A double-blind clinical trial of fenticonazole (2%) spray versus naftifine (1%) spray in patients with cutaneous mycoses

D. Leiste, M.D.,
W. Braun,[a] M.D.,
W. Fegeler,[b] M.D.,
K. Fegeler,[b] M.D.,
A. Stary,[c] M.D.,
K. W. Ruping,[c] M.D.,
F. Klaschka,[d] M.D.,
E. Colli,[e] M.D.,
and
A. Sartani,[e] M.D.

Specialist Dermatologists, Minden, [a]Hamm, [b]Münster, [c]Dortmund, [d]Klinikum Steglitz, Berlin, Federal Republic of Germany, and [e]Medical Department, Recordati S.p.A., Milan, Italy

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Summary

A multi-centre, double-blind trial was carried out in 100 patients with cutaneous mycotic infections, confirmed by direct microscopy and/or culture, to compare the efficacy and tolerability of spray formulations of 2% fenticonazole and 1% naftifine. On entry, patients were allocated at random to receive once daily topical applications of one or other drug over a period of 2 to 4 weeks, treatment being stopped when patients had recovered or substantially improved. Clinical and mycological assessments were made before (baseline), at weekly intervals during treatment and, if possible, 2 to 3 weeks after the end of treatment (drug-free period). Treatment was continued for 19.25 days with fenticonazole and 19.62 days with naftifine. All patients had positive mycological findings on entry. The most frequently isolated pathogens were dermatophytes, mainly Trichophyton rubrum; however, Candida albicans was present in 33.3% of patients in the fenticonazole group and in 20.8% of those treated with naftifine. At the end of treatment, only 3 (6.3%) and 5 (10.4%) patients, respectively, of the 48 patients assessed in each group still had positive mycological findings. Assessments of symptoms indicated comparable, significant improvement in both groups, and at the end of treatment the overall opinion of doctors and patients was that about 90% of patients were cured or greatly improved. The end of the drug-free period evaluation showed that, of the patients assessed as cured or greatly improved at the end of treatment, only 1 (3.2%) patient who had received fenticonazole and 2 (6.3%) who had received naftifine were confirmed mycologically as having relapsed. Local burning after topical application of the spray was the only side-effect reported by 4 (8.2%) of 49 patients on naftifine and 3 (6%) of 50 patients on fenticonazole, 1 of whom voluntarily interrupted treatment. Both drugs, there-

fore, proved to be remarkably effective and well-tolerated in the treatment of superficial dermatomycoses and no significant differences could be demonstrated between them.

Key words: Fenticonazole — naftifine — antifungal agents, topical — dermatomycoses

Introduction

Of the thousands of fungal species classified, more than 100 are potentially pathogenic in man.[9] Some of them localize in the superficial layers of the skin, in the nails and hair, producing irritating lesions which, even if they rarely evolve into serious disfiguring lesions, need an appropriate treatment to be eradicated. *Trichophyton, Epidermophyton* and *Microsporum* species, collectively called dematophytes, are the most frequent causative organisms of superficial skin lesions. *Candida albicans,* a yeast which lives within the intestinal flora of man and usually behaves as an harmless saprophyte, can also produce cutaneous mycoses in some instances.

The introduction of topical antifungal treatment with the imidazole derivatives in the early 1970s resulted in a remarkable improvement in the therapeutic possibilities for treating dermatomycoses, particularly in the last few years when new, more active compounds became available.

Fenticonazole is an imidazole derivative synthesized in Italy by the Recordati Research Division;[7,11] it is a broad-spectrum antimycotic agent with a fungistatic or fungicidal activity against dermatophytes, *Candida* and many other yeasts and fungi.[2,12-14] In controlled clinical trials,[1,3,4,6] fenticonazole has been shown to be equal or superior in efficacy to commonly used imidazole compounds such as miconazole, econazole, clotrimazole and bifonazole. Most of the previous clinical studies have been performed using cream or lotion formulations of fenticonazole applied at least twice daily.

Naftifine is a recently introduced member of the allylamines,[8] a new class of antifungal agents, which has been shown to be effective topically when applied once a day in dermatomycoses and skin candidiasis.[15]

Because patient compliance is of utmost importance to achieve good therapeutic results, it was decided, therefore, to carry out a comparative trial of fenticonazole using a single daily application of its well-accepted spray formulation and a similar spray formulation of naftifine, also used once daily. Jung *et al.*[4] in their double-blind trial against bifonazole had already shown that fenticonazole cream was effective in dermatomycoses when applied once daily.

