Comparative clinical trial of fenticonazole ovule (600 mg) versus clotrimazole vaginal tablet (500 mg) in the treatment of symptomatic vaginal candidiasis

J. W. W. Studd, M.D., F.R.C.O.G.,
M. M. Dooley, M.B., M.S., M.R.C.O.G.,
C. C. Welch,* F.R.C.S. (Ed.),
K. Vijayakanthan,* M.B., B.S.,
J. M. Mowat,** F.R.C.S., F.R.C.O.G.,
A. Wade,*** M.B., Ch.B., F.F.A.R.C.S.,
and
M. Newell,† M.B., Ch.B.

*King's College Hospital, London, *Basildon Hospital, Basildon, England, **Victoria Infirmary, Glasgow, ***Clydebank Health Centre, Glasgow, Scotland, and †St. Giles Hospital, London, England*

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Summary

A multi-centre, randomized, single-blind, parallel-group clinical trial was undertaken in 50 patients (26 fenticonazole, 24 clotrimazole) with symptomatic vaginal candidiasis to compare the antifungal efficacy and tolerability of single-dose intra-vaginal treatment with a fenticonazole ovule (600 mg) or a clotrimazole vaginal tablet (500 mg). Assessment was by laboratory mycological investigation and symptomatic assessments for a period of 3 weeks from the day of treatment. Of the 50 patients, 43 (23 fenticonazole, 20 clotrimazole) returned for assessment 1 week after drug administration and 32 (17 fenticonazole, 15 clotrimazole) were re-assessed 3 weeks after drug administration. Both treatments resulted in very similar and highly significant improvements in symptoms, associated with disappearance of detectable Candida in approximately 70% of patients. There were no significant differences between treatments and no appreciable incidence of relapse during the 3-week period of observation. At the end of this period, 10 (59%) of 17 fenticonazole patients were totally disease-free, as compared with 10 (67%) of 15 patients after clotrimazole treatment. The cure rate observed was somewhat less than that previously seen when intra-vaginal cream formulations of the same two drugs were given on a multiple-dose basis. Both drugs were very well tolerated, with no reports of appreciable local or systemic adverse reactions to either drug.

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

Introduction

Fenticonazole nitrate, or 1-[2-(2,4-dichlorophenyl)-2-[[4-(phenylthio) phenyl]

methoxy] ethyl]-1H-imidazole nitrate, is an antifungal agent of the imidazole series (Recordati SpA, Milan, Italy). It is the most active of a series of imidazolylalkylbenzyl ethers[6] and has a broad spectrum of both antifungal and antibacterial activity.[2,7,8] The drug has very satisfactory activity against dermatophytosis and other cutaneous fungal infections,[1,5] whilst activity against *Candida albicans* has been demonstrated both *in vitro*[3] and clinically.[4]

After clinical evaluation of fenticonazole cream, fenticonazole ovules have been formulated to enable single-dose intra-vaginal treatment of fungal infections. Each ovule contains 600 mg active constituent in an oily excipient admixture within a soft gelatin shell.

Clotrimazole is an established agent of the imidazole group which is used widely for the treatment of vaginal candidiasis. In particular, its availability in a single-dose vaginal tablet makes it suitable for use as a reference compound in a clinical trial of single-dose fenticonazole treatment.

An earlier trial was undertaken in which multiple-dose application of the corresponding intra-vaginal creams was assessed (unpublished). A further, multi-centre, randomized, single-blind, parallel-group clinical trial has now been conducted in order to assess and compare the formulations available for single-dose treatment.

Patients and methods

Female patients attending a gynaecological out-patients' clinic were considered for the trial if they were suffering from mycologically confirmed (positive microscopy) symptomatic vaginal candidiasis. To be acceptable for trial entry, patients were required to be aged between 18 and 80 years and to have given informed consent to participate in the trial. Patients were excluded from the trial if they were pregnant, lactating or at risk of pregnancy, if they had previously diagnosed renal/hepatic disease or diabetes mellitus, if they were immunosuppressed or immunodeficient, in poor general health or known to be hypersensitive to imidazole derivatives. Patients were also excluded if they were considered unlikely or unable to comply with the trial protocol or if they had received any intra-vaginal drugs or any systemic antifungal agents during the preceding 4 weeks.

The trial was conducted under the terms of a Clinical Trials Certificate Exemption (CTX) granted by the Committee on Safety of Medicines and was approved by the local Ethical Committees. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. All patients gave informed consent to participate in the trial and were aware that they were free to withdraw from the trial at any time.

