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A clinical double-blind trial comparing amorolfine cream 0·5% (RO-14-4767) with bifonazole cream 1% in the treatment of dermatomycoses

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Summary

In a double-blind parallel study, 40 patients with dermatomycoses (one cutaneous candidosis and 39 dermatophyte infections) were treated topically with amorolfine (RO-14-4767) cream (0·5%), a new antifungal compound, or with bifonazole cream (1%). The treatment was applied once daily and was continued until 1 week after resolution of the symptoms, the maximum duration of treatment was limited to 6 weeks. Assessment of results was based on both clinical and mycological parameters. The percentages of amorolfine- and bifonazole-treated patients who were clinically and mycologically cured were 83·33% and 78·95%, respectively. Two patients treated with amorolfine and one patient treated with bifonazole were withdrawn from the trial because of side-effects. There was no significant difference between the two creams in clinical and mycological cure rates and tolerance.

Amorolfine (RO-14-4767) (F. Hoffman La Roche & Co., Basel) is a new topical antimycotic compound, and is a phenyl-propyl-morpholine derivative unrelated to the imidazoles or the polyene antibiotics.[1]

Experiments *in vitro* and *in vivo* (candida vaginitis in rats, tricophytosis in guinea-pigs) have shown that the activity of amorolfine was superior to that of imidazole derivatives and polyene antibiotics.[1–3] In volunteers no visible skin reaction was observed after occlusion with cream for 24 h. After dermal application of amorolfine to the intact and stripped skin of human volunteers, the compound was not detected in plasma, urine or faeces.[4] Application of vaginal tablets (one tablet on 6 consecutive days) was also well tolerated without systemic absorption.[4]

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Bifonazole (Mycospor, Bayer), a new topical imidazole antimycotic with a wide range of antifungal activity *in vitro*,[5] has been found to be effective in many clinical studies for the treatment of superficial fungal infections (dermatophytoses, cutaneous candidosis, pityriasis versicolor and erythrasma).[6] Bifonazole is retained for long periods on the skin, and based on this, the manufacturers recommend that the compound can be applied once every 24 h and the duration of therapy can be reduced to 2 or 3 weeks, depending on the causative organism and site of the infection.[6] In several studies bifonazole has been shown to be equal or superior to comparable imidazole antifungals, to have fewer side-effects and to have the distinct advantage of a single-daily-dose treatment.[7] Bifonazole is available in cream, solution, gel and powder formulations containing 1% of the active antifungal. It has been recently introduced into clinical use in several European countries.

The aim of this study was to try to determine the efficacy and tolerance of amorolfine (0·5%) compared with bifonazole cream (1%) in the treatment of patients with superficial fungal infection.

Patients and methods

Medication

The trial was a double-blind parallel study and patients were randomized into one of the two treatment groups, either receiving 0·5% amorolfine or 1% bifonazole cream. Neither the clinician nor the patient knew which preparation was being used. Patients were instructed to apply the cream once daily to the affected areas and to spread it thinly. Treatment was continued for 1 week after disappearance of clinical symptoms but the maximum duration of the treatment was limited to 6 weeks.

Patients

All patients were assessed prior to treatment with a detailed history and clinical examination. Only patients suffering from cutaneous candidosis and dermatophytosis confirmed by direct microscopy and culture were included in the study. Written consent was obtained from all patients. Pregnant women, women in whom pregnancy could not be excluded with certainty, patients with secondary bacterial infection and patients who had used antimycotics during the 2 weeks prior to the start of the study were excluded from the trial.

Clinical assessment

The patients were seen once a week during treatment, at the end of treatment (Control 1) and 3 weeks later (Control 2). Parameters of clinical disease activity (itching, burning, redness, weeping, scaling, pustulation, incrustation) were assessed and scored as: 1, not present; 2, slight; 3, moderate; 4, severe. To evaluate tolerance, adverse effects were recorded and rated according to severity as slight, moderate and severe.

Evaluation

At the conclusion of the trial (Control 1) the clinical efficacy of the test drug was rated globally as: cured, improved, unchanged, and deteriorated.

The overall evaluation of the results was made 3 weeks post-therapy (Control 2) by correlating the clinical and mycological findings.