Patients and methods

Patients selected for inclusion in the trial were ambulant or bedridden patients of either sex who were affected by cutaneous mycoses produced by dermatophytes or other pathogenic fungi, the diagnosis being confirmed by microscopic and/or cultural tests. Patients who had received previous antimycotic treatment within

2 weeks before the beginning of the study were not included. Pregnant or breast-feeding women, patients affected by serious systemic and metabolic diseases, subjects with a known hypersensitivity to imidazole derivatives or to topical treatments in general and non-compliant patients were also excluded.

The study was designed as a multi-centre, double-blind, parallel group trial and 100 patients were recruited at 5 centres in Germany. On entry, patients were allocated at random into two equal groups to receive treatment with either 2% fenticonazole or 1% naftifine solution. Both drugs were supplied in identical containers and, after thorough cleansing of the lesions, were applied topically as spray once daily for 2 to 4 weeks. The actual duration of treatment depended on the evaluation of the patient's clinical and mycological condition, treatment being stopped when patients recovered or were substantially improved.

Clinical and mycological controls (direct microscopic examination and/or cultures) were performed before the beginning of the study (basal evaluation), at weekly intervals during the treatment and, whenever possible, 2 to 3 weeks after the end of the treatment (drug-free period).

The following local symptoms were considered for the clinical evaluations: itching, burning, pain, erythema, exudation, weeping, pustules, scaling, rhagades, keratosis. Each was evaluated using a 5-point semi-quantitative scale (0=none, 1=slight, 2=slight/moderate, 3=moderate, 4=severe).

At the end of the treatment period, a global evaluation of the therapeutic efficacy, as judged by the patients' condition, was given using the following scale: 0=worse, 1=no improvement, 2=slight improvement (less than 70%), 3=good improvement (70% to 90%), 4=healed (no clinical or mycological evidence of disease). At the end of the drug-free period, patients were classified as: (i) relapse – clinical situation indicative of an active infection (with positive or negative mycological findings); (ii) sub-clinical persistence – clinical situation moderately worsened in relation to the results obtained at the end of the treatment and/or positive mycological findings; and (iii) recovered – complete clinical recovery with negative mycological findings.

Tolerability of the treatment was assessed by evaluating the possible appearance of local and/or systemic untoward events.

Statistical analysis

Data are presented as means±S.D. Between-groups statistical evaluation of parametric variables (age and duration of the infection, duration of the treatment and of the drug-free period) was carried out using the unpaired Student's t-test. Contingency tables analysis (χ^2) was used for sex distribution, previous infections, efficacy evaluation at the end of the treatment and of the drug-free period.

Final evaluation scores for signs and symptoms were compared with basal values by means of the non-parametric intra-group Wilcoxon signed-rank test. Basal, final and drug-free period evaluation scores were also compared by the non-parametric analysis of variance of Friedman, utilizing Dunn's test for multiple comparisons. Intra-group differences at any time interval considered (basal, final, drug-free period) were compared by the Mann Whitney U-test.

Results

Patients

Fifty patients (31 male and 19 female), with a mean age of 40.28±15.24 years (range 20 to 81 years), were treated with fenticonazole. The other 50 patients (27 male and 23 female), with a mean age of 38.56±15.97 years (range 7 to 66 years), received naftifine. Duration of the mycotic infection at the time of entry to the trial was 38.26±28.45 days in the fenticonazole group and 41.56±36.81 days in the naftifine group. Thirteen (26%) patients in each group had suffered 1 or more infections during the previous 12 months. No systemic or metabolic concomitant diseases known to favour mycotic infections were present in any patient. The localization of the most relevant mycotic lesions recorded before starting treatment was similar in the two groups (Table I), as were the basal mycological and clinical situation (Tables II and III).

Table I. Localization of the mycotic lesions: number (%) of patients

Site	Fenticonazole	Naftifine
Hands	7 (14%)	3 (6%)
Feet	23 (46%)	26 (52%)
Hands and feet	2 (4%)	
Groin	8 (16%)	5 (10%)
Body	10 (20%)	14 (28%)
Armpit		2 (4%)

The two groups, therefore, would appear to be homogeneous, at least for the variables considered, and are suitable for comparison of the results in this study.