On satisfying the above inclusion and exclusion criteria patients were invited to participate in the trial. Those agreeing then underwent initial investigations and received trial medication, as described below.

After microscopical confirmation of vaginal *Candida albicans* infection, a vaginal swab was also obtained for mycological culture and sensitivity tests.

On Day 1 of the trial (Visit 1), consenting patients who fulfilled the entry criteria were allocated the next available treatment number which determined (according to a randomization code) whether they would receive fenticonazole or clotri-

mazole treatment. After initial assessment (see below), including the obtaining of a vaginal swab for mycological investigation, patients were given the trial medication appropriate to their trial number and were instructed in administration of the single nocturnal dose on that day.

On Day 7 or 8 (Visit 2) patients were again seen for symptomatic assessment (see below) and mycological investigations. Final assessment (Visit 3) was undertaken on Day 21 or 22. On this occasion, in addition to symptomatic and mycological assessment, the investigator also recorded a clinical grading of disease status at the end of the trial.

In accordance with the randomization code, the medication received by each patient consisted either of a fenticonazole nitrate ovule (gelatin vaginal capsule) containing 600 mg active material, or a clotrimazole vaginal tablet containing 500 mg active material.

Although the two trial medications were necessarily of different appearance, they were dispensed in identical packages bearing only the patient trial number and instructions for use (same for both drugs). Single-blind conditions were achieved by ensuring that the packages were not opened in the presence of the investigator. No antibiotic or antifungal therapy apart from trial medication was permitted during the period of the trial. Regular medications were allowed to continue provided that there were no major changes within the week prior to trial entry or during the study period.

Assessments

Assessments were undertaken at Visit 1 (Day 1), Visit 2 (Day 7 or 8) and Visit 3 (Day 21 or 22). A vaginal swab was obtained and subjected to microbiological examination (microscopy and culture and, where indicated, sensitivity tests). Three separate features of disease (erythema, discharge and irritation) were each graded for severity on a 4-point scale (1=none; 2=mild; 3=moderate; 4=severe). After the final assessment, on the basis of the mycological and symptomatic findings, a clinical evaluation of disease status at that time was made on a 3-point scale (1=overt disease, with or without positive mycology; 2=sub-clinical disease, positive mycology only; and 3=no disease, clinical or mycological).

At each assessment, patients were also questioned and examined to determine any possible local or systemic adverse reactions to therapy.

Statistical methods

Many of the assessments consist of scores on limited-range ordinal scales. Under these circumstances, non-parametric tests have limited power due to the multiply-tied ranks. Accordingly, the common practice has been adopted of applying parametric tests (paired t-tests within groups, unpaired t-tests between groups), where appropriate with the application of continuity-correction. However, findings were confirmed using non-parametric tests (Wilcoxon Signed Rank Tests within groups, Mann-Whitney 'U' tests between groups); in cases where results differed, the greater of the two p values (parametric and non-parametric) are quoted in this report.

Numbers of patients showing responses have been compared using Yates' Chi-Squared Tests. Kolmogorov-Smirnov Two Sample Tests have also been utilised for some comparisons of scores on rankable ordinal scales, in preference to the less powerful Chi-Squared Tests.

Two-tailed statistical tests have been used throughout and the threshold of significance taken as $p=0.05$.

Results

A total of 50 patients (26 fenticonazole and 24 clotrimazole) who fulfilled the inclusion requirements entered the trial and were allocated randomization codes. Details of these patients are summarized and compared for the two groups in Table I.

Table I. Details of patients studied: mean (S.D.) and range of values

Patients	Fenticonazole	Clotrimazole
No. studied	26	24
Age (years): Mean	32.0 ±10.8	28.9±10.2
Range	18 to 51	19 to 58
Height (cm): Mean	161.6±6.3	162.6±7.8
Range	150 to 175	152 to 185
Weight (kg): Mean	61.7 ±1.5	60.0±8.0
Range	44 to 76	45 to 76
Use of oral contraception:		
Yes	7	8
No	9	10
Not recorded	10	6
Duration of *Candida* infection (days): Mean	13.1±11.3	13.9±14.9
Range	2 to 45	2 to 60
No. previous episodes in 12 months: Mean	1.65±2.02	1.86±2.75
Range	0 to 6	0 to 12

The two groups were well matched as regards age, height, body weight, parity and contraceptive usage, with no significant differences between the groups. The mean age of the two groups was approximately 30 years. The duration of the current attack was very similar in the two groups (mean 13.9 days in the fenticonazole group, 13.1 days in the clotrimazole group). There had been slightly more similar episodes in the preceding 12 months in the fenticonazole group (mean 1.86 episodes) than in the clotrimazole group (mean 1.65 episodes).

