

Treatment of head and neck dermatitis comparing itraconazole 200 mg and 400 mg daily for 1 week with placebo

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ABSTRACT

Background Head and neck dermatitis (HND) is a variant of atopic dermatitis often seen in young adults. A hypersensitivity to *Malassezi* antigens is considered to be of pathogenic importance. Previous mostly uncontrolled studies have shown that oral antimycotics might be of use in this condition.

Objective To evaluate the efficacy of itraconazole in the treatment of HND in a randomized, double-blind, placebo-controlled trial.

Patients Adult patients with HND were included. Systemic steroids and oral/topical antimycotics were avoided 1 and 2 months prior to the trial. Topical steroids were not allowed in the head and neck area within 2 weeks. Patients in generally good health were included and female patients had to have had a negative urine pregnancy test. The patients signed an informed consent.

Study design The study included a 7-day treatment period and a follow-up period of 105 days. Control visits were carried out on days 3, 7 and 14 and after 15 weeks.

Methods The SCORAD index (one for the head and neck area and one for the remaining surface area) and global evaluations by patient and investigator were used for clinical evaluation at each visit. Prick tests with *Malassezia* antigens and *Candida albicans* antigen were carried out at the start of the trial and included positive and negative controls. The patients were randomized into three groups, which were treated with 400 mg itraconazole daily, 200 mg itraconazole daily or placebo, respectively, for 7 days.

Results The number of patients included was 53: 18 had 200 mg itraconazole daily, 17 had 400 mg itraconazole daily and 18 placebo. At days 7 and 14, significant improvement was seen in the SCORAD of the head and neck area for the groups given 400 mg itraconazole daily ($P = 0.0385$ and $P = 0.0134$), and 200 mg daily ($P = 0.0104$ and $P = 0.0006$). Patients in the placebo group improved slightly ($P = 0.0785$). At day 14, comparison of improvement of SCORAD of the head and neck area between all three groups showed a significant difference in favour of the 200 mg itraconazole group compared to the placebo group ($P = 0.0318$). The prick test was positive for *Pityrosporum ovale* in 37% and negative for *C. albicans* in all patients.

Conclusions One week of treatment with 200 or 400 mg itraconazole as a single treatment has a significant effect on the head and neck area. Compared to placebo there was a significant improvement in SCORAD of the head and neck area in favour of the 200 mg itraconazole group after 14 days. The important observation seems to be that antifungal systemic treatment has a significant SCORAD reduction of atopic dermatitis, irrespective of the presence of allergy.

Key words: atopic dermatitis, SCORAD, itraconazole

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Introduction

In young adult patients with atopic dermatitis (AD), erythematous, scaling and itching eczema of the face, neck and the upper part of thorax, that is head and neck dermatitis (HND), is often an essential problem. The eczema varies in intensity with sudden flares causing great discomfort. Concomitant eczema is frequently present on the anterior aspects of the forearms and the hands, but the eczema activity on the rest of the body is moderate or mild. However, HND may be part of a generalized eczema. *Malassezia furfur* is a family of mainly lipophilic yeasts normally colonizing human skin especially in the head and neck area and intertriginous folds. The yeast is especially abundant in young people after puberty. The family includes seven subspecies of which *M. furfur*, *M. globosa*, *M. sympodialis* and *M. restricta* have been isolated from normal skin as well as from patients with AD, seborrhoeic dermatitis and pityriasis versicolor.¹ Positive skin prick tests to *Malassezia* antigens (MA) and specific immunoglobulin E (IgE) antibodies have been demonstrated in a large number of patients with AD and especially in those with HND. A delayed type of hypersensitivity to MA also seems to play a role.^{2–7} In the study by Kieffer *et al.*,² 79% of 33 patients with HND were prick-test positive vs. 44% of 22 AD patients without HND. IgE antibodies were found in two-thirds of AD patients and predominantly in the HND group. Furthermore, a delayed-type hypersensitivity to MA was seen in some of the patients. Rokugo *et al.*³ found 71% of 35 patients with AD prick-test positive to MA and also demonstrated delayed hypersensitivity to MA in 64% of 118 AD patients. IgE antibodies to MA was demonstrated by Wessels *et al.*⁴ in 49% of 72 AD patients compared to 1 of 27 atopic patients without eczema. Kim *et al.*⁵ observed that 68% of 80 patients with HND had specific IgE antibodies against MA and 45% had a positive prick test to MA. Based on these examinations antimycotics have been used in HND dermatitis in open and controlled studies during the past 20 years.^{6–10} In the first controlled study by Clemmensen and Hjorth,⁸ ketoconazole 200 mg daily for 4 weeks was shown to be very effective in the group of patients with HND only, while the effect in patients with generalized eczema was more dubious. Itraconazole (ITR) has been used in open studies in doses of 100–200 mg daily for several months.^{9,10} The success of the treatment was evaluated by the clinical improvement and/or measured by the reduction of topical steroids used. The results have shown that oral ketoconazole and ITR may be of benefit in HND. However, concomitant treatment with topical steroids may produce less clear-cut answers to the question about the proper efficacy of antimycotics in this condition.⁷