Ninety-six patients were included in the efficacy evaluations because 4, 2 in each treatment group, had to be excluded. In the fenticonazole group, 1 patient interrupted treatment due to side-effects (burning) and 1 was non-compliant. In the naftifine group, there was 1 protocol violation and 1 patient was lost to follow-up immediately after admission.

Final evaluations were performed after 19.25±5.15 days of treatment (range 7 to 29 days) in the case of fenticonazole and after 19.62±4.86 days (range 11 to 28 days) in the case of naftifine. The difference between the two groups was not statistically significant.

Drug-free period evaluations were performed 22.56±12.12 days (range 8 to 64 days) after the end of the treatment in 36 (75%) patients in the fenticonazole group and after 23.25±11.01 days (range 10 to 59 days) in 36 (75%) patients of the naftifine group. The time interval of the drug-free period evaluation did not differ significantly between the two groups.

Microbiological evaluation

Microscopic findings. All the patients included in both groups had positive microscopic findings at the beginning of the trial. In both treatment groups, there were 44 (91.7%) negative and 4 (8.3%) positive findings at the end of the treatment. At the end of the drug-free period, of the 36 examinations performed in each

group, 3 (8.3%) were positive in the fenticonazole group, and 4 (11.1%) were positive in the naftifine group. In both treatment groups, 3 patients with positive findings at the end of the treatment also had positive microscopic findings at the end of the drug-free period, and the examination was not performed in 1 patient.

There was no case of relapse, therefore, in the fenticonazole group, but there was 1 in the naftifine-treated patients.

Cultural findings. The results of cultures performed on skin samples scraped off from affected areas are presented in Table II.

Table II. Micro-organisms isolated from skin cultures made before treatment (baseline), at end of treatment, and 2 to 3 weeks afterwards (drug-free period): number (%) of patients

Fenticonazole		Naftifine	
Micro-organisms	No. (%) patients	Micro-organisms	No. (%) patients
Baseline (n=48)			
Sterile	2 (4.2)	Sterile	1 (2.1)
Yeasts	1 (2.1)	Yeasts	1 (2.1)
Dermatophytes	2 (4.2)	Dermatophytes	1 (2.1)
T. rubrum	15 (31.3)	*T. rubrum*	19 (39.6)
T. mentagrophytes	5 (10.4)	*T. mentagrophytes*	6 (12.5)
T. violaceum	1 (2.1)	*T. violaceum*	1 (2.1)
E. floccosum	3 (6.3)	*T. schoenleini*	1 (2.1)
C. albicans	16 (33.3)	*Microsporum* sp.	1 (2.1)
Torulopsis sp.	1 (2.1)	*M. canis*	1 (2.1)
Aspergillus fumigatus	1 (2.1)	*E. floccosum*	1 (2.1)
Polyinfection*	1 (2.1)	*C. albicans*	10 (20.8)
		Penicillium sp.	1 (2.1)
		Aspergillus flavis	2 (4.2)
		Polyinfection**	2 (4.2)
End of treatment (n=48)			
Sterile	47 (97.9)	Sterile	45 (93.8)
Not performed	1 (2.1)	*C. albicans*	3 (6.2)
Drug-free period (n=36)			
Sterile	33 (91.7)	Sterile	29 (80.6)
T. rubrum	1 (2.8)	*T. rubrum*	1 (2.8)
C. albicans	1 (2.8)	*T. mentagrophytes*	1 (2.8)
Not performed	1 (2.8)	*T. violaceum*	1 (2.8)
		C. albicans	2 (5.6)
		Not performed	2 (5.6)

**T. mentagrophytes* + *T. rubrum* ****C. albicans* + dermatophytes; *T. rubrum* + *C. albicans*

At trial entry, cultures were obtained from all the patients and were all positive except in 3 patients (2 in the fenticonazole and 1 in the naftifine group). In 2 cases, 1 in each group, yeasts were present in cultures but a specific causative micro-organism could not be identified. Dermatophytes, mainly *Trichophyton rubrum,* were the most frequent pathogens isolated in both groups; however, *Candida*

albicans was identified in 33.3% of the patients of the fenticonazole group and in 20.8% of the patients of naftifine group.