Six patients in the fenticonazole group and 3 patients in the clotrimazole group had received antifungal medication, at least 31 days prior to the trial. This previous treatment had been miconazole in 1 patient and nystatin in another, but in all other cases had consisted of clotrimazole.

Of the 50 patients who entered the trial, 7 patients (3 fenticonazole group, 4 clotrimazole group) failed to return for assessment on Day 7/8; it is not known,

therefore, whether or not the trial medication was administered or what was the subsequent course of their disease. In none of these cases was there a known reason for the patient's failure to re-attend. Hence, 43 patients (23 fenticonazole, 20 clotrimazole) were assessed 'acutely' on Day 7/8. Of these 43 patients, 32 (17 fenticonazole, 15 clotrimazole) returned for final re-assessment on Day 21/22. Of those who did not return at this time, 1 patient was withdrawn from the trial by the investigator in order that the unsuccessful trial medication could be replaced by an alternative therapy; in the remainder of cases, it is not known why patients did not re-attend.

Only a very small number of instances of concomitant medication was recorded, in no case was a drug involved that would affect vaginal candidiasis.

Clinical/symptomatic assessment

Results for all three symptomatic assessments were very similar, as shown in Tables II and III.

Table II. Symptomatic response at 1 and 7 or 8 days after single-dose treatment: mean (±S.E.M.) and median scores

Symptom	Fenticonazole		Clotrimazole	
	Day 1 (n=26)	Day 7/8 (n=23)	Day 1 (n=24)	Day 7/8 (n=20)
Vaginal erythema:				
Mean	2.27±0.20	1.30±0.12**	1.83±0.18	1.05±0.11**
Median	2.0	1.0	2.0	1.0
Vaginal discharge:				
Mean	2.46±0.19	1.30±0.15**	2.54±0.16	1.50±0.15**
Median	2.5	1.0	3.0	1.0
Vaginal irritation:				
Mean	2.52±0.21	1.57±0.14**	2.50±0.18	1.40±0.13*
Median	3.0	1.0	3.0	1.0

*$p<0.01$, **$p<0.002$, significance of change from Day 1

Table III. Patients symptom-free at Day 7 or 8: number (%) of patients

Symptom	Fenticonazole (n=23)		Clotrimazole (n=20)	
	No.	%	No.	%
Vaginal erythema	15	65	15	75
Vaginal discharge	15	65	12	60
Vaginal irritation	12	52	13	65

There was a highly significantly ($p<0.002$) decrease in mean vaginal erythema scores during the week after drug administration in both groups; fenticonazole from 2.27 to 1.30, clotrimazole from 1.83 to 1.05. There were no significant differences between the groups. On Day 7/8, 15 (65%) of 23 patients were erythema-free in the fenticonazole group, as compared with 15 (75%) of 20

patients in the clotrimazole group. This difference was also not significant.

Mean vaginal discharge scores decreased highly significantly ($p<0.002$) in both groups; from 2.46 to 1.30 in the fenticonazole group and from 2.54 to 1.50 in the clotrimazole group. There were no significant differences between the groups. On Day 7/8, 15 (65%) of 23 patients were free of vaginal discharge in the fenticonazole group, as compared with 12 (60%) of 20 patients in the clotrimazole group (not significant).

Mean vaginal irritation scores decreased highly significantly in both groups; from 2.52 to 1.57 with fenticonazole ($p<0.002$) and from 2.50 to 1.40 with clotrimazole ($p<0.01$). There were no significant differences between the groups. On Day 7/8, 12 (52%) of 23 patients were irritation-free in the fenticonazole group, as compared with 13 (65%) of 20 patients in the clotrimazole group (not significant).

Mycological results

In accordance with the trial entry criteria, vaginal swabs from all patients included in the analysis were positive for *Candida* at trial entry (Table IV). Mycological findings as regards *Candida* during the course of the trial observation period are summarized in Table IV.

