

Single blind comparison of ketoconazole 200 mg oral tablets and clotrimazole 100 mg vaginal tablets and 1% cream in treating acute vaginal candidosis

J S BINGHAM

From James Pringle House, The Middlesex Hospital, London

SUMMARY A single blind study of 103 women with vaginal candidosis was undertaken to compare treatment with conventional topical clotrimazole and oral ketoconazole. Both treatment regimens were equally effective in terms of clinical symptoms, negative results on culture for *Candida albicans*, and relapse rates.

As treatment for vaginal candidosis takes several days, patient compliance is important and the success of a treatment regimen may depend on its acceptability to patients. Those in this study who had previously been treated for vaginal candidosis were asked to compare their current and previous treatments. Significantly more ($p < 0.001$) of those treated with ketoconazole than those treated with clotrimazole found it more acceptable than previous treatment. This indicated a strong preference for oral treatment, and oral antifungal agents may be the treatment of choice for vaginal candidosis in the future.

Introduction

The introduction of ketoconazole, which is an orally active derivative of imidazole-piperazine, offered an alternative to conventional topical treatment for vaginal candidosis. The initial open studies suggested that the drug was very effective,^{1,2} but there was an obvious need for comparative studies. Clotrimazole, which is a topical derivative of imidazole, is well documented as being an effective treatment for vaginal candidosis^{3,4} and was chosen for this study with the objective of comparing the efficacy, safety, and acceptability of the two treatments.

Patients and methods

We studied 103 patients presenting at James Pringle House with acute vaginal candidosis, all of whom gave their informed consent. In all patients a Gram stained vaginal smear showed yeast cells, pseudomycelia, or both, and the diagnosis was subsequently confirmed by culture. We recorded the patients' relevant medical histories, including the numbers of previous episodes, predisposing factors,

and any other medical conditions. Patients were excluded if they had had more than two attacks of vaginal candidosis in the previous year, were pregnant, not using a reliable form of contraception, had a mixed infection, or had received antifungal medication for vaginal candidosis within the previous 14 days. We assessed the signs and symptoms of discharge, pruritus, vulvitis, and vaginitis as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Gram stained vaginal smears were examined microscopically for the presence of *Candida* spp, and Sabouraud slopes were inoculated and sent to the laboratory for confirmation of the presence of *Candida* spp by culture.

Patients were randomly allocated on a single blind (to the investigator) basis to one of two treatment regimens: either 10 ketoconazole 200 mg tablets, or six clotrimazole 100 mg vaginal tablets with applicator and a 20 g tube of clotrimazole 1% cream. The dosage regimen for ketoconazole was one tablet by mouth with meals twice a day for five consecutive days. Clotrimazole vaginal tablets were inserted once at night for six consecutive nights, with application of the cream to the vulval and perianal areas. No time limitations were specified for application of the cream. Patients were instructed to return 14 to 42 days later, when signs and symptoms were reassessed and further mycological examinations completed. At the follow up visit on day 14, patients who had

Address for reprints: Dr J S Bingham, Director, James Pringle House, The Middlesex Hospital, London W1N 8AA

Accepted for publication 17 November 1983

previously received other treatment for vaginal candidosis were asked to compare the acceptability of the trial medication with their previous treatment and rate it as very much better, better, the same, worse, or very much worse. In addition they were asked if the trial medication had upset them in any way, and details of any side effects were recorded by the physician.

STATISTICAL ANALYSIS

The severity of each of the four clinical signs and symptoms on days 14 and 42 was compared with that on day 0 using Wilcoxon's matched pairs signed ranking test. The two treatments were compared at days 0, 14, and 42 using the Mann-Whitney U test. The results of cure and failure, relapse and no relapse, comparisons with previous treatment, and analysis of the patient entry profile were analysed using the χ^2 test.

Results

The two treatment groups were well matched for demographic data. The age range in the group treated with ketoconazole was 18 to 35 (mean 24.8) years and in the group treated with clotrimazole was 17 to 45 (mean 25.2) years. Thirty eight (67.8%) of the 56 patients who received ketoconazole and 28 (59.6%) of the 47 who received clotrimazole had previously been treated for vaginal candidosis. Ten of the patients treated with ketoconazole and eight treated with clotrimazole had been taking antibiotics, and two patients in the ketoconazole group were diabetic: diabetes and treatment with antibiotics are both recognised predisposing factors.

