

Patch Test Study with Calcipotriol Ointment in Different Patient Groups, Including Psoriatic Patients with and without Adverse Dermatitis

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One hundred and sixty-eight individuals (psoriatic patients treated with calcipotriol with dermatitis due to calcipotriol, psoriatic patients treated with calcipotriol with no dermatitis, psoriatic patients never treated with calcipotriol, patients with eczema and healthy volunteers) were patch-tested (Finn chambers, back, 48 h) with dilutions of calcipotriol ointment (50, 10, 2, 0.4 µg/g) and an ointment vehicle. Test evaluation was based on clinical scoring and various non-invasive measuring methods. Doubtful (?+) and weak (1+) reactions were common, irrespective of patient group and history. Moderate (2+) reactions were uncommon and with no increased frequency among psoriatic patients with adverse dermatitis during calcipotriol treatment. The blood flow of test sites measured by laser Doppler flowmetry was, however, increased in psoriatics, who developed dermatitis during calcipotriol treatment as an isolated finding. Furthermore a 1-week repeated open application test (ROAT) was performed on all subjects. None of the persons having a strong reaction in the patch test showed any dermatitis in the ROAT test, indicating that they were not sensitized.

Calcipotriol was found to be a mild irritant of the non-corrosive type, i.e. with no influence on the skin barrier. Reactions were dominated by redness (increased laser Doppler flow and chroma a*) and only oedema formation in advanced reactions. The calcipotriol dose-irritation curve was found to be scattered. Calcipotriol induced no increase of transepidermal water loss (TEWL) versus the ointment vehicle, but the ointment vehicle itself increased TEWL. The special ointment vehicle needed for calcipotriol for stability reasons may itself be irritant and cause some impairment of the skin water barrier, with increase in TEWL values. Future patch test studies for calcipotriol allergy should not be done with this vehicle. The non-irritant threshold concentration of calcipotriol in an appropriate test vehicle is still unknown. *Key words: clinical study; patient group comparison; ROAT test; non-invasive methods.*

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The vitamin D₃ analogue calcipotriol (Dovonex[®], Daivonex[®]) is widely accepted as an effective treatment of psoriasis vulgaris (1–3). Treatment with calcipotriol in psoriasis may, however, cause lesional, perilesional and ectopic facial irritation in 5–25% of patients treated (2, 4, 5). However, only a few patients drop out for that reason. It is a general experience

that patients who are intolerant to calcipotriol may tolerate the drug later, and treatment can often be reinstated after some time. For this reason the adverse dermatitis of calcipotriol is considered irritant. The reason why some patients are prone to develop irritation is obscure. Maybe they represent, in the spectrum of patients, those with an especially sensitive skin. The threshold level for irritation is in general dependent on endogenous factors, such as skin type, menstrual phase and other constitutional factors. Environmental conditions, like season, may also have an influence. It is also known that concurrent active eczema may lower the threshold of reactivity, i.e. the skin is "exacerbated".

In the literature, four case reports of possible allergic contact dermatitis during treatment with calcipotriol ointment (Daivonex[®]) have appeared. Yip & Goodfield (6) observed one case of acute dermatitis during treatment of psoriasis on the leg. Patch test with Daivonex[®] gave a strong positive test reaction on day 4, interpreted by the authors as an allergic contact reaction.

Bruynzeel et al. (7) described a case of possible allergic contact dermatitis in association with psoriasis treatment with Daivonex[®]. The patch test was positive, indicating that the patient had been sensitized. Two further cases of allergic contact dermatitis have recently been reported (8, 9). However, none of the studies allow a definite conclusion, since the concentration of non-irritating of calcipotriol remains unknown.

When testing substances already known to be irritants, an open test may be preferable (10, 11). Open application can be performed as a "provocative" use test, where the test substance is applied onto normal skin at the flexor aspect of the forearm twice daily for 1 week (ROAT, repeated open application test), as outlined by Hannuksela & Salo (12). Eczematous reactions after 7 days may be interpreted as allergy, but the rate of false positive and false negative reactions is not known. The skin of the antecubital fossa is usually avoided, since application can easily result in irritative contact dermatitis.

The aim of the present study was to characterize skin reactions caused by calcipotriol in different patient groups and healthy volunteers. Patient groups included psoriasis patients with dermatitis during calcipotriol treatment.

MATERIAL AND METHODS

Study design

The study was a multicentre, double-blind, placebo-controlled, randomised study in five parallel patient groups. The trial was approved

Table I. Demographic data for the five groups

	Group 1 (n=35)	Group 2 (n=32)	Group 3 (n=36)	Group 4 (n=32)	Group 5 (n=33)
Age (years)					
mean	48.0	49.8	47.0	46.4	36.4
range	24-69	19-72	21-68	20-69	21-64
Sex (n)					
male	15	19	18	12	10
female	20	13	18	20	23
Skin phototype (n)					
type I+II	4	4	3	11	4
type III+IV	18	19	20	13	23
type V+VI	13	9	13	8	6

by the local Ethics Committee and was reported to the National Board of Health in Denmark.