At the end of the treatment period, cultures were negative in all patients in the fenticonazole group (culture not performed in 1 patient), although 3 patients were positive in the direct microscopy tests. In the naftifine group, 3 of the 48 patients were positive for *Candida albicans;* 2 of these patients were also positive microscopically and the other negative. Two patients with negative cultures were positive microscopically.

At the drug-free period examination, cultures were taken from 35 patients in the fenticonazole group and 34 in the naftifine group. Two (5.7%) of the fenticonazole-treated patients had positive cultures (1 for *Candida albicans,* 1 for *T. rubrum*). The patient with the positive *Candida albicans* culture was also positive microscopically as were 2 patients with negative cultures. In the naftifine group, 5 (14.7%) patients had positive cultures (2 *Candida albicans,* 1 *T. mentagrophytes,* 1 *T. violaceum* and 1 *T. rubrum*). One of the patients with a positive culture for *Candida albicans* had also been positive for this micro-organism at the end of treatment examination, whilst the second patient developed candidiasis during the drug-free period. Three of the 5 patients with positive cultures also had positive microspical findings. Moreover, 1 patient with a negative culture was positive microscopically.

In summary, therefore, cultures and/or microscopic findings were still positive after treatment in 4 (11.1%) patients in the fenticonazole group and in 5 (13.8%) in the naftifine group. There was no significant difference in the incidence of positive microbiological findings at the end of treatment or at the end of the drug-free period between the two groups.

Clinical evaluation

Details of the mean scores for local symptoms on entry, after treatment and at the end of the drug-free period are given in Table III.

The results show that for all the symptoms evaluated there were significant reductions ($p<0.01$) from baseline values in both groups after treatment. Moreover, these improvements had been maintained at the end of the drug-free period. No significant variation was observed between values recorded at each time point between the two treatment groups.

Global evaluations

Global evaluations of efficacy carried out by doctors and patients at the end of treatment are given in Table IV.

More than 85% of patients were evaluated as recovered or greatly improved with each of the two drugs, both in the investigators' and in the patients' opinion. There was no statistically significant difference between treatments.

Table V shows the results of the investigators' evaluation of the final outcome of treatment at the end of the drug-free period.

In the fenticonazole group, 1 patient classified as relapsing had a positive culture for *T. rubrum.* Two of the patients classified as having sub-clinical persistence of

Table III. Symptom evaluation scores on entry (baseline), at end of treatment, and 2 to 3 weeks afterwards (drug-free period): mean (±S.D.) values

Symptoms	Baseline (n=48)	End of treatment (n = 48)	Drug-free period (n=36)
Fenticonazole			
Itching	2.33±1.15	0.42±0.71*	0.30±0.67*
Burning	1.15±1.11	0.14±0.50*	0.17±0.51*
Pain	0.67±0.91	0.06±0.24*	0.06±0.23*
Erythema	2.48±0.82	0.73±0.74*	0.69±0.85*
Exudation	1.77±1.15	0.25±0.56*	0.17±0.45*
Weeping	1.62±1.08	0.06±0.24*	0.14±0.42*
Pustules	1.23±1.11	0.04±0.20*	0.06±0.23*
Scaling	2.10±1.07	0.62±0.70*	0.69±0.82*
Rhagades	1.27±1.21	0.17±0.48*	0.25±0.55*
Keratosis	0.73±0.96	0.15±0.41*	0.14±0.42*
Naftifine			
Itching	2.23±1.21	0.35±0.73*	0.47±0.94*
Burning	1.15±1.22	0.15±0.54*	0.17±0.61*
Pain	0.73±1.07	0.06±0.32*	0.08±0.37*
Erythema	2.33±0.75	0.87±0.70*	0.92±0.90*
Exudation	1.44±1.16	0.19±0.49*	0.08±0.28*
Weeping	1.39±1.08	0.15±0.54*	0.14±0.42*
Pustules	1.10±0.90	0.08±0.40*	0.06±0.23*
Scaling	1.87±1.00	0.65±0.73*	0.80±0.85*
Rhagades	1.02±1.04	0.12±0.44*	0.14±0.35*
Keratosis	0.54±0.82	0.15±0.46*	0.14±0.42*

*$p<0.01$ versus baseline

the infection had negative mycological findings. In the naftifine group, 2 of the patients who were considered to have relapsed had positive cultures, 1 for *T. rubrum* and 1 for *Candida albicans*. Of the 2 patients classified as having subclinical persistence, 1 had negative mycological findings and 1 had a positive microscopic result.