Because of the changing course of AD and the many complicating factors we have found it necessary to conduct a trial in patients with HND. ITR was chosen because of its more favourable safety profile compared to ketoconazole and because the experience with the drug in open treatment of HND has been beneficial. To

determine whether the treatment was effective, ITR was given as monotherapy. Thus, steroids should be completely avoided in the head and neck area during therapy. The objective was to assess the efficacy of ITR 200 mg or 400 mg daily for 1 week in HND compared to placebo, with 15 weeks of follow-up. A secondary objective was the assessment of the efficacy of the whole body.

Materials and methods

Patients

Patients between 18 and 50 years with AD involving the head and neck area were included. The diagnosis of AD was defined according to the criteria of Hanifin and Rajka.¹¹ At least four of the clinical signs, erythema, oedema/papulation, oozing/crust, excoriation, lichenification and/or dryness, should be present. The total intensity score of the head and neck area should be greater than the total intensity score of the remaining surface area. In addition, inclusion criteria were a generally good health, negative urine pregnancy test for women and signed informed consent.

Exclusion criteria included systemic steroid therapy within 1 month prior to entry and/or systemic or topical antifungal therapy within 2 months before entry. The patients were recruited from four dermatological outpatient departments and one dermatological private clinic.

Experimental design

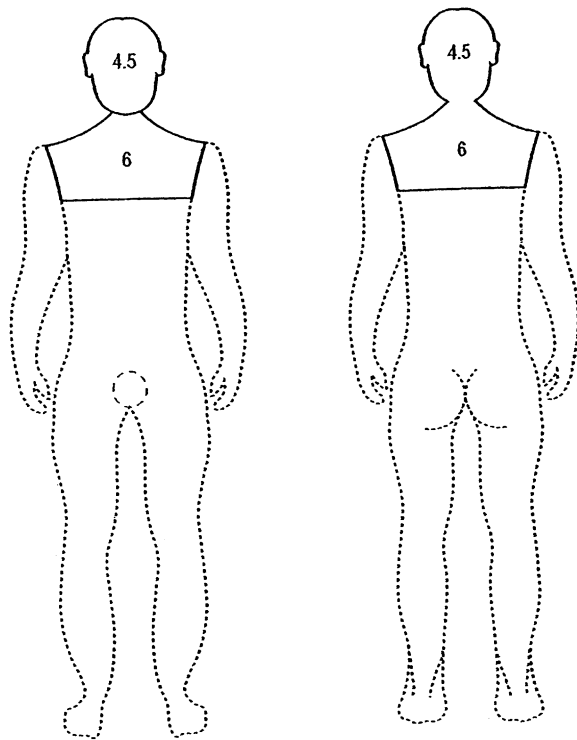
The study was performed as a randomized, placebo-controlled trial with a 7-day treatment period and 105 days of follow-up. The patients were seen and evaluated at baseline, on days 3, 7 and 14, and after 15 weeks. Patients were excluded from the study if adjuvant therapy for HND was needed.

Investigations

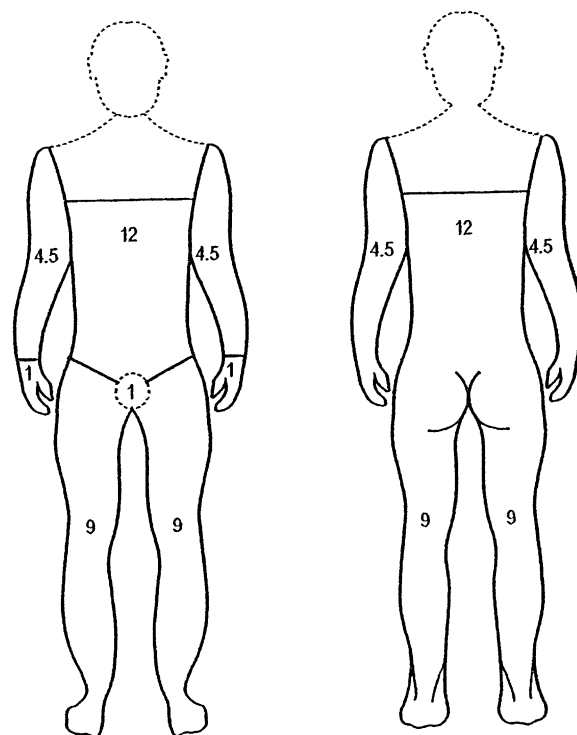
For the clinical evaluation the SCORAD index was used.¹² The SCORAD index is calculated by the formula i.e. $(0.2 \times A) + (3.5 \times B) + C$, in which A is the extent, and B the intensity of eczema. C is itch and sleep loss. Intensity accounts for 60% of the total score. In measuring the extent the rule of nine was used. Two separate body areas were evaluated: one including head, neck and upper thorax above a line through the nipples and another including the remaining surface area of the trunk and the extremities (fig. 1).

