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In-patient treatment with calcipotriol versus dithranol in refractory psoriasis

CARINE J.M. VAN DER VLEUTEN, ELKE M.G.J. DE JONG, ERNA H.F.C. RULO, MARIE-JEANNE P. GERRITSEN, PETER C.M. VAN DE KERKHOF

Calcipotriol (50 µg/g) ointment recently became available for the treatment of psoriasis. Calcipotriol has been shown to be superior to home treatment with dithranol. The time-honoured regime of in-patient topical treatment with dithranol in paste or petrolatum for 24 hours is the gold standard of optimal efficacy of antipsoriatic therapy. This treatment regime is adopted in case of insufficient control of psoriasis by out-patient treatments. The aim of the present study was to challenge the position of in-patient dithranol treatment. A left-right comparative case-control study was designed in ten patients hospitalised with refractory psoriasis, comparing classical dithranol treatment and calcipotriol treatment. In contrast to what was expected, six of the ten patients showed a more pronounced improvement after two weeks at the calcipotriol treated sides. Irritation from calcipotriol was observed in four patients after one week and in two patients after two weeks treatment. At the dithranol treated sides three of the ten patients showed a better improvement. Four patients experienced irritation after one week and eight patients after two weeks. Irritation due to calcipotriol was not associated with an increased irritation due to dithranol, which implies that both treatments have a different mechanism of irritation.

The present case-control study indicates that calcipotriol has challenged the untouchable superiority of classical in-patient treatment with dithranol. Further studies are indicated to improve compliance in out-patient calcipotriol treatment with cream formulations and once a day schedules.

Chronic plaque psoriasis can be treated with various out-patient therapies [1]. However, in patients with extensive, therapy resistant and severely disabling psoriasis it is our policy to admit the patient. For this group of patients with refractory psoriasis, dithranol so far has been the therapy of choice at our in-patient department. Where lesions prove to be resistant to this treatment or if new lesions continue to appear or in the case of severely itching psoriasis various combination approaches are indicated.

Dithranol is a very safe and effective therapy [2]. Previously, dithranol has been used in petrolatum [3, 4] and Lassar’s paste [5]. Bioavailability varies significantly with its vehicle [6]. Irritation and discoloration of the skin and textiles have always been limiting its use [7]. For home treatment dithranol in a cream base has been developed which is easier to apply and wash off and therefore has proved to be more acceptable [8]. A disadvantage is the lower efficacy of this formulation [2, 8]. In-patient treatment with dithranol in paste or petrolatum, however, is the gold standard of therapy, resulting in the clearing of psoriasis in more than 90% of the patients within three to five weeks [2]. Dithranol in a cream base at the out-patient department only results in clearing in 10-35% of the patients in seven to eight weeks [2].

Over the last decade vitamin D analogues have been shown to have an important anti-psoriatic effect [9-12]. Recently, calcipotriol, 50 µg/g in ointment (Daivonex®, LEO Pharma-
Calcipotriol (Schering-Plough Products), became available as a routine treatment [13]. Several comparative studies on the efficacy of calcipotriol and the classical anti-psoriatic therapies have been carried out to elucidate and establish the position of calcipotriol in dermatology. Betamethasone 17-valerate [14] and short contact dithranol treatment [15] have been compared with calcipotriol for efficacy and safety. Calcipotriol proved to be equally effective compared to betamethasone 17-valerate. Remarkably, home treatment with calcipotriol appeared to be more effective compared to home treatment with short contact dithranol in a cream base.

In the present study the efficacy of treatment with dithranol and calcipotriol was compared in a group of patients with severe, therapy-resistant and disabling psoriasis who were, for this reason, admitted to our department.

The aim of the present study is to challenge the common belief that dithranol is the treatment of choice in severe psoriasis. In particular we addressed the following questions: i) does calcipotriol have a beneficial effect in severe psoriasis to the same extent as dithranol? ii) which aspects limit the use of calcipotriol in severe psoriasis?

As this study involves patients with severe psoriasis we set out a two week left-right comparative case-control study to explore the first two weeks of the in-patient treatment phase with calcipotriol and dithranol in Lassar's paste or in petrolatum.

Materials and methods

Patients

The investigation was carried out at the in-patient department. Patients with extensive and disabling plaque psoriasis, resistant to topical therapy, were admitted and included in the study. Four males and six females were included with ages ranging from 20-72 years and with a duration of psoriasis ranging from 3-53 years. The patients had used no oral treatment for psoriasis within the six weeks prior to the study except for one patient who had taken fumaric acid. Topical treatment was allowed until the date of submission to the hospital.