Cured at Control 2 (3 weeks post-treatment) was defined by an absence of clinical signs except for residual features (slight erythema, slight scaling or hypopigmentation) with negative direct microscopy and culture.

Improved was defined by improvement of clinical symptoms, with negative direct microscopy and culture.

Treatment failed was defined by improvement, stability or deterioration of clinical symptoms with positive direct microscopy and/or positive cultures.

Statistical analysis

Patients' symptoms and clinical improvement were analysed using the Wilcoxon test to compare successive time points for each treatment group and using the Mann–Whitney *U*-test to compare results of treatments at each visit. The χ^2-test was used to compare the mycological response (KOH and culture) and Fisher exact test to compare the side-effects of amorolfine and bifonazole.

Table 1. Demographic characteristics of patients and history

	Amorolfine ($n=20$)		Bifonazole ($n=20$)	
	Male	Female	Male	Female
Number of patients	7	13	11	9
Mean age (years)	24·71	24·46	25·45	21·22
Age range (years)	(17–37)	(8–58)	(2–48)	(9–47)
Mean duration of the mycoses (weeks)	32·28	3·07	33	4·55
Duration range (weeks)	(1–84)	(1–8)	(1–96)	(1–13)
Previous antifungal therapy (Number of patients)	4	0	0	1
Previous topical corticosteroids (Number of patients)	2	6	3	1

Results

A total of 40 patients were included in the trial.

The amorolfine group included 20 patients, seven males and 13 females. The demographic characteristics and patients' history are recorded in Table 1. Four patients in this group had undergone previous antifungal therapy and eight patients had been treated with topical corticosteroids (the majority were fluorinated derivatives) before entering the trial. In this group one patient was a diabetic.

The bifonazole-treated group included 20 patients, 11 male and nine female. The patients' characteristics and history are also recorded in Table 1. Only one patient in this group had received previous antifungal therapy and four had been treated topically with corticosteroids.

Infection was present at more than one site (forearm and face) in one patient treated with bifonazole. One patient in the amorolfine group had a superficial candida infection that involved the groin (Table 2). The rest of the patients in both groups had dermatophyte infection. The body and feet were the most common sites of infection. *Microsporum canis* was the predominant dermatophyte species, being isolated from 15 of the 39 patients (38·5%) with dermatophyte infections. All the fungi isolated before treatment were sensitive to both antifungals *in vitro*, having minimal inhibitory concentrations (MIC) between 0·1 μg/ml and 1·6 μg/ml for amorolfine and between 0·2 μg/ml and 3·12 μg/ml for bifonazole. None of the strains isolated after treatment was stopped were shown to have developed resistance to either compound *in vitro*.

Acceptability

All the patients found the creams easy to apply and cosmetically acceptable in terms of the lack of greasiness, pleasantness of fragrance, ease of spreading and lack of local irritation.

Table 2. Dermatophyte infections—distribution of infected sites and fungi isolated

	Amorolfine	Bifonazole	Total
Sites involved			
Body	13	10	23
Feet (interdigital spaces)	3	6	9
Groin	3	2	5
Hand	0	1	1
Face	0	1	1
Fungi isolated*			
Microsporum canis	9	6	15
E. floccosum	4	2	6
Trichophyton rubrum	3	5	8
T. mentagrophytes var. *granulosum*	1	4	5
T. mentagrophytes	2	2	4
T. mentagrophytes var. *interdigitale*	0	1	1

* One patient treated with amorolfine had *Candida albicans* infection in the groin.

Side-effects

Two patients in the amorolfine group (Table 3) had to interrupt therapy due to adverse reactions and were therefore not evaluated for efficacy. Both patients developed burning, itching and redness at the onset of medication. This irritation gradually increased and after 2 weeks of therapy treatment had to be stopped. Both patients had groin infections one with *Trichophyton rubrum* and the other with *Candida albicans.*

In the bifonazole group, one patient with *T. mentagrophytes* var. *granulosum* infection of the hand developed side-effects on the tenth day of treatment, which were sufficiently severe to require treatment to be stopped. Erythematous vesicles and blisters appeared on the lesion, forearm and arm and lasted for 6 days. Moderate itching, burning and reddening also appeared on the lesion; this patient was consequently excluded from the analysis of efficacy.

Patch tests were not performed because all the patients refused consent.