The patients as well as the investigator gave a global evaluation, which comprised both the head and neck area and the body and extremities, at each visit. The scores for global clinical evaluation were 1 = cured, 2 = markedly improved, 3 = moderately improved, 4 = no change, and 5 = deterioration.

Hypersensitivity to MA was evaluated at day 0 by the prick test with a standardized extract of MA 5 mg/mL (ALK-Abello, DK). In addition, the prick test with *Candida albicans* 1 : 20 w/v



a) Head and neck area (extent in %)



b) Area below the nipples (extent in %)

fig. 1 Areas for SCORAD evaluation: (a) head and neck area (extent in %); (b) area below the nipples (extent in %).

(Soluprick) was performed to evaluate an eventual cross-reactivity between the fungi. Histamine 10 mg/mL (Soluprick) and NaCl 0.9% (Soluprick) were used as positive and negative controls, respectively.

Treatment

The patients were treated with ITR 200 mg daily, 400 mg daily or placebo for 7 days. The drugs were provided in capsules with 100 mg ITR or placebo. The patients took two capsules morning and night together with a meal. Patients and physicians were blinded. Code envelopes were kept unbroken at the site.

Statistics

An intention-to-treat analysis was carried out on all patients receiving treatment. The main comparison of efficacy parameters was performed between day 0 and days 3, 7, 14, 56 and 112. There was a high dropout rate because of the need for adjuvant therapy between days 14 and 56, so the results obtained at day 14 were chosen as the basis for conclusion.

The primary endpoint for success was a reduction in the initial SCORAD HND by 50% during or after treatment.

The Kruskal–Wallis test was applied for the differences between the three groups on the following parameters: (1) baseline characteristics, that is differences in age, weight, height, heart rate, blood pressure, itch and sleep loss; (2) the primary parameters, SCORAD HND and global evaluation; and (3) the secondary parameter SCORAD body minus HND. The χ^2 -test was applied to differences in sex, race and prick test. For differences within the groups Wilcoxon's matched pairs signed rank sum test was applied to SCORAD HND and SCORAD body without the head and neck area.

Results

Demographics

Fifty-three patients (29 females and 24 males) were included in the study from December 1997 to December 1998 after informed consent was obtained. Eighteen patients had ITR 200 mg daily, 17 ITR 400 mg daily, and 18 placebos. Baseline characteristics for the three groups are shown in Table 1. At day 14, the numbers of patients were 15, 14 and 14, respectively. After that day the number of participants was reduced to less than half in all groups because flare up of the eczema needed adjuvant therapy thus violating the protocol. No patients left the study because of adverse events.

SCORAD

The results of the intention-to-treat analysis of SCORAD HND are given in fig. 2 and fig. 3. At day 3 there was a clear but only

Table 1 Demographics. The Kruskal–Wallis test was used for comparison between groups. A Vas scale (0–100 mm) for registration of itch and sleep loss was kept by the patient for the first 14 days

Treatment	ITR 400 mg (n = 18)	Placebo (n = 17)	ITR 200 mg (n = 18)	P
Age (years)	28.5 ± 7.5	26.1 ± 4.3	29.7 ± 8.4	0.6506
Weight (kg)	71.3 ± 11.2	68.1 ± 11.0	72.1 ± 11.4	0.3399
Height (cm)	172.6 ± 8.6	174.2 ± 11.2	176.2 ± 11.3	0.6696
Itch (mm)	37.3 ± 28.3	47.2 ± 29.9	58.4 ± 25.0	0.0608
Sleep loss (mm)	13.1 ± 24.4	25.8 ± 28.4	34.7 ± 26.9	0.0204

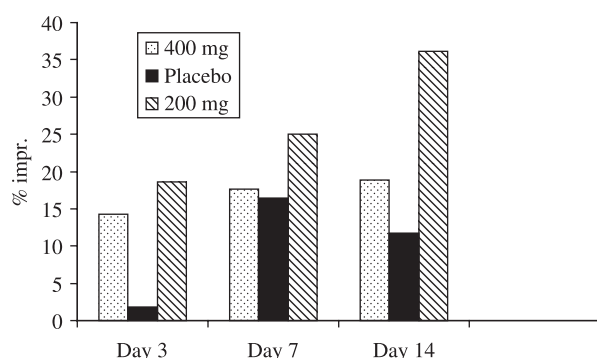


fig. 2 Percentage improvement of SCORAD HND on days 3, 7 and 14 compared to baseline. At day 14, $P = 0.0318$ (Kruskal–Wallis).

