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# Comparison of Two Application Schedules for Clobetasol 17 Propionate

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Received June 30, 1981

*Abstract.* In a double-blind trial, intermittent treatment of psoriasis, designed to take advantage of the tachyphylaxis phenomenon and consisting of 3 days of twice daily application of 0.05% clobetasol-17-propionate ointment alternating with 4 days of the base alone, gave results that were no better than obtained with continuous treatment. In 10 patients, a weekly treatment consisting of 3 successive days with as little as 8 g 0.05% clobetasol-17-propionate ointment (24 g a week) followed by 4 days of bland ointment, sufficed to reduce the desquamation to 'hardly any' and the erythema/infiltration to 'slight'. This might be attributable to the drug reservoir in the stratum corneum, as postulated by Vickers.

Little is known about the optimal frequency for the application of topical corticosteroids. Some authors advise four inunctions a day, but a larger group recommends two a day. Observations on corticosteroid-induced tachyphylaxis (1) suggest that for corticosteroid-responsive dermatoses, intermittent treatment with corticosteroids would give better results than daily treatment.

## MATERIAL AND METHODS

To test this hypothesis, the following double-blind trial was carried out in two centres. Two groups of psoriasis patients were treated for 3 weeks with either 8 g 0.05% clobetasol-17-propionate ointment (Dermovate® ointment) daily, divided over two applications, or the same treatment on 3 days each week and the same amount of only the ointment base on the other 4 days. All patients with psoriasis distributed at least over the trunk and extremities and an intensity score of 4–6 for at least one area, were considered eligible for the trial. The treatment was carried out double-blind as follows. In a randomized way, each patient received either three sets of 7 active 8-g tubes each (continuous treatment) or three sets of 3 active and 4 placebo tubes each (intermittent treatment). Each set was labelled with the name of the patient and the day of the week the tube was intended for. Scaling and erythema/infiltration were scored separately for the scalp, arms, trunk, hands, and feet at the beginning of the treatment and after 1, 2, and 3 weeks, according to the following intensity scale (to facilitate scoring, a photograph of each of the indicated states was provided):

*Desquamation*

8 very thick desquamation
6 relatively thick desquamation
4 moderate desquamation
2 slight desquamation
1 hardly any desquamation
0 no desquamation

*Erythema/infiltration*

8 strong infiltration
6 moderate infiltration
4 slight infiltration
2 erythema only
1 slight erythema
0 normal skin colour or leukoderma

## RESULTS

At the end of the trial, 20 patients had been treated, 8 in one centre and 12 in the other, both groups divided equally between the two treatments. Because the differences between the results obtained in the two centres were relatively small, the data were pooled for the statistical analysis. Furthermore, since the number of patients was small and in some the psoriasis was not present on all five

Table 1. *Means of the intensity scores for arms, trunk, and legs at the start of the trial and at three weekly intervals during treatment (column 0–3 gives the total improvement over the 3-week period)*

| | Group A: Intermittent treatment | | | | | Group B: Continuous treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Week | | | | | Week | | | |
| | 0 | 1 | 2 | 3 | 0–3 | 0 | 1 | 2 | 3 | 0–3 |
| *Scaling* | | | | | | | | | | |
| | 2.7 | 1.3 | 0 | 0 | 2.7 | 4.0 | 2.7 | 0.7 | 0.7 | 3.3 |
| | 2.0 | 1 | 0.7 | 0.7 | 1.3 | 5.3 | 3.3 | 1.7 | 0.7 | 4.6 |
| | 4.0 | 1.3 | 1.3 | 0.7 | 3.3 | 4.0 | 2.0 | 0.7 | 0.7 | 3.3 |
| | 5.3 | 3.3 | 1.7 | 0.7 | 4.6 | 4.0 | 2.0 | 2.0 | 1.3 | 2.7 |
| | 2.7 | 2.7 | 2.0 | 1.0 | 1.7 | 6.7 | 0.7 | 0.7 | 0 | 6.7 |
| | 4.0 | 3.3 | 0.7 | 0 | 4.0 | 3.3 | 1.0 | 0.3 | 1.3 | 2.0 |
| | 5.3 | 0.7 | 1.3 | 0.7 | 4.6 | 3.3 | 2.0 | 0.7 | 0.7 | 2.6 |
| | 2.3 | 0.7 | 1.0 | 1.0 | 1.3 | 4.0 | 2.0 | 0 | 0 | 4.0 |
| | 5.3 | 2.7 | 1.0 | 2.3 | 3.0 | 3.3 | 2.0 | 0.7 | 0.3 | 3.0 |
| | 2.7 | 0.7 | 0.7 | 1.3 | 1.4 | 6.0 | 0.3 | 0 | 0 | 6.0 |
| Mean | 3.6 | 1.8 | 1.0 | 0.8 | 2.8 | 4.4 | 1.8 | 0.7 | 0.6 | 3.8 |
| *Erythema/infiltration* | | | | | | | | | | |
| | 2.0 | 0.3 | 0.3 | 0.3 | 1.7 | 2.0 | 1.3 | 1.3 | 1.3 | 0.7 |
| | 3.3 | 0.7 | 0.3 | 0 | 3.3 | 3.3 | 0.7 | 0.7 | 0.3 | 3.0 |
| | 2.7 | 2.0 | 0 | 1.3 | 1.4 | 2.7 | 2.7 | 0.7 | 1.3 | 1.4 |
| | 4.0 | 2.0 | 2.0 | 2.0 | 2.0 | 4.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| | 3.3 | 2.7 | 2.0 | 2.0 | 1.3 | 6.7 | 1.0 | 1.0 | 0.3 | 6.4 |
| | 4.0 | 3.3 | 2.7 | 0.7 | 3.3 | 3.3 | 1.7 | 1.0 | 2.7 | 0.6 |
| | 6.0 | 2.0 | 2.0 | 1.3 | 4.7 | 3.3 | 3.3 | 3.3 | 2.7 | 0.6 |
| | 6.0 | 3.7 | 1.3 | 0.7 | 5.3 | 6.0 | 2.0 | 0.7 | 0.3 | 5.7 |
| | 5.3 | 3.7 | 1.3 | 0.7 | 4.6 | 6.0 | 3.3 | 1.3 | 0.7 | 5.3 |
| | 2.7 | 2.0 | 1.0 | 1.3 | 1.4 | 8.0 | 3.3 | 2.0 | 1.3 | 6.7 |
| Mean | 3.9 | 2.2 | 1.3 | 1.0 | 2.9 | 4.5 | 2.1 | 1.4 | 1.3 | 3.2 |

