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New Therapeutic Approach in Skin Mycoses: A Comparative Trial Once Versus Twice Daily Applications of Fenticonazole in Comparison to Miconazole

Neuer Therapieansatz bei Hautmykosen: Studie über die tägliche Einmal- und Zweimalanwendung von Fenticonazol im Vergleich mit Miconazol

P. Vannini[1], E. M. Difonzo[1], C. I. Cordaro[2], A. Sartani[2] and E. Panconesi[1]

[1] Istituto di Clinica Dermosifilopatica, Università di Firenze, Italy
[2] Recordati S. P. A., Medical Department, Milano, Italy

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Summary: Fenticonazole is a new potent antimycotic agent. Its efficacy and tolerability in once and twice daily applications were compared in a double-blind trial with those of miconazole, in the treatment of superficial skin mycoses, in 60 patients randomly assigned to the 3 treatment groups. A comparison of the mycological and clinical cure rates of these well-matched groups showed no difference between treatments. It is concluded that fenticonazole is a useful treatment for cutaneous fungal infections and when applied once daily it has clear advantages due to improved patient's compliance.

Zusammenfassung: Fenticonazol ist ein neues potentes Antimykotikum. In einer Doppelblindstudie wurden Wirksamkeit und Verträglichkeit einer täglichen Einmal- und Zweimalanwendung von Fenticonazol mit der von Miconazol bei der Behandlung von Hautmykosen an 60 randomisierten Patienten in drei Behandlungsgruppen verglichen. In der mykologischen und klinischen Heilungsrate zeigten sich in den drei Behandlungsgruppen keine Unterschiede. Daraus wird geschlossen, daß Fenticonazol ein wirksames Mittel gegen Hautmykosen darstellt und daß die tägliche Einmalanwendung wegen der verbesserten Patienten-Compliance klare Vorteile hat.

Introduction

The increasing incidence of superficial skin mycoses requires a continuous pharmacological research for new efficacious and safe compounds with antifungal activity. Compliance with treatment is also becoming a major factor in determining the therapeutic response (1).

Imidazole derivatives form a well known class of compounds endowed with antifungal activity. Recently a new imidazole derivative, fenticonazole, was developed by Recordati SPA (Milano) (2). In vitro studies evidenced

its activity against dermatophytes and yeasts responsible for superficial mycoses (3–8). Animal studies confirmed its efficacy as well as its good tolerability (8–11). Clinical trials, both controlled and uncontrolled, have clearly shown its efficacy through high cure rates attained in patients with superficial skin mycoses (12–16). Most of these trials were conducted with twice daily applications.

The present trial was performed in order to investigate the efficacy of a new regimen of one application daily as compared to two applications per day of fenticonazole and miconazole.

Materials and Methods

Sixty outpatients seen at the Mycological Department of the University Dermatology Clinic in Florence were included in the study. They were of both sexes, over 18 years of age, and suffered from superficial mycoses, *Candida* infections and pityriasis versicolor (Table 1). They were randomly assigned to one of the 3 treatment groups:

A – fenticonazole 2% cream applied twice daily,
B – fenticonazole cream applied once daily,
C – miconazole 2% cream applied twice daily.

Treatments were fully blinded and patients on once daily applications had an identical placebo cream applied in the morning in addition to the active treatment applied in the evening. Adhesion to the treatment scheme was checked at the end of the trial by control of the used tubes. The treatment period was of 3 weeks duration and no concomitant topical applications of other medications or systemic anti-fungal agents were allowed.

Symptoms and signs such as: itching, burning, erythema, edema, desquamation, discolouration, were assessed on a 0–3 points scale (0 = absent to 3 = severe) before treatment and the clinical status reassessed on days 7, 14 and 21 as: unchanged or worsened, mild improvement, remarkable improvement, and cured. Mycological examinations including: direct microscopy, culture on Sabouraud Agar, and Wood's light for pityriasis, were also performed upon recruitment and weekly thereafter while under treatment.

