Single dose therapy of vaginal candidiasis: a comparative trial of fenticonazole vaginal ovules versus clotrimazole vaginal tablets

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Summary

An open, randomized comparative clinical trial was performed in 153 patients suffering from symptomatic vaginal candidiasis confirmed by mycological tests. Patients were allocated at random into two groups: the first group (consisting of 75 subjects) was treated with a single vaginal ovule of fenticonazole (600 mg) and the second group (consisting of 78 subjects) was treated with a single vaginal tablet of clotrimazole (500 mg). Therapeutic efficacy was assessed by microbiological and clinical criteria 7 days and 1 month (when possible) after the single dose treatment. At the first follow-up visit, complete disappearance of the signs and symptoms or a highly significant reduction of their intensity was observed in both treatment groups. No significant difference was evident between the two drugs. At 7 days, the mycological tests gave negative results in 92% of the patients in the fenticonazole group and in 88.5% of the patients in the clotrimazole group. The difference between the two treatment groups was again not statistically significant. The second follow-up visit was performed in 55 (73.3%) patients of the fenticonazole group and in 52 (66.7%) patients of the clotrimazole group. The results indicate that 83.6% of patients in the fenticonazole group and 69.2% of patients in the clotrimazole group were still disease free at the time of this visit. Both drugs were well tolerated. Mild, local and short lasting side-effects were reported in only 5 cases of the group treated with fenticonazole. These results demonstrate that the treatment of vaginal candidiasis with fenticonazole ovules or clotrimazole tablets after a single dose regimen is equally highly effective and well tolerated.

Key words: Fenticonazole – clotrimazole – antifungal agents – moniliasis, vulvovaginal

Introduction

Non-specific vulvovaginitis, with accompanying symptoms such as vaginal discharge, pruritus and dyspareunia, is one of the most common diseases which leads

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women to the gynaecologist. The majority of these infections are caused by the *Candida* species, particularly *Candida albicans*. Moreover, this fungus is often present in the female genital tract without causing symptoms of infection. Overt clinical disease may appear in the presence of certain local, e.g. altered vaginal pH, or systemic (diabetes, pregnancy, etc.) host factors.[6,8]

The highly effective synthetic imidazoles were introduced into therapy in the early 1970s. At the beginning, 2-week treatment periods were suggested to eradicate the fungus and to prevent recurrences. This length treatment regimen, however, was not well accepted by many patients who failed to comply with treatment as soon as their symptoms subsided. More recently, shorter treatment periods of 5 and 3 days have been reported for many imidazole compounds.[1,7,10]

A new imidazole derivative recently synthesized by the Recordati Research Division,[9,11] fenticonazole [alpha-(2-4-dichlorophenyl)-β,N-imidazolylethyl-4-phenylthiobenzyl ether nitrate], has been shown to possess a powerful *'in vitro'* anti-*Candida* activity with a minimum inhibitory concentration (MIC) in the range of 5 to 40 μg/ml, depending on the strain and on the pH of the culture medium.[4,5] Fenticonazole increases its antimycotic activity in the presence of an acidic pH, and seems particularly suitable, therefore, for treating vulvovaginal infections as the mucous membranes of the female genital tract, at least in the reproductive years, have a pH of around 4 to 5.

Fenticonazole has been shown to be at least as effective as clotrimazole[3] when administered as intravaginal cream applied daily for 7 days. Since it has recently been demonstrated[12] that a single application of fenticonazole ovules is equally as effective as a multiple application schedule, we decided to compare in a large number of patients the effectiveness of a single administration of fenticonazole (600 mg) vaginal ovules versus clotrimazole (500 mg) vaginal tablets in the treatment of mycologically confirmed vaginal candidiasis.

Patients and methods

A randomized comparative open clinical trial was performed in 153 patients suffering from symptomatic vaginal candidiasis confirmed by mycological tests.

The patients enrolled were aged between 17 and 52 years, were otherwise in good general health, and were not suffering from serious metabolic or systemic diseases. Patients taking oral contraceptives or using intrauterine devices (IUD) were also included. Pregnant or lactating women, patients treated with intravaginal agents (including spermicide creams) or systemic antimycotic drugs in the preceding 2 weeks or presenting any other genital tract infection were excluded from the trial. Patients with known hypersensitivity to any imidazole derivative or considered unreliable or unsuitable were also excluded from the trial.

All the patients gave their written informed consent to participate in the study.

On entry, patients were randomized into two groups: the first group (consisting of 75 subjects) was treated with a single vaginal ovule of fenticonazole (600 mg) and the second group (consisting of 78 subjects) was treated with a single vaginal tablet of clotrimazole (500 mg). Patients were instructed to introduce the vaginal medication last thing at night before going to bed.

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In the presence of consistent signs of external candidiasis the patient was allowed, depending on the treatment group, to apply either fenticonazole cream (2%) or clotrimazole cream (1%) to the vulvar area.