locations, analysis by location was not feasible and use was made of the mean score for the three most important localizations (trunk, arms, and legs). The mean scores are given in Table 1, where a dashed line separates the patients of the two centres. The overall mean scores for scaling and erythema/infiltration before, during, and after the two treatments are shown in Fig. 1. The cortisol values were determined before the treatment and at the end of the trial. (The determinations were carried out by Dr C. J. Muller, clinical chemist, St. Joseph Ziekenhuis, Deventer.) No reduction in mean cortisol level was observed for either of the treatments.

## DISCUSSION

Apparently, both treatment schedules led to satisfactory improvement in the psoriasis patients. For *desquamation*, the overall mean score for the intermittent-treatment group dropped from 3.6 (moderate) to 0.8 (just perceptible) and for the continuous-treatment group from 4.4 to 0.6. As can be seen from Fig. 1, the overall means of the two treatments show roughly the same downward trend, the mean improvement after the continuous treatment being one point higher than that after the intermittent treatment. This difference is not significant at the 10% level (Student's two-sample test, $t=-1.61$, with 18 d.f., $p=0.12$, two-sided).

For *erythema/infiltration*, the overall mean score for the intermittent treatment dropped from 3.9 to 1.0 and for the continuous treatment from 4.5 to 1.3. As Fig. 2 shows, here too the downward trend was roughly the same for both treatments, but in this case the difference in improvement between the two treatments is negligible and far from significant (Student's two-sample test, $t=-0.42$, 18 d.f., $p>0.60$, two-sided).

Consequently for desquamation as well as for erythema/infiltration, the null hypothesis that the two treatment schedules are equally effective cannot be rejected at a 10% level of significance.

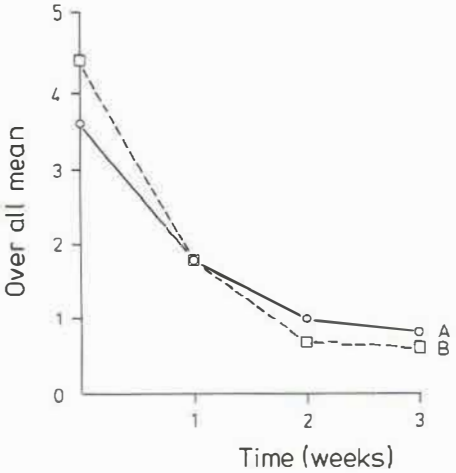


*Fig. 1.* Scaling: trend of the overall means before (0) and during treatment. A = intermittent, B = continuous.

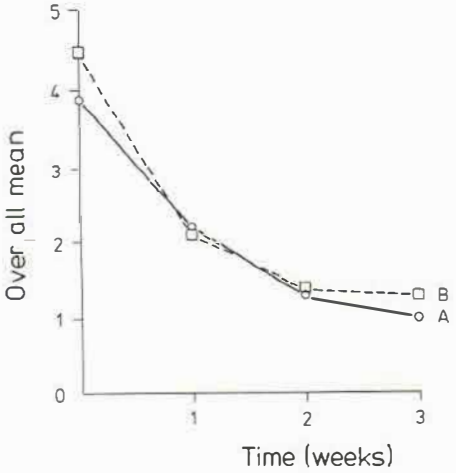


*Fig. 2.* Erythema/infiltration: trend of the overall means before (0) and during treatment. A = intermittent. B = continuous.