Patients

A total of 168 subjects (94 females and 74 males) participated in the study. Subjects included in the study belonged to one of the following patient groups:

- Group 1: Psoriatic patients never treated with Daivonex®.
- Group 2: Psoriatic patients previously treated with Daivonex® for at least 3 weeks and with a history of dermatitis related to the treatment.
- Group 3: Psoriatic patients previously treated with Daivonex® but without a history of dermatitis.
- Group 4: Patients without psoriasis and with an outbreak of active eczema (irritative or allergic) regardless of localisation except for the test sites.
- Group 5: Healthy volunteers without eczema or psoriasis. The subjects had not previously been treated with Daivonex®.

Demographic data for the five treatment groups are shown in Table I. There was no difference in sex distribution between the groups. The mean age was 45.5 years, but in group 5 it was significantly lower ($p < 0.001$). This difference of age within the adult range was probably clinically and experimentally not relevant in the present study. The characterization of skin phototype was based on subject history (14), and no difference was observed between the groups.

Subjects participated after receiving verbal and written information about the study and after giving their signed consent. Subjects were not included if treated with systemic corticosteroids or immunosuppressive medicine, if treated at the test sites with anything else but ordinary skin care products for the past 2 weeks or if treated with UVB or with PUVA for the past 2 months. Excluded were also persons with a widespread dermatological disease not belonging to one of the described treatment groups.

Patch test on the back

Occlusive patch testing for 48 h on the back was performed using dose titration with calcipotriol 50 µg/g, 10 µg/g, 2 µg/g and 0.4 µg/g ointment and a placebo ointment vehicle. Patch testing was performed using large Finn chambers® (12 mm Ø, Epitest, Helsinki, Finland) on Scanpor® tape.

Repeated open application test (ROAT)

Daivonex® ointment was applied BID (morning and evening) for 7 days within a 5 × 5 cm test site marked out centrally on the flexor side of the left forearm. The right forearm was left untreated. This part of the study was not blinded.

Clinical assessment

Clinical assessment of test sites on the back and on the forearm took place on day 2 (30 min after removal of patches) and again on day 3 and day 7. Visual scoring was performed according to Table II.

Table II. Scale used for visual scoring of test sites

Test reactions were ascribed to either I or II.

I: Dermatitis reaction (allergic or irritant reading)	
?+	Doubtful reaction: faint erythema only
+	Weak (non-vesicular) positive reaction: erythema, infiltration, possible papules
++	Strong (vesicular) positive reaction: erythema, infiltration, papules, vesicles
+++	Extreme reaction: bullous reaction*
II: Special reactions	
SP 1	Follicular reaction
SP 2	Wrinkled, parchmentish epidermal reaction ("effect de savon").
SP 3	Circular reaction that apply to the test chamber edge
SP 4	Other specific reaction pattern, describe
III: Additional registration	
-	Negative reaction
NT	Not tested
MD	Missing data

* Define if skin reaction towards surrounding skin is sharp (s) or diffuse (d).

Non-invasive measuring techniques

Non-invasive measuring techniques were used for evaluation and comparison of the individual treatments and treatment groups. Comprehensive descriptions of these methods have earlier been published (13). Non-invasive evaluations were performed on day 3. Three measurements were carried out within each test site. Three measurements were also carried out on untreated skin of the upper right side of the back and centrally on the untreated right forearm. The median value within each site was used. Ultrasound measurement of skin thickness (see below) was carried out only once within each test site.

Skin colour was measured using two different measuring techniques, i.e. by chromametry (Minolta ChromaMeter CR 200, Minolta, Osaka, Japan) with tristimulus analysis of the colour of the skin according to the CIE system using the a* value and by measuring the erythema index and melanin index by a narrow-band spectrometer (Dermaspectrometer, Cortex Technology, Hadsund, Denmark).

Blood flow in the skin was measured using a laser Doppler flowmeter PF 2 B (Periflux, Perimed, Sweden). The light from the laser penetrates approximately 1 mm into the skin and illuminates an area of about 2 mm². The Doppler shift of the reflected light depends on the flux of red blood cells. The blood flow is expressed in arbitrary units.

TEWL, indicating the skin water barrier function, was measured using an Evaporimeter EP-1 (Servomed, Kinna, Sweden). TEWL is expressed in g/m²h. Measurements were performed using printer registration and an equilibration time of 30 s.

Electrical capacitance, indicating hydration of the outer epidermis, was measured using a Corneometer CM-420 (Courage-Khazaka, Cologne, Germany) according to a capacitance measuring principle. The capacitance is expressed in arbitrary values.

Skin thickness, as an indication of inflammatory skin oedema, was recorded by ultrasound scanning of the skin (Dermascan-C, Cortex Technology, Hadsund, Denmark). The scanner was a 20 MHz skin scanner. Measurements were taken using the C-probe and standard set-up with a gain setting ranging from 33 to 57 when scanning the back and ranging from 20 to 45 when scanning the forearm skin. The scanning was performed from the centre of the test sites. The image analysis of the cross-sectional images comprised measurement of skin thickness using the ROI function and cursor of the Dermascan C software. The length of the area was noted and used in the calculation of skin thickness.

