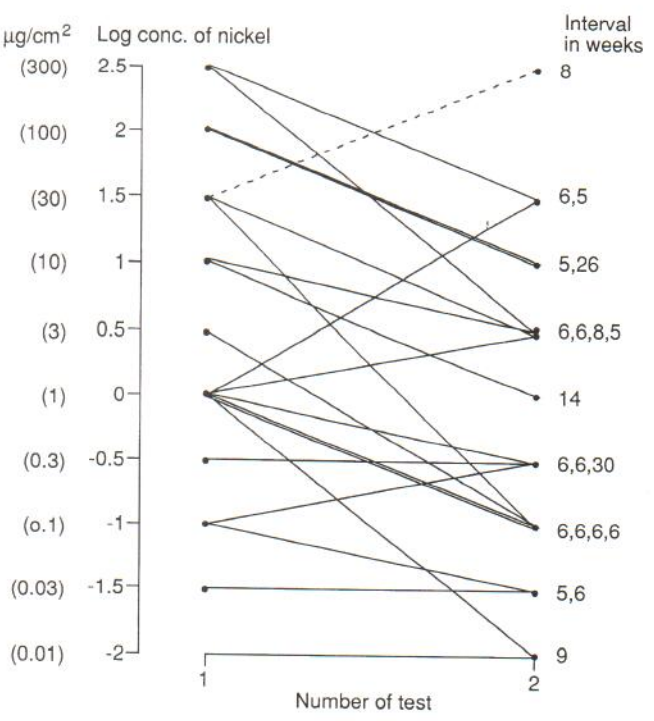

Fig. 2. The lowest concentration (Log_{10}) (µg/cm²) of nickel sulphate is given to which each woman showed a doubtful positive (+?) patch test reaction at the first and second patch test ($n = 20$). There was a significantly higher sensitivity at the second test, suggesting a booster effect of the first patch test ($0.02 < p < 0.05$). The *dotted line* represents the patient who showed no reaction at the test in the postmenstrual phase. The time interval between the tests in weeks is given.

showed reactivity to a higher nickel concentration in their premenstrual period, while 2 showed the same reactivity at the two tests. The median threshold concentration of nickel sulphate was 3 µg/cm² and 1 µg/cm² at day 7–10 and day 20–24, respectively. The lowest concentration to which there was a doubtful (+?) patch test reaction was 0.01 µg/cm². All patients had negative placebo readings. Seven women had their first patch test performed on day 20–24, whereas 13 women had the first test on day 7–10. One patient had a positive patch test in the premenstrual phase with + at a nickel concentration of 30 µg/cm² (first test), but there was no reaction at the patch test in the postmenstrual phase (second test).

When we looked upon the degree of nickel sulphate reactivity in the women in relation to the two patch test procedures, we found a significantly higher degree of sensitivity (lower threshold concentrations) at the second patch test compared to the first test ($0.02 < p < 0.05$). The median threshold concentration of nickel sulphate was 3 µg/cm² and 1 µg/cm² at the first and second patch test, respectively (Fig. 2).

DISCUSSION

Changes in the severity of various diseases are known to occur in relation to the menstrual cycle. Premenstrual exacerbation of asthma has been reported concurrent with a modest fall in peak expiratory flow rate. This is recognized in approximately one third of affected women (12, 13). Among patients with lupus erythematosus about 20% describe premenstrual cutaneous exacerbation (4). A cyclic variation has been shown in the reactivity of female skin following the menstrual cycle by Agner et al. (6). The skin response to an irritant patch test with sodium lauryl sulphate in normal females with a regular menstrual cycle was found statistically increased at day 1 in the menstrual cycle compared to day 9–11. In the study of McLelland & Lawrence (2), 6 of 8 nickel allergic patients had a similar response at both times of the cycle and there was no effect of the order of application of the patches. However, only 8 patients were included. In this study the patch test reactivity to nickel sulphate did not vary with the menstrual cycle. We included 20 nickel-sensitive women based on the history of nickel sensitivity and a previously positive patch test to nickel sulphate. One patient had a positive patch test response at day 20–24, but a negative response at day 7–10. She had earlier complained of a premenstrual exacerbation of her dermatitis. A similar case has been reported previously (1).

When studying patch test reactivity at different points of the menstrual cycle, the investigator should consider the problems with the reproducibility of positive patch test results (14, 15). Gollhausen et al. (14) applied a series of 39 substances to the skin using Finn chambers® and found that 40% of positive reactions were non-reproducible at sequential testing and 44% were non-reproducible at concomitant testing. For nickel sulphate alone, 20% were non-reproducible at sequential testing. However, only one concentration of each allergen was used. We used sequential testing and a 10-step dilution series of nickel sulphate in our study.

Another report showed a better reproducibility of positive reactions using the TRUE® test compared to the Finn chambers® (16). This may be due to a significant variation in the amount of petrolatum material applied from syringes on chamber patches, even with experienced technicians (17). The higher reproducibility of the TRUE® test could be explained by the better surface distribution of the allergen in the vehicle and a better bioavailability. The reproducibility for nickel sulphate alone in the TRUE® test was high, with only 10% non-reproducible.