Table 3. Results at Control 1 (end of treatment)

	Amorolfine* ($n=18$)	Bifonazole† ($n=19$)
Clinical results		
Cure	17	19
Improvement	0	0
Failure	1	0
Mycological results		
Positive microscopy	0	0
Positive culture	7	7

* Treatment stopped in two patients due to adverse reactions.
† Treatment stopped in one patient due to adverse reactions.

Table 4. Overall therapeutic results 3 weeks post-therapy

	Amorolfine ($n=18$)	Bifonazole ($n=19$)
Cure	15(83·33%)	15(78·95%)
Improvement	0	0
Failure	3(16·67%)	4(21.05%)

End of therapy

In the amorolfine group the mean duration of treatment was 4·66 weeks (3–6 weeks) and in the bifonazole-treated group the mean duration was 4·95 weeks (2–6 weeks). The clinical and mycological results are recorded in Table 3.

In the amorolfine-treated group, only one patient was judged to be a clinical failure. The rest of the patients in this group and all patients in the bifonazole group were evaluated as clinically cured although slight erythema, scaling or hypopigmentation persisted in some and were considered residual.

In all patients in both groups direct microscopy with KOH was negative and seven patients in each group had positive cultures.

Follow up

The overall evaluation 3 weeks post-treatment is recorded in Table 4.

Amorolfine group. Fifteen patients (83·3%) out of 18 evaluated were clinically and mycologically cured (the infected body sites were: groin, 1; feet, 3; and body lesions, 10). The fungi responsible for the infection were: *T. mentagrophytes* var. *granulosum,* 1;*T. mentagrophytes,* 2; *T. rubrum,* 2; *Epidermophyton floccosum,* 4; and *M. canis,* 6. The three patients (16·67%) considered failures had ringworm infection due to *M. canis.*

Bifonazole group. Nineteen patients were evaluated in this group and 15 patients (78·95%) were cured clinically and mycologically (the infected body sites were: face, 1; groin, 2; body, 6; and feet, 6). The fungi responsible for the infection were: *T. mentagrophytes* var. *interdigitale,* 1; *E. floccosum,* 2; *T. mentagrophytes* var. *granulosum,* 3; *M. canis 4; and T. rubrum,* 5.

Four patients were assessed as failures (21·05%), all had ringworm on the body. In two cases *T. mentagro-*

phytes was cultured and in two cases *M. canis* was responsible for the infection.

Discussion

Most of the clinical studies of amorolfine in superficial mycoses are still in progress. Preliminary efficacy evaluation of the first therapeutic results of a double-blind, dose ranging trial in dermatomycoses with a once-daily application comparing three cream concentrations (0·125%, 0·25% and 0·5%) of amorolfine with bifonazole cream 1% have shown that amorolfine, at all concentrations, is at least as effective as the control drug, bifonazole.[4]

In our study the statistical analysis showed no significant difference between amorolfine and bifonazole in terms of acceptability, side-effects, length of therapy and overall clinical and mycological response, but the mean duration of treatment (days) was longer in our study with both compounds than that reported in other clinical studies using amorolfine 0·5% cream and bifonazole 1% cream.[4] Possibly the predominance of *Microsporum canis* (38·5%) as the infecting organism in 15 patients may explain the slow clinical response. Furthermore the poorest mycological responses in both groups were shown by *M.canis.*, however, all but five patients infected by this organism were clinically and mycologically cured in the overall evaluation.

Eight patients in the amorolfine group and four in the bifonazole group (32·4%) had been treated locally with fluorinated corticosteroids before entering the trial, and could be defined as having steroid modified tinea[8] or tinea incognito.[9] Stopping the corticosteroids often leads to a flare up and may necessitate a much longer period of treatment with antifungals. This could also explain the slow clinical response in our group of patients.

The imidazole derivatives are widely used for the treatment of dermatomycoses, and bifonazole[6] has been shown to be equal or superior in several clinical trials when compared with other imidazoles. In our study the antifungal effects, acceptability and tolerance of amorolfine were comparable to bifonazole. However, because of the limited numbers included in the trial, more experience is necessary with higher numbers of patients and longer follow-up assessments; hopefully this would indicate the role of amorolfine in the topical treatment of dermatophytosis.

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