Vehicle supplementary study

Two additional patches (an empty chamber and a chamber containing petrolatum (pet.)) were applied on the back of 22 of the healthy subjects belonging to treatment group 5. These two additional patches were not blinded. Test procedures and test evaluations were as described above.

Statistics

The five different groups were compared with respect to distribution of gender and skin type by the chi-square test. Age was analysed by analysis of variance. Clinical assessment of response was analysed by analysis of variance including patient group (inter group), subjects (intra group) and concentration. Due to the large number of observations ($n=840$), mean values are approximately normally distributed. Non-invasive measurements were analysed by analysis of variance including patient group (inter group), subjects (intra group) and concentration. F-tests were performed accordingly to test the hypothesis of homogeneity of overall group means and homogeneity of response to different concentrations.

ROAT sites were analysed by analysis of variance including patient group, subjects (intra group) and treatment (active, none).

Comparison of treatments in the vehicle supplementary study was carried out as analysis of variance, with subsequent multiple comparison of mean values of each treatment by Tukey's studentized range in case of statistically significant difference (evaluated by F-test).

A level of 5% was regarded as significant.

RESULTS*Baseline values, non-invasive methods*

Baseline values were measured at three test sites on the back and centrally on forearm skin. No statistically significant differences in baseline values were found between the five treatment groups, except for skin hydration measured by the Corneometer CM 420 ($p=0.03$) and for melanin index measured by the Deraspectrometer ($p=0.03$). In both cases, a difference between group 3 and group 4 was found, but not between the other groups. In group 4 the melanin index was decreased and the skin hydration value increased compared with the values for group 3. The reason for this difference is not obvious.

Clinical patch test scoring on days 2, 3 and 7

The results of patch test scoring of test sites on day 2 and day 3 are shown in Figs. 1 and 2. In the figures the percentage of subjects having a clinical reaction as a function of the concentration of calcipotriol is shown for the five treatment groups. No statistically significant difference in clinical scoring was observed between groups 1 to 5. A trend was observed towards a somewhat higher responsiveness in group 2. Pooling all the data for group 1 to 5, we found a statistically significant relation between treatment dose and skin reactions. Thus, patch testing with increasing doses of calcipotriol resulted in stronger skin reactions. Patch test with the ointment vehicle itself, however, resulted in a number of doubtful and weak positive reactions in all five patient groups as well.

Comparing the results for days 2, 3 and 7 showed that the number of skin reactions in all patient groups decreased over time. The calcipotriol reactions faded out at the day 7 reading.

Non-invasive measurements of patch test sites on day 3

Fig. 3a-d shows the mean values for the five treatment groups for skin colour, skin blood flow, TEWL and skin thickness.

Measurement of erythema showed no statistically significant difference between the five groups ($p=0.15$). A statistically significant difference between concentrations of calcipotriol was found ($p<0.001$). Thus a dose response dependence was seen with increasing concentration of calcipotriol, resulting in increased erythema.

Dermaspectrometer measurement of erythema index showed a statistically significant difference, both between patient groups ($p=0.002$) and between test concentrations of calcipotriol ($p<0.001$), with increasing concentrations of calcipotriol resulting in an increasing erythema index value. The interaction between patient group and concentration was also significant ($p=0.004$), and it was therefore not possible to evaluate which treatment groups differed from the other groups. For melanin index a statistically significant difference between treatment groups was found. Group 4 showed significantly lower post exposure values than group 3. This was in accordance with the finding when untreated skin in the two patient groups was compared before exposure. There was no dependence of test concentration of calcipotriol on the melanin index.

Laser Doppler flowmetry of cutaneous blood flow showed a statistically significant difference between treatment groups ($p=0.002$) and between test concentrations ($p<0.001$). Group 2 was significantly different from the other treatment groups. This group as a whole reacted more intensely. Patch test with 50 $\mu\text{g/g}$ and with 2 $\mu\text{g/g}$ was found significantly different from the placebo ointment treatment.

TEWL was measured by the *Evaporimeter*. No statistically significant effect was found either for the treatment group or for the test concentration of calcipotriol. Thus there was no indication of barrier damage related to calcipotriol at any patch test site.

Skin hydration showed a statistically significant difference between patient groups ($p=0.020$). Group 4 showed significantly higher values than group 3. This was in accordance with the results comparing untreated skin in the two patient groups. There was no dependence of test concentration of calcipotriol on this parameter.

Groups 1 and 4 showed significantly increased skin thickness as compared with group 3. No effect of test concentration of calcipotriol was observed. Oedema formation was only observed on ultrasound scans in the few cases with strong positive reactions.

The clinical patch test results were differentiated into no response or clinical response (including the doubtful reactions) in order to investigate whether some methods were more useful than others. The statistical evaluation showed that only the Minolta ChromaMeter and the laser Doppler flowmeter could differentiate between response and no response. This was statistically significant, giving $p<0.008$ for the Minolta ChromaMeter method and $p<0.007$ for the laser Doppler flowmetry method.