However, because the number of patients in this trial was small, it remains possible that in general the continuous treatment leads to somewhat more improvement than does the intermittent treatment [see (4)]. Nevertheless, it is remarkable that the intermittent treatment, which uses only 43 % of the dose of clobetasol-17-propionate administered in the continuous treatment, gave results similar to those obtained with the continuous one. This finding might be of importance in relation to the frequently raised question as to the optimal dosage schedule for topical corticosteroid application.

Schedules differing from the conventional two or more applications a day have been proposed (5, 6). Good results have been obtained with clobetasol-17-propionate cream given first in huge amounts (mean: 49 g a day) for 4 days and then on 1–2 days a week much smaller quantities of the active cream alternated with a bland cream (5). Similar effects were observed with halcinonide 0.1 % given one or three times daily in cases of atopic dermatitis and psoriasis (3).

It is not necessary to assume tachyphylaxis to explain the good results obtained with much smaller quantities of a corticosteroid cream than are currently used. The hypothesis that current dosages might be unnecessarily high is supported by the following observations. In diffusion cells after one application a steady-state penetration was found, starting on the second day and persisting for at least 10 days (7). It is also reported that after one application of hydrocortisone the drug was excreted in the urine for at least 5 days (2). Finally, a reservoir function of the stratum corneum has been observed (8, 9).

As to the question whether the reduction in the number of inunctions will diminish the side effects, atrophy in particular, this is open to doubt, since a therapeutic effect and atrophogenicity seem to be closely correlated. From an economic point of view, it is certainly advantageous to use corticosteroid-containing applications as infrequently as possible and to select for emolliency only bland bases.

Good results with a 4-day interval treatment schedule closely resembling ours have been published (6). Further trials are needed to determine whether other types of intermittent treatments give equally or better results than the one used by us. It is already certain, however, that it is possible to achieve much more economical treatment than is at present current.

## ACKNOWLEDGEMENT

We are indebted to Mr A. J. Massaar of Glaxo Netherlands for his assistance in carrying out the trial and for providing us with the necessary material.

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# Ketoconazole® in Trichophyton rubrum

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Received August 10, 1981

*Abstract.* 10 patients with *T. rubrum* infection were treated with Ketoconazole® 200–400 mg a day for 8 weeks. All patients had a skin infection and 2 in addition infection of the toe nails. Previous treatment with Griseofulvin and at least two different antifungal topicals had been ineffective. The infection was evaluated by clinical findings and mycological examination. The skin lesions disappeared in 6 patients, while none of the nail lesions were cured. However, at a follow-up 2 months after the end of the Ketonocazole treatment, recurrence was observed in 3 of 6 patients. It is suggested that Ketoconazole treatment of previously resistant *T. rubrum* infection should be continued for more than 2 months.

*Key words:* Ketoconazole®; Dermatophytosis; Trichophyton rubrum

Ketoconazole®, a new imidazole derivative with a broad *in vitro* antifungal activity, has been found to be effective in the treatment of dermatophytoses in which earlier treatments were without result (6). Its primary mechanism of action is effected by the blocking of enzymes, resulting in cell membrane defects (3).

*T. rubrum* infections often present therapeutical difficulties and we therefore decided to try Ketoconazole in patients with *T. rubrum* infections in which earlier treatments, both topical and systemic, had not been followed by cure.

## MATERIAL AND METHODS

Ten patients, 8 males and 2 females, aged 31–58 years (mean: 44.5) with *T. rubrum* skin infections participated. Two patients had concomitant infection of the toe nails.

Mycological examination was carried out before and at the end of the treatment period and at a follow-up examination 2 months later. Specimens from the lesions were microscopically examined immediately and cultured on Sabouraud agar, potato agar, corn meal agar and urea agar for further identification of the pathogen.

All patients had earlier been treated with at least two topical antifungal preparations as well as Griseofulvin for more than 2 months.

The dose of Ketoconazole was 200 mg/day for 2 months. If no improvement was seen after one month, the dose was increased to 400 mg/day for the next month. No other antifungal treatment was given during that treatment period.

The patients were seen at 2-weekly intervals, when the clinical picture was evaluated and any side effects were noted.

Laboratory tests concerning liver, kidney and bone marrow function were performed before and at the end of the study.

## RESULTS

In 7 patients the dose was maintained at 200 mg/day, while it was increased in 3 patients because of unsatisfactory effect.

At the end of the study 5 patients were cured, as evaluated by clinical and mycologic examination. Four patients still had their fungal infection and in one the fungus had disappeared from the skin, but could still be isolated from the nails.

At follow-up after 2 months only 3 patients were still in remission, while *T. rubrum* was isolated from the remaining 7 patients, all having clinical signs of infection.

Ketoconazole was well tolerated by all but one patient who claimed a mild nausea. Taking the tablet at bedtime prevented this side-effect.

## DISCUSSION

In earlier studies *T. rubrum* affection of the skin responded well to treatment with Ketoconazole (1,