Andersen et al. (11) retested 9 patients 5–7 months after the first test, and all reacted to nickel sulphate to the same degree at the rechallenge using the TRUE® test. In the present study, patch test reactions were significantly stronger at the second test compared to the first test. This could be explained by a booster effect (18). The clinical implication of this finding needs further studies. It may be advisable not to retest patients with their known allergens too often and within a short time period. A balanced view must be taken. Sometimes it is necessary to reproduce/confirm earlier test results, i.e. in the case of non-standard patch test materials and for legal purposes.

The provocation threshold varies widely among nickel-sensitive individuals. Emmett et al. (19) found a 250-fold variation. The minimal amount of nickel sulphate in petrolatum which produced a positive reaction was 0.94 $\mu g/cm^2$. In our study the minimal amount was 0.01 $\mu g/cm^2$ with a 10.000-fold variation. It is important to be aware of such variations in patch test experiments.

Further studies on the patch test reactivity at different points of the menstrual cycle should be performed to improve our understanding of non-reproducible reactions in women. If women with a history of premenstrual exacerbation are selected, a different result cannot be excluded. However, the fact that 13 of the 20 women were patch-tested first on day 7–10 gives further support to the conclusion that there is no significant increase in the sensitivity premenstrually to a nickel sulphate path test in nickel allergic women. Their second patch test response, i.e. the "boosted" response, appeared simultaneously with the premenstrual phase, where an increased sensitivity was suspected – but not found.

ACKNOWLEDGEMENT

We thank Pharmacia A/S, Hillerød, Denmark, for supplying the nickel sulphate TRUE® test panels.

REFERENCES

1. Alexander S. Patch testing and menstruation. Lancet 1988; ii: 751.
2. McLelland J, Lawrence CM. Premenstrual exacerbation of nickel allergy. Br J Dermatol 1991; 125: 83.
3. Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. Br J Dermatol 1991; 125: 59–61.
4. Yell JA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. Br J Dermatol 1993; 129: 18–22.
5. Harvell J, Hussona-Saeed I, Maibach HI. Changes in transepidermal water loss and cutaneous blood flow during the menstrual cycle. J Invest Dermatol 1992; 98: 601.
6. Agner T, Damm P, Skouby SO. Menstrual cycle and skin reactivity. J Am Acad Dermatol 1991; 24: 566–570.
7. Gordon BD. Patch testing and the menstrual cycle. J Am Acad Dermatol 1991; 24: 152–153.
8. Bryunzeel DP, van Ketel WG, Scheper RJ, von Blomberg-van der Flier BME. Angry back or the excited skin syndrome – a prospective study. J Am Acad Dermatol 1983; 8: 392–397.
9. Fischer TI, Maibach HI. The thin layer rapid use epicutaneous test (TRUE-test), a new patch test method with high accuracy. Br J Dermatol 1985; 112: 63–68.
10. Wilkinson DS, Fregert S, Magnusson S, Bandmann HJ, Calnan CD, Cronin E, et al. Terminology of contact dermatitis. Acta Derm Venereol (Stockh) 1970; 50: 287–292.
11. Andersen KE, Lidén C, Hansen J, Vølund Aa. Dose-response testing with nickel sulphate TRUE test in nickel sensitive individuals. Multiple patch test reactions do not cause "Angry back". Br J Dermatol 1993; 121: 50–56.
12. Beynon HLC, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. Lancet 1988; i: 370–371.
13. Eliasson O, Scherzer HH, DeGraff AC. Morbidity in asthma in relation to the menstrual cycle. J Allergy Clin Immunol 1986; 77: 87–94.
14. Gollhausen R, Przybilla B, Ring J. Reproducibility of patch tests. J Am Acad Dermatol 1989; 21: 1196–1202.
15. Hasan T, Jansen CT. Reproducibility of contact and photocontact tests with photoallergens. In: Frosch PJ, Dooms-Goossens A, Lachapelle J-M, Rycroft RJG, Scheper RJ, eds. Current topics in contact dermatitis. Berlin: Springer Verlag, 1989: 493–498.
16. Gollhausen R, Przybilla B, Ring J. Reproducibility of patch test results. Comparison of TRUE test and Finn Chamber test results. J Am Acad Dermatol 1989; 21: 843–846.
17. Fischer T, Kihlman I. Patch testing technique. J Am Acad Dermatol 1989; 21: 830–832.
18. Friedmann PS, Rees J, White SI, Matthews JNS. Low-dose exposure to antigen induces sub-clinical sensitization. Clin Exp Immunol 1990; 81: 507–509.
19. Emmett EA, Risby TH, Jiang L, Ket Ng S, Feinman S. Allergic contact dermatitis to nickel: bioavailability from consumer products and provocation threshold. J Am Acad Dermatol 1988; 19: 314–322.