ROAT on forearm skin

Clinical scoring showed a doubtful reaction, with faint erythema only, on the calcipotriol-treated forearm at day 7 in the

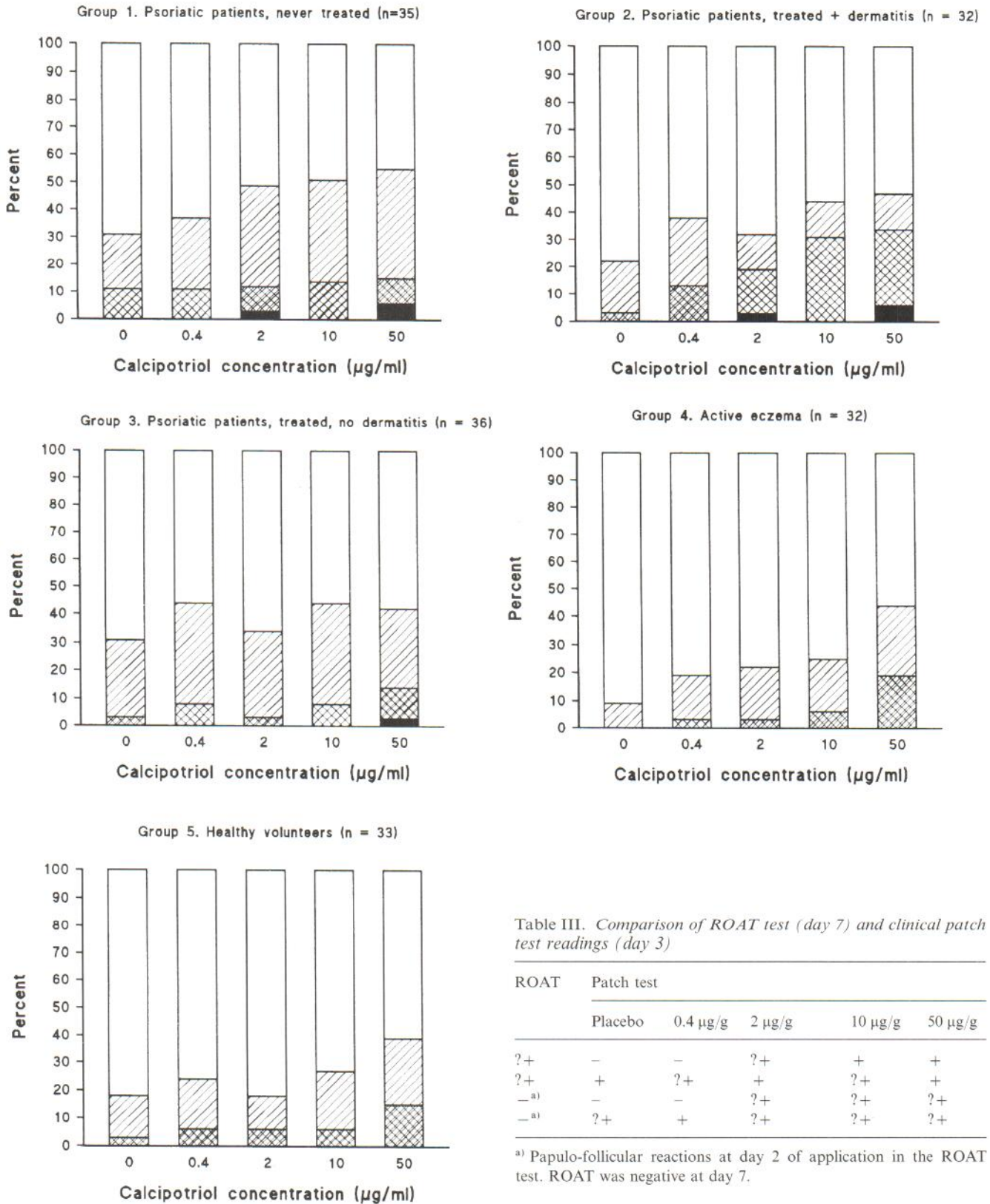


Fig. 1. Clinical scoring of patch test reactions on day 2 for the five different treatment groups. ■: ++, ▣: +, ▤: ?+, □: -

Table III. Comparison of ROAT test (day 7) and clinical patch test readings (day 3)

ROAT	Patch test				
	Placebo	0.4 µg/g	2 µg/g	10 µg/g	50 µg/g
?+	-	-	?+	+	+
?+	+	?+	+	?+	+
- ^{a1}	-	-	?+	?+	?+
- ^{a1}	?+	+	?+	?+	?+

^{a1} Papulo-follicular reactions at day 2 of application in the ROAT test. ROAT was negative at day 7.