Table I summarises the treatments for psoriasis of the patients during six weeks prior to admission. No oral medication that could influence the course of psoriasis was allowed. Hydroxyzine was allowed for those patients with severe pruritus. No additional topical or systemic treatment for psoriasis was permitted during the trial except for corticosteroids for the scalp and face.

Approach

Patients were treated for two weeks using a left-right within-subject comparison. One side of the body was treated with dithranol in paste or petrolatum and the other side with calcipotriol. Which side of the body was treated with what therapy was randomly chosen. The regimen for dithranol consisted of a 24 hour application of dithranol in paste or petrolatum in increasing concentrations ranging from 0.05-4%. The concentration of dithranol was increased on alternate days. Calcipotriol was applied twice daily on lesional skin to a maximum of 100 grams per week. Individualisation of the treatment with adjunct therapies was postponed until after the two weeks' evaluation. The clinical scores were recorded before and after one and two weeks of therapy. Extent and severity of the disease were recorded as shown in Table II. The extent of the disease was scored as a percentage of involved skin. This percentage was transposed into an area score. Arms, trunk and legs were scored separately. The severity of erythema, induration, scaling and pruritus was assessed using a 5 point-scale (Table II). After one and two weeks of treatment the skin-irritation as a result of therapy was recorded using the 5 point scale. PASI-scores were calculated according to the formula in Table III.

Statistical analysis

Changes in clinical scores and comparisons between the two body-sides of the same patients were analysed using the Student t-test for paired values.

To obtain insight into the correlation between different parameters which characterise the disease, a regression analysis was performed (Pearson-r).

Table I. Previous therapy

<table>
<thead>
<tr>
<th>Therapy 6 weeks prior to study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy</td>
<td>1</td>
</tr>
<tr>
<td>Topical steroids</td>
<td>5</td>
</tr>
<tr>
<td>Calcipotriol</td>
<td>4</td>
</tr>
<tr>
<td>Tar</td>
<td>1</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>1</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>1</td>
</tr>
<tr>
<td>Dithranol</td>
<td>1</td>
</tr>
</tbody>
</table>

Table II. Scoring for extent and severity of disease

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - no involvement</td>
<td>0 - no involvement</td>
</tr>
<tr>
<td>1 - &lt; 10%</td>
<td>1 - slight</td>
</tr>
<tr>
<td>2 - 10-29%</td>
<td>2 - moderate</td>
</tr>
<tr>
<td>3 - 30-49%</td>
<td>3 - severe</td>
</tr>
<tr>
<td>4 - 50-69%</td>
<td>4 - severest possible</td>
</tr>
<tr>
<td>5 - 70-89%</td>
<td></td>
</tr>
<tr>
<td>6 - 90-100%</td>
<td></td>
</tr>
</tbody>
</table>

Table III. PASI-score

Calculation of the PASI-score

\[
\text{PASI} = 0.2 \times A \text{ arms} \times \Sigma(E + I + S) + 0.3 \times A \text{ trunk} \times \Sigma(E + I + S) + 0.4 \times A \text{ legs} \times \Sigma(E + I + S) \\
A = \text{Area score} \\
\Sigma(E + I + S) = \text{Sum of scores for erythema, induration and scaling}
\]
Results

At the start of the study severity-scores for both body-sides were comparable; the average PASI-score was 17.1 ± 2.1 (mean ± SEM) for the whole body. Both treatment regimens induced a statistically significant decrease in PASI-scores after one week of treatment (p = 0.0005 for calcipotriol and p = 0.0003 for dithranol). In the second week of treatment there was a significant, further decrease of the PASI-score (p = 0.03 for calcipotriol and p = 0.03 for dithranol) compared to scores after one week. The calcipotriol treated side tended to respond slightly better to therapy than the dithranol treated side but this difference was not statistically significant (p = 0.08).

Figure 1 illustrates the difference (Δ) between the PASI-score before and after one and two weeks treatment for the calcipotriol and dithranol treated body-sides of the individual patients. Before treatment the PASI-scores for both body-sides were equal except in one patient (patient 8). After one week of therapy, however, three patients showed a therapy response in favour of dithranol and five patients showed a therapy response in favour of calcipotriol. Two patients showed no difference between the two therapies. After two weeks of therapy six patients responded better to the calcipotriol therapy and three patients responded better to the dithranol therapy. In one patient there was no difference in response to either therapy.