Both forms of treatment were highly effective in reducing the signs and symptoms of vaginal candidosis. Table I shows that there were no appreciable differences between them, except a

TABLE I *Reduction of signs and symptoms of candidosis*

	Ketoconazole*	Clotrimazole*	Clotrimazole v Ketoconazole**
Discharge			
Day 14	p<0.001	p<0.001	NS
Day 42	p<0.001	p<0.001	p<0.005
Vulvitis			
Day 14	p<0.001	p<0.001	NS
Day 42	p<0.01	p<0.001	NS
Pruritus			
Day 14	p<0.001	p<0.001	NS
Day 42	p<0.001	p<0.001	NS
Vaginitis			
Day 14	p<0.001	p<0.001	NS
Day 42	p<0.005	p<0.001	NS

* = Wilcoxon matched pairs, signed ranking test

** = Mann-Whitney U test

significantly ($p<0.05$) lower mean score for discharge at day 42 in favour of clotrimazole. All patients in both treatment groups had positive results on culture for candida on entry to the study. Table II shows that the cure rate for ketoconazole on day 14 was 92.8% (52 out of 56) and for clotrimazole 91.5% (43 out of 47). The corresponding relapse rate on day 42 for ketoconazole was 24.1% (7 out of 29) and for clotrimazole 16.7% (4 out of 24). There was no significant difference between the two treatments at either follow up visit (χ^2 test). Of the patients who relapsed mycologically in the group treated with ketoconazole, one was totally asymptomatic, one had mild discharge, two had mild pruritus, and three had both symptoms. These relapsing patients included the two with diabetes. Of the patients treated with clotrimazole who relapsed, two were asymptomatic and two had a mild discharge.

TABLE II *Culture results for Candida spp*

Treatment	Results on day 14 (n = 103)		Results on day 42 (n = 53)	
	Negative No (%)	Positive No (%)	Negative No (%)	Positive No (%)
Ketoconazole (n = 56)	52 (92.8)	4 (7.2)	22 (75.9)	7 (24.1)
Clotrimazole (n = 47)	43 (91.5)	4 (8.5)	20 (83.3)	4 (16.7)

Of the patients who had previously received treatment for vaginal candidosis and who answered the question comparing the treatment they had received with that previous treatment, 79% (26 out of 33) in the group treated with ketoconazole and 25% (6 out of 24) in the group treated with clotrimazole rated their treatment as better or very much better. This difference was significant (χ^2 test, $p<0.001$). There were no serious adverse effects resulting from either treatment regimen. Two patients treated with ketoconazole complained of nausea, and one of facial flushing. One patient treated with clotrimazole complained that the medication "stung a lot", and one of vulval spots.

Discussion

In this study both treatments were found to be equally effective in reducing all signs and symptoms by day 14 and in reducing pruritus, vaginitis, and vulvitis by day 42. It is interesting that this should have been so because no topical vulval treatment, which so often produces symptomatic relief, was used with the ketoconazole regimen.

Ketoconazole and clotrimazole produced similar high mycological cure rates, 92.8% and 91.5%

respectively. The 24.1% relapse rate seen with ketoconazole was higher than that previously reported,² (and Scudamore J, unpublished report) although that seen with clotrimazole (16.7%) is somewhat lower than in earlier studies.^{1 4} Reading did report a relapse rate of 15% with clotrimazole.⁵ Diabetes is accepted by many as a predisposing factor in vaginal candidosis, probably because traces of urine containing sugar around the introitus may offer a suitable culture medium for yeasts.⁶ Two diabetic patients were included in the analysis; both happened to receive ketoconazole and both had relapsed by day 42, one being symptomatic and the other asymptomatic. If they are excluded from the analysis the relapse rate in the ketoconazole group becomes 18.5%, a figure approaching that reported in other studies.

The development of a broad spectrum antifungal agent which is effective against yeasts represents a significant advance in treatment. Clayton has stated that the success of a drug in the treatment of vaginal candidosis may ultimately depend on the acceptability to the patient of the formulation.³ Of the patients who had previously received treatment for vaginal candidosis, 78.8% of those treated with ketoconazole, but only 25% of those treated with clotrimazole, rated the treatment that they had

received as better or very much better than previous therapy. This was a significant difference ($p < 0.001$) that suggested a strong patient preference for oral treatment. No doubt further oral antifungal agents will be developed, and perhaps this will be the treatment of vaginal candidosis in the future.

I thank my medical and nursing colleagues who helped in this study, and particularly Mr James Erdman and his staff who undertook the laboratory work. The drugs used in the study were supplied by Janssen Pharmaceutal Ltd.

References

1. Balsdon MJ. Comparison of miconazole-coated tampons with clotrimazole vaginal tablets in the treatment of vaginal candidosis. *Br J Vener Dis* 1981;57:275-8.
2. Balsdon MJ, Rosedale N, Blatchford NR, Jones J. The systemic treatment of recurrent vaginal candidosis: an evaluation of ketoconazole therapy. *Curr Ther Res* 1982;31:511-6.
3. Clayton YM. Antifungal drugs in current use: a review. *Proc Roy Soc Med* 1977;70 suppl 4:15-8.
4. Eliot BW, Howat RCL, Mack A. A comparison between the effects of nystatin, clotrimazole and miconazole on vaginal candidosis. *Br J Obstet Gynaecol* 1979;80:572-7.
5. Reading JH. Efficacy and acceptability of miconazole coated tampons in comparison with clotrimazole vaginal tablets. *Clinical Research Review* 1981;1:123-7.
6. Oriel JD. Clinical overview of candidal vaginitis. *Proc Roy Soc Med* 1977;70 suppl 4:7-9.