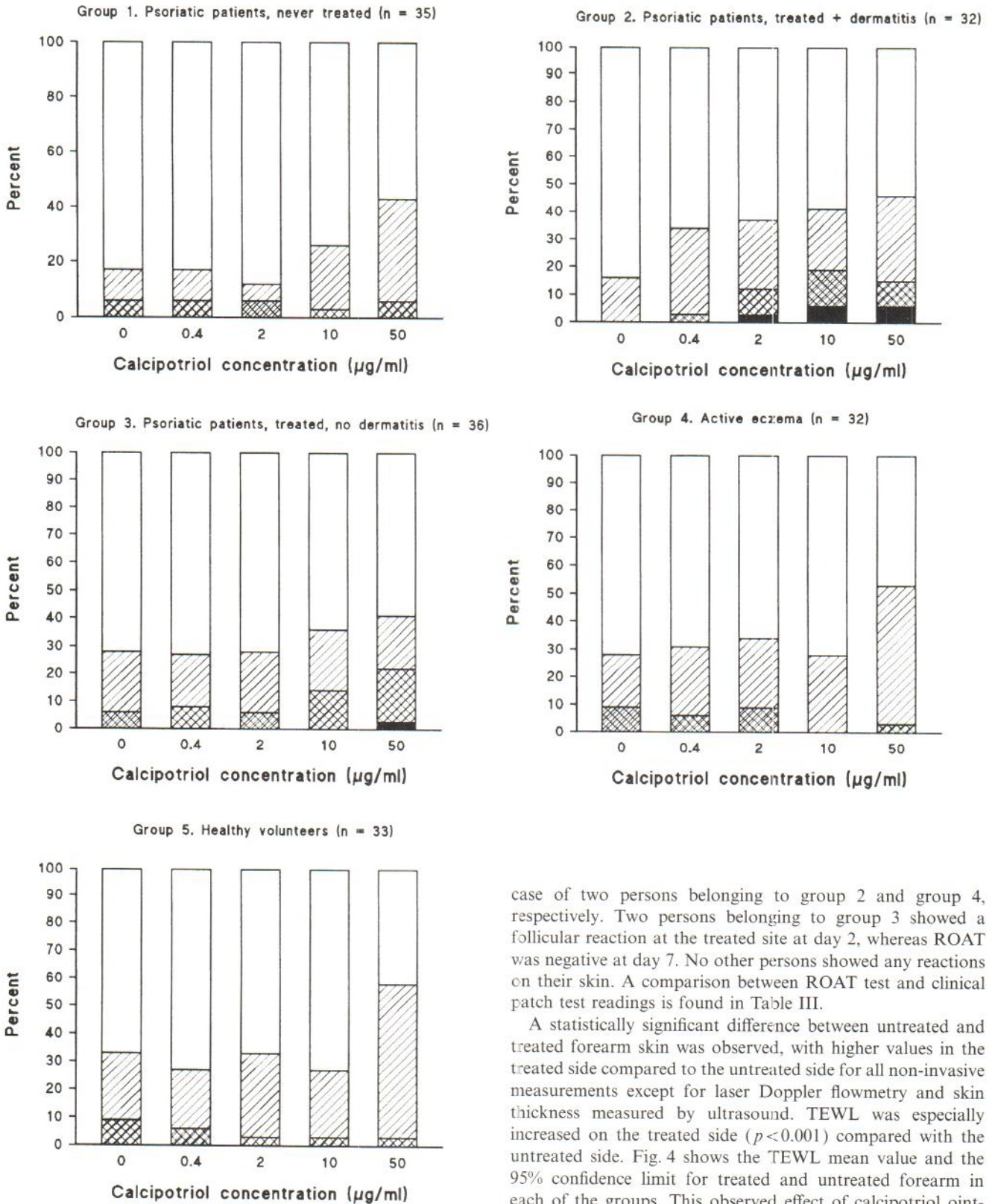


Fig. 2. Clinical scoring of patch test reactions on day 3 for the five different treatment groups. ■: ++, ▨: +, ▩: ?+, □: -

case of two persons belonging to group 2 and group 4, respectively. Two persons belonging to group 3 showed a follicular reaction at the treated site at day 2, whereas ROAT was negative at day 7. No other persons showed any reactions on their skin. A comparison between ROAT test and clinical patch test readings is found in Table III.

A statistically significant difference between untreated and treated forearm skin was observed, with higher values in the treated side compared to the untreated side for all non-invasive measurements except for laser Doppler flowmetry and skin thickness measured by ultrasound. TEWL was especially increased on the treated side ($p < 0.001$) compared with the untreated side. Fig. 4 shows the TEWL mean value and the 95% confidence limit for treated and untreated forearm in each of the groups. This observed effect of calcipotriol ointment on TEWL must be caused by the ointment vehicle and not calcipotriol, since it was shown in the patch test series that calcipotriol does not cause increase in TEWL and therefore does not induce changes in the skin barrier function. However, the level of the TEWL indicated no strongly corrosive effect of the ointment vehicle.