Efficacy of the treatment was assessed by microbiological and clinical criteria. On entry and 7 days after treatment the patients were evaluated as follows: (i) microbiology: specimens were taken for mycological evaluation, by direct microscopic examination and/or culture; and (ii) clinical evaluation: the following vaginal symptoms and signs of irritation, dyspareunia (superficial and deep), soreness, discharge, erythema, oedema, fissures, and excoriation were rated for severity according to a 4-point semi-quantitative scale (1=none, 2=mild, 3=moderate, and 4=severe).

On the basis of the mycological and symptomatic findings, an overall clinical evaluation was made according to the following reference scale: worse; no change; improved=symptoms reduced (independently from mycological findings); and cured=disappearance of clinical signs and symptoms in the presence of negative microbiological findings.

A second follow-up visit was performed, if possible, 4 weeks after treatment: mycological evaluation was carried out on the vaginal swabs and a global evaluation of the patients was assessed as follows: overt disease; sub-clinical disease=positive mycology, no symptoms; and no disease.

Tolerability

Any possible local or systemic adverse reaction was carefully recorded during the course of the treatment in order to evaluate the tolerability of the administered drugs.

Statistical methods

Scores for symptoms, consisting of ordinal data on a limited range scale, were analyzed using non-parametric tests. Intra-group comparisons were made by means of the Wilcoxon signed-rank test; between-group comparisons were assessed using Mann-Whitney test. Nominal qualitative data were compared by the χ^2-test.

Demographic data, assumed to be normally distributed, were evaluated by paired or unpaired Student's t-test for comparisons within-groups or between-groups, respectively.

Results

The two study groups were well matched with regard to age, weight, contraceptive use and duration of the current attack (Table I). The basal clinical evaluation was also not significantly different in the two groups of patients (Table II).

Similar episodes of vaginitis had occurred in the preceding 12 months in 42 (56.1%) of the patients in the fenticonazole group and in 34 (43.5%) of the clotrimazole group, and the number of similar episodes was 1.3±2.1 in the fenticonazole-treated patients and 1.7±2.3 in clotrimazole-treated patients. The number of patients with a previous history of vaginitis differs between the two groups in a statistically significant way ($p=0.03$).

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Table I. Details of the women in the two treatment groups

Patients	Fenticonazole	Clotrimazole
No. studied	75	78
Age (years): mean (±S.D.)	26.7±6.9	26.9±4.0
Weight (kg): mean (±S.D.)	57.2±7.0	60.1±7.6
Contraceptive use:		
Oral	44	40
IUD	14	10
Condom	13	28
Duration of current attack (days): Mean±S.D.	16.3±41.5	17.5±44.7

Clinical findings

Symptomatic (objective and subjective) scores at baseline and at the Day 7 control visit are shown in Table II.

In both treatment groups, either the disappearance of the signs and symptoms or a highly significant reduction in the means of scores, as compared to baseline conditions, was recorded at the first follow-up evaluation. No significant difference was present between the two drugs at baseline or at the final evaluation.

In 63 (84.0%) patients of the fenticonazole group and in 58 (74.4%) patients of the clotrimazole group evidence of external candidiasis was present. Twenty and 21 of these patients, in the two treatment groups respectively, were also treated with topical applications to the vulvar area.

At the end of the first week, only 10 patients treated with fenticonazole (4 with the external applications) and 11 (3 with the external applications) patients treated with clotrimazole presented signs of external candidiasis.

Mycological findings

In agreement with the trial inclusion criteria, vaginal swabs from all patients included in the efficacy evaluation (evaluated by direct microscopic examination and/or culture) were positive for *Candida* and negative for other possible pathogens at the beginning of treatment. After 7 days, mycological results were negative in 69 (92.0%) patients in the fenticonazole group and in 69 (88.5%) patients in the clotrimazole group. The difference between the two treatment groups was not statistically significant (χ^2-test).

The overall clinical evaluation on the Day 7 control visit is shown in Table III.

The statistical analysis of the distribution of patients in the different classes of results (contingency table analysis, χ^2-test) indicate that no difference between the two drugs was present at the first follow-up examination.

The second follow-up visit was performed in 55 (73.3%) of the 75 fenticonazole-treated patients after 29.9±7.5 days and in 52 (66.7%) of the 78 clotrimazole-treated patients after 30.9±11.5 days. The results obtained are reported in Table IV. No significant difference was present between the two groups.