Pruritus was experienced in eight out of ten patients before treatment. Prior to therapy there was no difference between the two body-sides. The scores for pruritus were relatively high for psoriasis (2.0 ± 0.4) (mean ± SEM). After one week of therapy a significant decrease of pruritus was experienced at the calcipotriol treated sides (p = 0.003) as well as at the dithranol treated sides (p = 0.005). In the second week of treatment the scores for pruritus still tended to decrease. Calcipotriol was significantly better than dithranol in reducing pruritus (p = 0.04 after one week of treatment and p = 0.04 after the second week of treatment).

After one week of therapy, irritation was seen on both body-sides as a result of both therapies, but there was no significant difference between the two therapies. The initial irritation of calcipotriol tended to decrease in the period between one and two weeks. Two out of four patients indicated that irritation had decreased during continued treatment with calcipotriol; the irritation as a result of dithranol treatment increased significantly in the second week of therapy (p = 0.01). After two weeks of treatment the mean score for irritation due to dithranol was significantly higher than the score for treatment with calcipotriol (p = 0.006). There was no correlation between the scores for irritation on both body-sides in each patient after either one or two weeks of treatment. Regression analysis revealed that there was no association between pruritus before therapy and irritation as a result of two weeks of therapy for either calcipotriol or dithranol.

The mean duration of the in-patient treatment was 5.5 ± 0.7 (mean ± SEM) weeks. After the two week comparative study, coal tar treatment was added for five patients, phototherapy with ultraviolet B was added for five patients and phototherapy for one patient. In three patients oral treatment with acitretin had to be added in order to enhance clearing. Out of these patients with difficult psoriasis, four patients experienced total clearing and the other six patients saw a substantial improvement.

Discussion

Most of the investigations on the efficacy and side effects of calcipotriol deal with mild to moderate chronic plaque psoria-
essential for its anti-psoriatic effect but it is also a less acceptable adverse event. The concentration of dithranol is increased as a function of the tolerance of the individual patient. No correlation could be shown between dithranol irritation and calcipotriol irritation which suggests that the mechanism of irritation is different. It is of interest that those patients who experienced pruritus before treatment were not predisposed to develop irritation to calcipotriol or dithranol. It is striking to see that calcipotriol had a better effect on pruritus than dithranol in this group of patients. In the present study the second phase of the in-patient treatment after the two-week investigation was difficult to evaluate as to the strategy was to individualise treatment using combinations which were the most appropriate for the individual patient.

From this study it may be concluded that calcipotriol treatment at the in-patient department, carried out with care and precision, is highly effective to the extent that it challenges the time-honoured 24 hour application of dithranol. It is attractive to hypothesise that the development of cream formulations and once a day schedules to improve compliance for calcipotriol might diminish the gap between efficacy of home treatment and treatment at the in-patient department.

C.J.M. Van der Vleuten, E.M.G.J. de Jong, E.H.F.C. Rulo, M.-J. P Gerritsen, P.C.M. Van de Kerkhof: Department of Dermatology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Reprints C.J.M. Van der Vleuten.

Key words: psoriasis, calcipotriol, dithranol, in-patient treatment, home treatment.

Samenvatting
Calcipotriol zelf kwam onlangs beschikbaar voor de behandeling van psoriasis. Uit vergelijkend onderzoek bleek dat calcipotriol effectiever was in vergelijking met thuisbehandeling met dithranol. Applicatie van dithranol in pasta of vaseline gedurende 24 uur is heden ten dage de gouden standaard van optimale anti-psoriatische therapie in de kliniek. Dit behandelingsschema wordt gestart op het moment dat de psoriasis te verouderd is om te worden behandeld.

Het doel van deze studie is om de posities van dithranol zoals die gebruikt wordt in de kliniek uit te dagen. Een links-rechts vergelijkende case-control studie werd ontworpen voor tien patiënten met recalcitrante psoriasis. In deze studie werd de klassieke, klinische dithranol behandeling vergeleken met calcipotriol in de kliniek.

In tegenstelling met wat we verwachtten, hadden zes van de tien patiënten een sterkere verbetering van lichaamsdeel die met calcipotriol werd behandeld. Irritatie teneinde van calcipotriol was minder dan die van dithranol en was niet geassocieerd met een toegenomen irritatie teneinde van dithranol hetgeen kan impliceer dat beide therapieën verschillende mechanismen van irritatie hebben. Deze case-control studie laat zien dat calcipotriol de vergelijkingen met de schijnbaar onantastbare posities van de klassieke, klinische behandeling met dithranol kan versterken. Verdere stuurschijnsels zijn gecombineerd om therapietrouw voor thuisbehandeling te vergroten onder andere door crèmeformulaties en een maal daags schema.

References