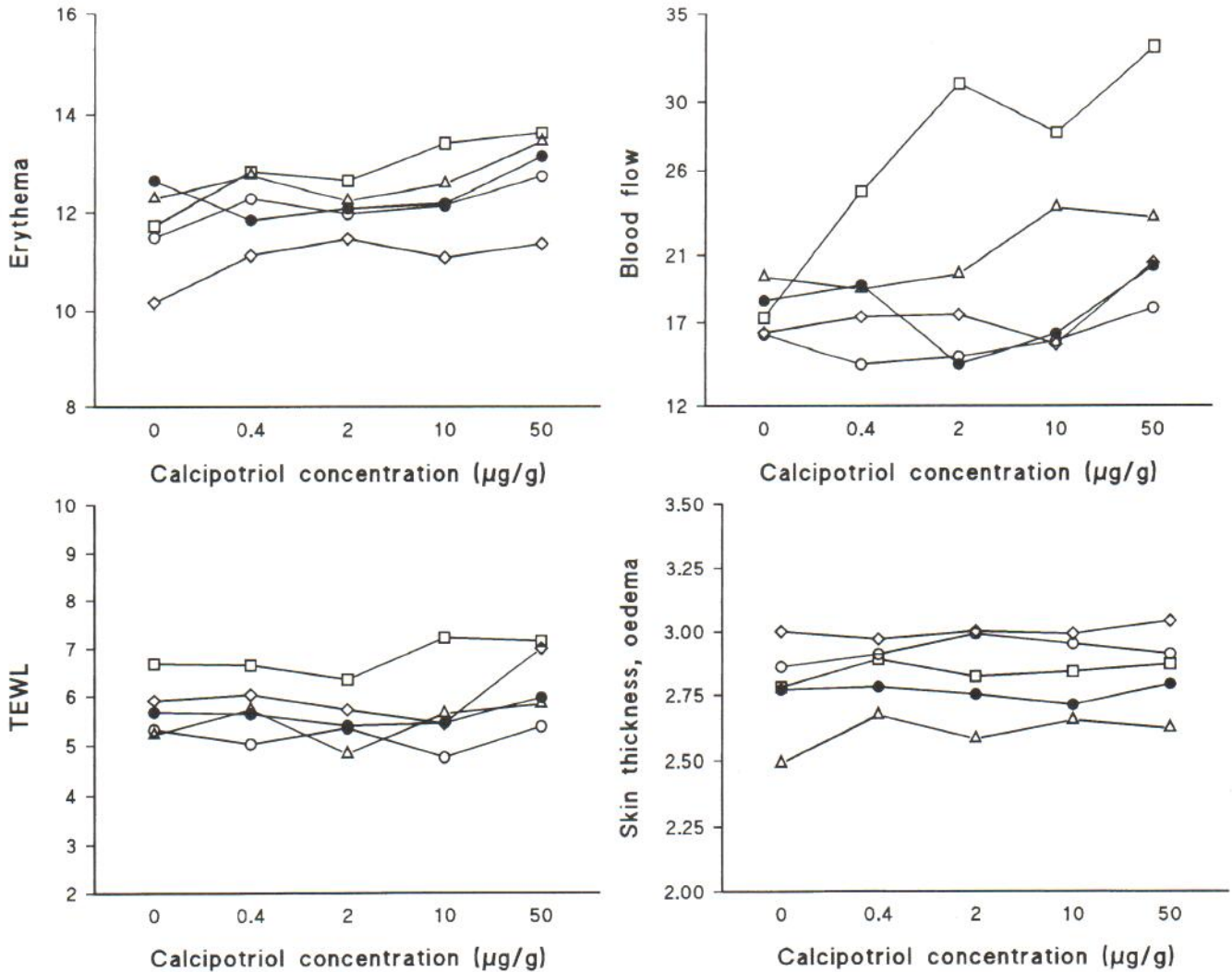


Fig. 3. Mean values on day 3 for the five different treatment groups. ○, psoriatic patients, never treated; □, psoriatic patients, treated + dermatitis; △ psoriatic patients, treated - dermatitis; ◇, active eczema; ●, healthy volunteers. a) Erythema measurement (Minolta ChromaMeter, CIE, a^* value); b) skin blood flow measurement (Laser Doppler flowmetry, a.u. value); c) transepidermal water loss (TEWL, Evaporimeter, $\text{g/m}^2\text{h}$); d) skin thickness, oedema (20 MHz high frequency ultrasound, mm).

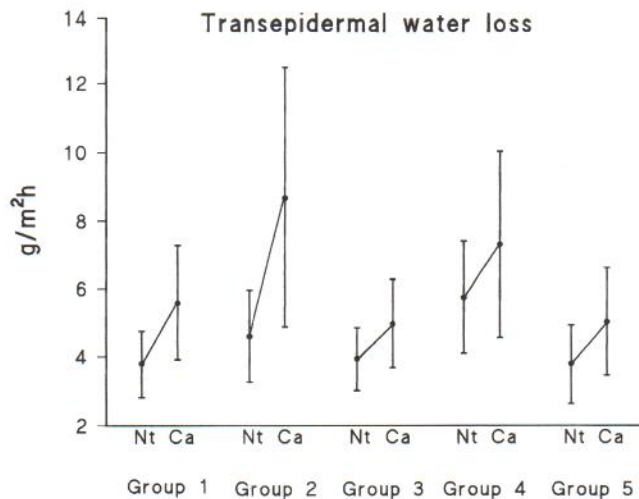


Fig. 4. ROAT on forearm skin. TEWL mean values and the 95% confidence limits for treated and untreated forearm, respectively, in each group. Nt: not treated; Ca: calcipotriol-treated.

Vehicle supplementary study

Twenty-two healthy volunteers in group 5 were patch-tested with petrolatum and an empty Finn chamber[®] in addition to the placebo ointment vehicle.