At the end of the trial the investigator gave a final overall judgement on efficacy on a 0–4 points scale (0 = nil to 4 = excellent). The final analysis took into consideration the following definitions of cure rate:

- clinical cure: complete disappearance of symptoms and signs
- mycological cure: negative mycological tests
- complete cure: clinical and mycological cure in the same patient.

All patients were checked for recurrences 2 weeks after cessation of treatment.

Tolerability was also assessed by monitoring side-effects.

Statistical analysis was performed using a one-way analysis of variance to analyse homogeneity of entry data between the 3 groups, and to evaluate the difference in symptoms ratings and final judgements between the groups. The Mantel-Haenszel chi square test was used to analyse differences between groups in cured versus non-cured patients, tolerability data and frequency of relapses.

Results

Homogeneity tests have shown no differences between the 3 groups as to age, type of mycosis distribution and initial severity of the disease. The 3 treatment groups are therefore comparable (Table 1).

Table 2 shows the clinical improvement rate during the 3 weeks treatment period. There was no statistical difference between treatments at any stage.

Table 3 shows the results of the microscopical examination at each control visit including a post-treatment check on day 35. There was no difference between treatment

Table 1: Distribution of patients by vital data (means ± SD) and initial diagnosis in the 3 treatment groups

	Groups		
	Fenticonazole b. i. d.	Fenticonazole o. d.	Miconazole b. i. d.
Age (years)	35.1±11	41.2±15	38.0±16
Duration of disease (days)	70.0±44	66.6±101	53.5±32
Severity (symptoms score)	2.7±0.5	2.7±0.5	2.7±0.5
Diagnoses and infective agent:			
T. corporis	4	4	3
— *T. rubrum*	3	4	2
– *M. canis*	–	–	1
– negative culture	1	–	–
T. cruris	2	4	2
– *T. rubrum*	–	1	1
– *M. canis*	2	3	1
T. pedis	1	4	–
– *T. rubrum*	1	–	–
– negative culture	1	–	–
Candidosis	6	7	7
– onichomycosis	2	4	3
– others	4	3	4
Pityriasis versicolor	7	5	8
Total	20	20	20

Table 2: Percentage of patients per degree of improvement for symptoms and signs at each control visit

	Days		
	7	14	21
Fenticonazole b.i.d. (n=20)			
no change	10	–	–
mild improvement	80	15	–
remarkable improvement	10	85	5
cure	–	–	95
Fenticonazole o.d. (n=20)			
no change	30	–	–
mild improvement	70	40	–
remarkable improvement	–	60	5
cure	–	–	95
Miconazole b.i.d. (n=20)			
no change	25	–	–
mild improvement	70	35	–
remarkable improvement	5	65	5
cure	–	–	95

Table 3: Percentage of patients with negative findings on microscopical examination at each control visit

	Days			
	7	14	21	35
Fenticonazole b.i.d.	50	95	95	90
Fenticonazole o.d.	50	80	95	80
Miconazole b.i.d.	35	90	95	90

Table 4: Percentage of patients with negative findings of either culture (C) or Wood's light (W) at each control visit

	Days							
	7		14		21		35	
	C	W	C	W	C	W	C	W
Fenticonazole b.i.d. (n_c=15, n_w=7)	23	100	92	100	92	100	85	100
Fenticonazole o.d. (n_c=15, n_w=5)	40	80	73	100	93	100	73	100
Miconazole b.i.d. (n_c=12, n_w=8)	33	37.5	83	100	92	100	83	100

n_c = number of cultures
n_w = number of Wood's light tests

groups although patients on fenticonazole tended to have a more rapid response.

Table 4 shows the mycological cure rate expressed as negative results on either culture or Wood's light. There was no statistical difference between treatments and the remarkable activity of both drugs on pityriasis versicolor was evident.