Table IV. Mycological findings of *Candida* in vaginal swabs at entry and after single-dose treatment

Patients	Fenticonazole	Clotrimazole
Day 1		
No. studied	26	24
No. with *Candida* present	26 (100%)	24 (100%)
Day 7/8		
No. studied	23	20
No. with *Candida* present	5 (22%)	6 (30%)
Significance of change from Day 1	$p<0.0001$	$p<0.0005$
Day 21/22		
No. studied	17	14
No. with *Candida* present	7 (41%)	5 (36%)
Significance of change		
from: Day 1	$p<0.0005$	$p<0.0005$
Day 7/8	N.S.	N.S.

N.S. = not significant (Yates' χ^2-tests)

In the fenticonazole group, *Candida* was still present in only 5 (22%) of 23 patients at Day 7/8 ($p<0.0001$) and in 7 (41%) of 17 patients at Day 21/22 ($p<0.0005$); the difference between Days 7/8 and 21/22 was not significant. In the clotrimazole group, *Candida* was present in 6 (30%) of 20 patients on Day 7/8 ($p<0.0005$) and 5 (36%) of 14 patients on Day 21/22; the difference between Days 7/8 and Day 21/22 was not significant. There were no significant differences between the treatment groups.

Only a very small number of pathogens other than *Candida* were isolated, in approximately equal numbers in the two treatment groups.

Overall clinical assessment at Visit 3

On the basis of both mycological findings and symptomatology, clinical response at the end of 3 weeks from the time of trial drug administration was assessed on a 3-point scale. Results are summarized in Table V.

Table V. Overall assessment of disease status at Day 21/22 after treatment: number (%) of patients

Assessment	Fenticonazole (n=17)	Clotrimazole (n=15)
Overt disease	5 (29)	4 (27)
Sub-clinical disease	2 (12)	1 (7)
No disease	10 (59)	10 (67)

In the fenticonazole group, 'overt' disease was present in 5 (29%) of 17 patients, 'sub-clinical' disease (positive mycology without symptoms) in 2 (12%) of 17, and 10 (59%) of 17 patients were disease-free. In the clotrimazole group, the corresponding figures were 4 (27%) of 15, 1 (7%) of 15 and 10 (67%) of 15 patients, respectively. There was no significant difference between the two groups.

Adverse effects

There were no reports of any possible systemic adverse reactions to either trial drug. One patient reported a burning sensation lasting 30 minutes after administration of the fenticonazole ovule, but no other patient reported any local symptoms resulting from administration of either trial drug.

Discussion

In this trial, two groups of patients with proven symptomatic vaginal candidiasis were studied. Single-dose treatment with the new drug fenticonazole was compared with a similar regimen of treatment using the established agent clotrimazole, by means of a single-blind trial in two well-matched groups of patients with this disorder. Assessment was by mycological laboratory investigation and clinical/symptomatic assessment during an observation period of 3 weeks after drug administration.

In general, all assessment criteria indicated that intra-vaginal fenticonazole ovules (600 mg) have the same efficacy as clotrimazole vaginal tablets (500 mg) in the treatment of vaginal candidiasis. Both treatments eliminated objective evidence and symptoms of *Candida* infection in a majority (65% to 80%) of patients treated, with few showing relapse during a 3-week observation period after either treatment. The loss of an appreciable number of patients to follow-up obviously has the potential to distort the results. However, the most likely reason for patient default would be that the trial medication had eliminated symptoms of the disease. It is probable, therefore, that the present study may somewhat underestimate the efficacy of both drugs.

The rate of elimination of detectable *Candida* that was seen in this trial (approximately 70%) was somewhat lower (for both drugs) than was seen in a

similar trial involving multiple applications of vaginal cream formulations of the same two drugs. This might suggest that more than one application of fenticonazole ovules may achieve a higher cure rate.

The data concerning incidence of relapse during the 3-week period of observation are difficult to interpret; it is well known that in 10% of healthy women *Candida albicans* is present but no clinical symptoms of vaginal infection are observed.

Both drugs were very well tolerated, with no evidence of either local or systemic adverse effects.

In conclusion, our results indicate that a single fenticonazole ovule (600 mg) is as effective as a single clotrimazole vaginal tablet (500 mg) in eliminating the symptoms and objective evidence of vaginal candidiasis. It is extremely well tolerated and should be suitable for routine treatment of this condition. The lower rate of *Candida* elimination than was seen with multiple-dose application of fenticonazole cream might suggest that more than one dose of fenticonazole ovules (or clotrimazole vaginal tablets) may achieve a higher cure rate.

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