Application of the ointment vehicle resulted in significantly higher values for skin redness, cutaneous blood flow, TEWL and skin hydration than found for sites exposed to petrolatum, empty chamber and untreated skin. The results are shown in Fig. 5a-d, giving the mean values and 95% confidence limits.

DISCUSSION

The result of the patch tests shows that doubtful and weak reactions are common and stronger reactions uncommon. Thus, calcipotriol belongs to the group of "mild" irritants. No difference in response was observed related to the medical history. Thus, there was no obvious difference in the reaction pattern of psoriatic patients who had developed adverse derma-

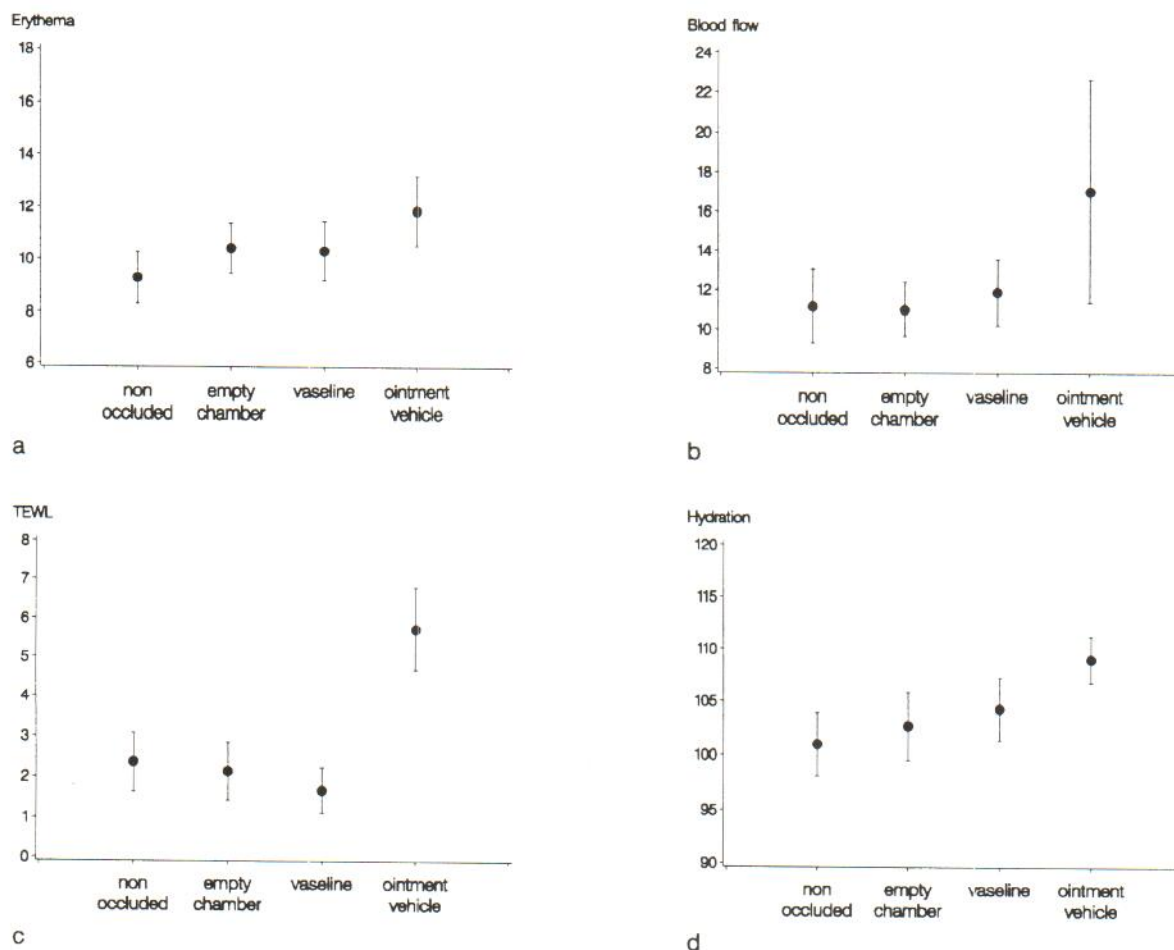


Fig. 5. Non-invasive measurements in 22 healthy volunteers patch tested with petrolatum and an empty Finn chamber[®] in addition to the ointment vehicle. Measurements on day 3. Mean values and the 95% confidence limits.

- a) Erythema measurement (Minolta ChromaMeter, CIE, a* value);
 b) skin blood flow measurement (Laser Doppler flowmetry, a.u. value);
 c) transepidermal water loss (TEWL, Evaporimeter, g/m²h);
 d) skin hydration (Corneometer).

titis during treatment and those who had not. A trend was, however, observed indicating that psoriatic patients with dermatitis show slightly stronger reactions than the other treatment groups. Laser Doppler flowmetry showed as the only parameter a significantly increased response. Psoriatic patients who develop dermatitis during calcipotriol treatment may have a more sensitive skin to this type of irritant. In the present study they represent a selected group. Persons with an outbreak of active eczema did not show an increased responsiveness, although their skin might be more sensitive as a manifestation of "excited skin syndrome".