borderline significant decrease in SCORAD within the groups treated with 400 or 200 mg ITR daily, but not in the placebo group. The improvement became more obvious at days 7 and 14 where the decrease in SCORAD HND became significant, i.e. $P = 0.0385$ and $P = 0.0134$, respectively, for the 400 mg group. For the 200 mg ITR group the improvement in SCORAD HND was more distinct, namely $P = 0.0104$ and $P = 0.0006$, respectively. The placebo group also improved at day 7, but the result was not statistically significant ($P = 0.0785$). This was also the case at day 14. Comparison of improvement of SCORAD HND between all three groups showed a significant difference at day 14 ($P = 0.0318$) in favour of the 200 mg ITR group. A reduction in the initial SCORAD HND by 50% at day 14 was obtained in eight patients treated with ITR vs. two on placebo, but was not found in the mean number of patients. Four of these eight patients had a lasting improvement noted at the visit 6 weeks later, while four relapsed 1 week later. In seven of eight itch and in five sleep loss had improved at the time when more than 50% improvement was registered.

Mean SCORAD body at day 1 was 30.5 and 35.5 for the treated groups, respectively. For the placebo group it was 28. These figures did not change significantly during the study in any group.

Global evaluation

The global evaluation by the investigator and the patients showed no significant improvement in general clinical condition in any

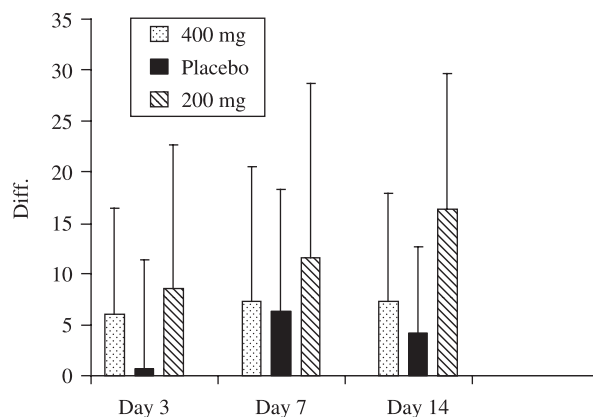


fig. 3 Mean difference in SCORAD HND on days 3, 7 and 14 compared to baseline. At day 14, $P = 0.0318$ (Kruskal–Wallis). The mean difference is the average of the individual differences.

group. In the treated group as a whole the mean scores were 3.5 and 3.6, respectively, meaning unchanged to moderate improvement. In the group of eight patients who improved more than 50% the mean scores were 2.3 and 2.5, respectively, meaning moderate to marked improvement.

Prick test

The prick test was performed in 51 patients. In 19 (37%) the prick test with MA was positive. None was positive to *C. albicans* antigen.

Adverse events

No adverse events were observed in the groups treated with ITR.

Discussion

From the present study it can be concluded that 1-week single treatment with 200 or 400 mg ITR has a significant effect on HND, but not on AD generally. However, only eight of 36 patients treated with the active drug obtained more than 50% improvement of SCORAD HND, which was the primary endpoint. Relapses were frequent probably because of gradual elimination of the drug from the skin. The rationale for the dose of 200/400 mg daily for 7 days was that ITR would be present in therapeutic concentrations for at least 1 week after treatment.¹³ Furthermore, this treatment schedule is sufficient to cure pityriasis vesicolor.¹⁴

Global evaluation included the whole body surface area. Although improvement in the head and neck area had taken place, the lack of improvement in the remaining body surface influenced the answer to the question negatively. Separate evaluation would clearly have been more appropriate.

The number of patients with a positive prick test to MA was relatively low (37%) compared to previous studies. A relationship

between a positive prick test to MA and the success of ITR therapy could not be demonstrated.

Intermittent treatment schedules in combination with topical steroids, for instance comprising 2 days treatment with ITR per week, have been practised in open trials with success. Future studies applying longitudinal and intermittent treatment might be indicated. The design of this study may be considered slightly unrealistic as steroids were not allowed, but because of this condition the effect of ITR, though modest, became convincing. The overall impression from this investigation is that there is a subgroup of patients with AD and HND who react with a clear reduction of clinical symptoms after short-term treatment with ITR, and that ITR might be considered a valuable alternative or supplement in the treatment of HND.

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