There was one relapse of onichomycosis due to *Candida* in a patient belonging to group A who had previously a negative culture, and which had already occurred 1 d after cessation of treatment. In group B there were 3 cases of recurrences on day 10 after stopping the treatment: 2 onichomycoses due to *Candida* and one tinea corporis due to *Microsporum canis*. One patient in group C suffering from onichomycosis *(Candida)* had a recurrence 10 d after the end of treatment.

Table 5: The number of patients by type of cutaneous mycosis and treatment who were cured or improved at the end of the treatment period, and the number of relapsing patients

	No. cases	Cured at 21 days	Clinical improvement persistence of fungus at 21 days	Relapse
Dermatophytosis	20	19	1	1
fenticonazole b.i.d.	7	7	–	–
fenticonazole o.d.	8	7	1	1
miconazole b.i.d.	5	5	–	–
Candidosis	20	18	2	4
fenticonazole b.i.d.	6	5	1	1
fenticonazole o.d.	7	7	–	2
miconazole b.i.d.	7	6	1	1
Pityriasis versicolor	20	20	–	–
fenticonazole b.i.d.	7	7	–	–
fenticonazole o.d.	5	5	–	–
miconazole b.i.d.	8	8	–	–

Table 5 reports the distribution of patients who were cured or showed improvement on day 21 and those who relapsed after cessation of treatment, by type of infection and treatment group. The number of patients in whom the infection was not cured was the same in all three groups and the relapse rate was not different.

Tolerability was good in all three groups. One patient in group A, two in group B and one in group C complained of mild itching and increased erythema during the first week of treatment. Correlation to the drugs was difficult to establish and there was no need to discontinue the treatments.

Discussion

Our data confirm the high cure rate achieved by fenticonazole cream applied twice daily in other trials (12–16). In this scheme fenticonazole was not significantly different from miconazole in another trial (12), although there was a trend in favour of the former in some of the parameters. Also in our study there seemed to be a somewhat faster response to fenticonazole, as shown by the percentage of microscopic negativization on day 7, but this did not reach a statistical significance.

Fenticonazole was also applied once a day yielding similar therapeutic results to those achieved by twice daily applications of either fenticonazole or miconazole. These results provide a clinical confirmation to the data from a recent skin retention time study in animals (17) which showed a preventive activity of fenticonazole on fungal infections of 48–72 h. Another clinical trial (E. Jung, personal communication) reported a 90% and 95% mycological cure rate with fenticonazole cream applied once daily at 21 and 28 d of treatment respectively.

In 3 patients the infection was not cured on day 21, and in an additional 5 patients reinfection or relapse was found on a control visit 2 weeks after cessation of treatment. These phenomena were not different between the 3 groups of treatments but were mostly found in patients suffering from onichomycosis due to *Candida*. It is well known that in many instances this kind of infection requires periods of treatment longer than 21 days.

Tolerability was good with all 3 treatment schemes.

We conclude that fenticonazole 2% cream is highly efficacious in the cure of superficial skin mycoses when applied twice daily. The same compound applied once daily is as

effective as miconazole 2% cream applied twice daily, achieving a high cure rate of 95%. Considering the importance of patient's compliance in achieving high cure rates, fenticonazole applied once a day provides the dermatologist with an important therapeutic means for the treatment of superficial skin mycoses.

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Correspondence:
Dr. M. L. Dal Prá Recordati,
Direzione Medica, Via Civitali, 1,
I-20148 Milano, Italy.

Erratum

mycoses 3 (1988), page 146, J. Van Cutsem, F. Van Gerven and P. A. Janssen:
In Vitro Activity of Enilconazole Against *Aspergillus* Spp. and its Fungicidal Efficacy in a Smoke Generator Against *Aspergillus fumigatus*.

In Table 4 of this article an important part indicating the position of the inocula as lying or hanging drops was left out. We apologize to the authors for that mistake.