Only a few moderate reactions were observed, however, irrespective of clinical group. These test reactions are of special significance. In theory, a patient may belong to a special type with a lower threshold of irritation, or a patient may be allergic to calcipotriol. However, these exceptional reactions also occurred among individuals who had never been treated with calcipotriol before, and the strong reactions in these individuals were certainly not allergic. The overlap of reactivity among psoriatic patients treated with calcipotriol and with

dermatitis and the other four groups and the negative finding of strong reactivity in the former group indicate that allergic sensitization is either uncommon, exceptional or non-existing despite manifest dermatitis during treatment. The study cannot of course exclude that selected cases of allergy might occur in widespread use.

The ROAT test method, as outlined by Hannuksela & Salo (12), was used for the study of irritant substances producing reactions, the allergic or irritant nature of which cannot easily be decided on the basis of the results of a closed patch test alone. In the present study the ROAT test was performed on the left forearm for 1 week. The ROAT test was found negative in subjects with a positive patch test, except in two patients who showed a doubtful reaction at day 7. Two patients had papulo-follicular reactions at day 2 in ROAT but no reaction at day 7. One of the subjects with a doubtful reaction also had doubtful reaction to calcipotriol ointment 2 µg/g in the patch test and a weak reaction to calcipotriol ointment 10 and 50 µg/g. The other subject with a doubtful reading in the ROAT test showed a doubtful reaction to calcipotriol ointment

0.4 µg/g upon patch test, and a weak reaction to the ointment vehicle and calcipotriol ointment 2 and 50 µg/g. None of the persons having strong reactions in the patch test showed any dermatitis in the ROAT test. The papulo-follicular reactions in the ROAT test seen in two patients belonging to group 3 and their nature remain obscure, although they might represent a special manifestation of irritancy on forearm skin with no direct correlation on the back. Hayakawa et al. (15) performed a dermal safety study of calcipotriol ointment in healthy volunteers and in patients with different dermatoses. They found the skin irritation index of calcipotriol ointment 50 µg/g and of calcipotriol ointment 100 µg/g to be almost identical, whereas an ointment containing 25 µg/g showed less skin irritation. Their results are in close accordance with the present results and indicate a plateau of maximum irritancy at 50 µg/g.

Most skin reactions caused by calcipotriol are seen at day 2 in the patch test set up. At day 3 the reactions fade and at day 7 most of the skin reactions have disappeared. Thus calcipotriol does not cause late reactions.

Based on the results of the bioengineering methods, it is found that calcipotriol primarily affects the vasculature and results in vasodilatation, since increase of blood flow and increase of erythema are the main parameters affected. Particularly in group 2 the increase in blood flow was prominent. Calcipotriol does not induce barrier injury since TEWL was not affected relative to ointment base. Thus the skin reactions caused by calcipotriol are non-corrosive, in contrast to the standard irritant SLS which causes caustic reactions and increase in TEWL (16). Ultrasound indicated no dermal thickening and oedema formation except in strongly positive cases.

Combining subjects in all the patient groups, we found that 54% of the 168 persons tested had negative reactions, 26% showed doubtful, 16% weak and 3% strong reactions to a patch test with calcipotriol ointment 50 µg/g at the day 2 reading. A patch test with the ointment vehicle alone resulted in 67% negative, 28% doubtful and 3% weak reactions at the day 2 reading. Thus the vehicle itself does not seem to be innocent. In the study by Hayakawa et al. (15), a number of doubtful patch test reactions were also observed with the ointment vehicle. In the ROAT test increased TEWL was found on the arm treated with calcipotriol ointment. Since calcipotriol does not affect the skin barrier when otherwise tested, this increase can only be caused by components in the ointment vehicle. A comparison of the ointment vehicle with empty chamber, petrolatum and unoccluded skin in 22 healthy volunteers showed that closed application of the ointment vehicle resulted in significantly higher values of erythema, skin blood flow as well as TEWL and skin hydration than found for the other treatment sites. The ointment vehicle itself therefore has the same inflammatory reaction pattern as various experimental irritants and calcipotriol, but additionally the ointment vehicle causes some impairment of the skin barrier. The influence of the ointment vehicle on the barrier function might not be straightforwardly negative but also enhancing, rendering the delivery of active substance into the skin more efficient. It should be noted that a special ointment with propylene glycol (10%) and pH 8.5 is needed to keep calcipotriol stable.

Based on the present results, it is recommended that future patch test study for calcipotriol allergy is not performed with

the ointment vehicle. Instead an indifferent vehicle, like isopropanol buffered with citrate to pH 8.5, should be used. The non-irritant threshold concentration of calcipotriol in this more appropriate test vehicle is still unknown.

In conclusion, the present study has shown that:

- Doubtful and weak patch test reactions are common irrespective of patient group and history (42% day 2 reading, 46% day 3 reading, 5% day 7 reading after application of calcipotriol 50 µg/g).
- Strong reactions are uncommon and have no special frequency among psoriatic patients with adverse dermatitis during calcipotriol treatment.
- Calcipotriol is a mild irritant of the non-corrosive type, i.e. with no influence on the skin barrier. Reactions are dominated by redness (increased laser Doppler blood flow and erythema) and only oedema formation and skin thickening in advanced reactions.

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