Table IV. Evaluation of the patients' condition at the end of treatment: number (%) of patients

Assessment	Fenticonazole (n=48)	Naftifine (n=48)
Doctors		
Recovery (clinical and mycological)	35 (72.9)	35 (72.9)
Greatly improved	7 (14.6)	7 (14.6)
Slightly improved	5 (10.4)	5 (10.4)
No improvement	1 (2.1)	
Worse		1 (2.1)
Patients	(n=47)*	
Recovery	33 (70.2)	37 (77.1)
Greatly improved	9 (19.2)	6 (12.5)
Slightly improved	3 (6.4)	3 (6.3)
No improvement	2 (4.3)	1 (2.1)
Worse		1 (2.1)

*Not recorded in 1 patient

Table V. Overall evaluation of response to treatment at the end of the drug-free period: number (%) of patients

Assessment	Fenticonazole (n=36)	Naftifine (n=36)
Recovery (clinical and mycological)	28 (77.8)	27 (75.0)
Sub-clinical persistence	5 (13.9)	4 (11.1)
Relapse	3 (8.3)	5 (13.9)

Tolerability

All patients except for the 1 in the naftifine group who was lost to follow-up were included in the evaluation of tolerability of the two drugs.

Three (6%) of the 50 patients in the fenticonazole group reported a feeling of burning after application of the spray. This side-effect was slight in 1 case and moderate in the other 2 patients, 1 of whom voluntarily interrupted treatment. Four (8.2%) of the 49 patients in the naftifine group also reported local burning, slight in 2 cases, severe in 1 and not specified in 1 patient.

Discussion

This double-blind controlled clinical study indicates that once-daily application of fenticonazole in its spray formulation is at least as effective as the once-daily application of naftifine spray in eradicating superficial dermatomycoses produced by common dermatophytes and also by other fungi, particularly *Candida albicans*. After 3 weeks of treatment, 93.8% of fenticonazole-treated patients and 89.6% of those treated with naftifine had negative microbiological findings. Clinically, in both treatment groups patients were evaluated as cured or greatly improved in about 90% of cases. Only a few of the patients assessed as cured or greatly improved at the end of the treatment relapsed; 1 (3.2%) in the fenticonazole group and 2 (6.3%) in the naftifine group with confirmed mycological findings.

The results obtained with the two drugs, therefore, appear to be comparable although there was a trend in favour of fenticonazole. In the fenticonazole group, all 16 patients in whom *Candida* infection was confirmed by culture had negative cultures at the end of treatment whereas in the 10 patients with confirmed *Candida* infection, 3 still had positive cultures at the end of treatment. Moreover, although the difference was not statistically significant, the number of micro-organisms isolated at the end of the drug-free period was larger in the naftifine-treated than in the fenticonazole-treated patients, i.e. 5 (17.2%) versus 2 (5.7%).

Previous published results have indicated that fenticonazole is at least as effective as other currently widely used topical antifungal agents,[1,3-6] and a comparable cure rate of more than 90% was achieved irrespective of the formulation used. In the present study, the overall results were comparable with those obtained in most controlled clinical trials in which cream or lotion formulations were applied twice daily and confirm the therapeutic efficacy of fenticonazole applied once daily. In a recently published report[10] of a multi-centre trial, 162 of the 752 patients studied were treated with a spray formulation of fenticonazole using once and multiple daily applications. However, a direct double-blind comparative trial of once versus

twice daily applications has only been performed for the cream formulation.[3] The results of this study indicated that both application regimens were substantially equi-effective. Although the present study did not attempt to compare different dosing schedules, it is difficult to believe that the results obtained could be improved further by using more frequent applications of the medication.

Slight to moderate burning was the only side-effect reported for both treatments. The frequency, not significantly different for the two test drugs, was similar to that observed in previous studies in which fenticonazole and other well known imidazole derivatives were used.

In conclusion, fenticonazole spray appears to be an effective and well-tolerated treatment for superficial dermatomycoses and is at least comparable to or perhaps even better than naftifine.

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