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Table II. Assessment of the severity of symptoms at baseline and after 7 days in the two treatment groups: mean (±S.D.) scores

Symptom	Baseline	Day 7
Irritation		
Fenticonazole	1.48±0.93	0.39±0.65**
Clotrimazole	1.51±0.98	0.40±0.67**
Dyspareunia, superficial		
Fenticonazole	0.91±1.23	0.12±0.37**
Clotrimazole	0.56±0.97	0.11±0.36**
Dyspareunia, deep		
Fenticonazole	0.24±0.78	0
Clotrimazole	0.39±0.88	0.11±0.4**
Soreness		
Fenticonazole	1.28±1.05	0.28±0.60**
Clotrimazole	1.38±1.10	0.28±0.62**
Discharge		
Fenticonazole	1.36±0.97	0.40±0.70**
Clotrimazole	1.37±0.94	0.38±0.65**
Erythema		
Fenticonazole	1.52±0.86	0.33±0.58**
Clotrimazole	1.45±0.92	0.40±0.63**
Oedema		
Fenticonazole	0.41±0.72	0.03±0.23*
Clotrimazole	0.33±0.62	0
Fissures		
Fenticonazole	0.25±0.62	0.05±0.28*
Clotrimazole	0.23±0.58	0.03±0.16**
Excoriation		
Fenticonazole	0.41±0.66	0.04±0.20**
Clotrimazole	0.49±0.75	0.10±0.34**

Note: significance of difference compared to baseline, *$p<0.05$, **$p<0.01$ (Wilcoxon signed-rank test)

Table III. Overall clinical evaluation at the Day 7 control visit: number (%) of patients

Evaluation	Fenticonazole (n=75)	Clotrimazole (n=78)
Cured	42 (56.0)	45 (57.8)
Improved	30 (40.0)	28 (35.9)
No change	1 (1.3)	5 (6.4)
Worse	2 (2.7)	

At the second follow-up visit the mycological evaluation was carried out in 36 (65.5%) of the 55 patients in the fenticonazole group and in 34 (65.4%) of the 52 patients in the clotrimazole group. The mycological results indicate that 9 (25%) of the fenticonazole-treated patients and 16 (47%) of the clotrimazole-treated

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patients had a relapse. The difference between the two groups was at the limit of statistical significance ($p=0.054$, χ^2-test).

Table IV. Overall clinical evaluation of the 1 month follow-up visit: number (%) of patients

Evaluation	Fenticonazole (n=55)	Clotrimazole (n=52)
No disease present	46 (83.6)	36 (69.2)
Sub-clinical disease	5 (9.1)	9 (17.3)
Overt disease	4 (7.5)	7 (13.5)

The mycological results give the impression of a higher relapse incidence than the global evaluation shown in Table IV, due to the fact that the mycology was performed in all the patients in whom infection was clinically suspected, but not in all symptom-free patients.

Tolerability

Both drugs were well tolerated in most of the patients. Only in 5 patients treated with fenticonazole were mild, local and short lasting side-effects reported: burning in 2 cases, soreness in 2 cases and vaginal discharge in 1 case.

Discussion

In this open, comparative multi-centre clinical trial, 153 patients, suffering from symptomatic vaginal candidiasis confirmed by mycological tests, were treated with a single vaginal ovule of fenticonazole (600 mg) or with a single vaginal tablet of clotrimazole (500 mg). The results indicate that both treatments were equally highly effective and well tolerated.

At 7 days after the application of the drug, the mycological results were negative in 92% of patients in the fenticonazole group and in 88.5% in the clotrimazole group. Signs and symptoms of the disease disappeared or were significantly reduced in the responding patients. Of the patients who returned for the second control visit at 1 month (73.3% of the fenticonazole group and 66.7% of clotrimazole group), 83.6% of the patients treated with fenticonazole and 69.2% treated with clotrimazole were still disease free.

The good results achieved in this trial, performed in a large number of patients, confirm that a single application of vaginal ovules of fenticonazole leads to a mycological and clinical cure of vaginal candidiasis comparable to that obtained with a more prolonged course of treatment.

In particular, the cure rate obtained in this trial was comparable to that obtained in previous studies in which fenticonazole was administered either as a cream for 1 week[3] or as 100 mg ovules for 2 to 3 weeks.[2] In a recent open, randomized parallel group trial in which three different therapeutic dose regimens of fenticonazole vaginal ovules (200 mg daily for 3 days; 600 mg and 1000 mg in a single administration) were compared, the three administration schedules tested appeared to be equally effective and well tolerated.[12]

The percentage of patients who had a recurrence at the 1-month follow-up visit was slightly higher in this study than in previous studies. This is probably due to

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the fact that 1 month is a relatively long time interval at which to assess relapses if re-infection sources, particularly partners' infections, are not controlled. One should remember that 56.1% of the patients in the fenticonazole group and 43.5% in the clotrimazole group had previous infections in the year prior to this treatment regimen.

The tolerance of the drugs was good and only a few mild and transient local side-effects were reported in 5 patients treated with fenticonazole. These local side-effects are very often difficult to correlate with the drug application due to the fact that they were reported by the patient as an exacerbation of the symptoms of the infection. In previous studies, fenticonazole proved to be very well tolerated in all its formulations.[2,3,12]

In conclusion, the vaginal application of a single vaginal ovule of fenticonazole or of a single vaginal tablet of clotrimazole proved to be a very effective treatment capable of eradicating vaginal candidiasis in a high percentage of patients. No difference seems to exist between the efficacy of the two drugs as shown by the findings of this study. The single application of a vaginal ovule gives results comparable with those previously obtained with multiple application schedules and appears, therefore, to be the treatment of choice since it improves the patient's compliance.

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