

# Treatment of vaginal candidosis: A comparative study of the efficacy and acceptability of itraconazole and clotrimazole

JM Tobin, P Loo, SE Granger

## Abstract

**Objective**—To compare the clinical and mycological efficacy and patient acceptability of the oral antifungal itraconazole with vaginal clotrimazole in the treatment of vaginal candidosis.

**Design**—A multicentre, single-blind, randomised, parallel group comparison of itraconazole and clotrimazole.

**Setting**—17 Genito Urinary Medicine clinics in UK hospitals.

**Subjects**—Women with symptomatic, culture positive vaginal candidosis.

**Methods**—Patients were randomly allocated 2 × 100 mg itraconazole capsules to be taken twice in a 24 hour period, or a 500 mg clotrimazole vaginal tablet. Clinical and mycological assessments were made at entry and after approximately seven and 35 days.

**Outcome measures**—Cure rate was defined in terms of mycological results, and patients were questioned on their opinion of treatment.

**Results**—Of 214 patients, 109 received itraconazole and 105 clotrimazole with similar improvement in clinical signs and symptoms. Mycological cure rates one week after treatment were obtained in 72 of 97 patients (74%) in the itraconazole group and 64 of 89 patients (72%) in the clotrimazole group. Identical mycological cure rates six weeks after treatment were obtained with 40 of 79 patients (51%) receiving itraconazole and 39 of 78 patients (50%) receiving clotrimazole.

**Conclusion**—Clotrimazole and itraconazole were found to be equally effective. A majority of patients receiving the latter preferred it to previous treatments.

## Introduction

Vaginal candidosis is a common gynaecological problem amongst women of child bearing age. The development of broad spectrum azole antifungal agents has resulted in the introduction of a variety of treatment formulations for this condition. During the past decade the tendency has been towards shorter treatment courses. Clayton stated in 1977 that patient acceptance of a treatment for vaginal candidosis may ultimately decide which drug is most successful.<sup>1</sup> Attention has thus begun to focus on patient acceptability and compliance.<sup>2,3</sup>

In the UK, oral systemic therapy for vaginal candidosis became possible with the introduction in 1981 of the first orally active imidazole antifungal agent, ketoconazole. More recently, the introduction of the broad spectrum orally active triazole antifungal, itraconazole, has provided a choice of oral therapy with a good safety and efficacy profile and the added benefit of a one day treatment course for vaginal candidosis.

The aim of this study was to compare the clinical and mycological efficacy of a one day course of itraconazole capsules (200 mg/bd) with a single dose clotrimazole pessary (500 mg/od) in the treatment of vaginal candidosis. Patient acceptability of these therapies was also compared.

## Patients and methods

The trial was designed as a multicentre, single-blind, randomised, parallel group comparison of itraconazole and clotrimazole in vaginal candidosis. Women presenting at genitourinary medicine clinics at 17 UK hospitals were recruited into the study if they gave written informed consent and met the following entry criteria. Patients over the age of 18 years were included if they presented with symptoms of vaginal discharge and irritation and on examination were found to have vulvitis and vaginitis with a subsequent positive candida culture. Pregnant women and breast-feeding mothers were excluded from entry as were women of child-bearing age not using adequate contraception. Known unstable diabetics and patients with known impaired liver function were also excluded, as were patients receiving concomitant rifampicin, anticholinergics, antacids or H<sub>2</sub> antagonists. Concomitant use, or use within the previous 14 days, of any antifungal other than the study medication or a known sensitivity to azole antifungals also excluded patients from entry to the study.

Clinical and mycological assessments were carried out on entry, at "short term" follow up (between days 5 to 10) and at "long term" follow up (between days 30 to 40). The investigator scored the signs of vulvitis and vaginitis and the symptoms of discharge and pruritus on a 4 point scale.

Mycological assessment was carried out by culture of a high vaginal swab for *Candida* spp. All mycology was carried out at a central laboratory using standard culture techniques.

Patients were randomly allocated to receive

St Mary's Hospital,  
Milton Road,  
Portsmouth,  
Hants PO3 6AD  
J M Tobin

Kettering General  
Hospital, Kettering  
P Loo

Janssen  
Pharmaceutical  
Limited, Oxford, UK  
S E Granger

Address correspondence to:  
Dr J M Tobin

Accepted for publication  
21 October 1991

treatment with either itraconazole (2 × 100 mg capsules to be taken twice in a 24 hour period with food) or clotrimazole (1 × 500 mg vaginal tablet). Treatment packages were identical and handed to the patient unopened by the investigator. She was told she would receive either capsules or a pessary and full instructions for use were included inside the pack. The patient was also told she could use a bland soothing agent if necessary but such use should be recorded on a diary card along with a daily record of symptoms of vaginal candidosis.

At the short term follow up visit the investigator questioned the patient as to whether she considered the study treatment to be better than, no different from, or worse than previous treatments she had received for vaginal candidosis.

All patients who proved to be culture negative for candida on entry were excluded from the efficacy analysis. Where patients had used another antifungal agent during the study, data has been included up to the point at which the antifungal was used.

#### Statistical methods

Change in severity scores for vaginal discharge, irritation, vulvitis and vaginitis from entry were compared between groups using the Mann-Whitney U test. This was also used for the patients' comparison of the study medication with previous treatments.

The cure rate for this study was defined in terms of the mycological outcome. "Complete cure" was defined as negative cultures at both follow up assessments, "delayed cure" where a culture was positive at short term but negative at long term follow up, "recurrence" when culture was negative at short term but positive at long term and "failure" when cultures were positive at both assessments. The cure/failure rates at each visit were analysed using the Chi square test to compare groups and the outcome at the final assessment was analysed using the Mann-Whitney U test. For patients who were withdrawn from the study all available data were included in the efficacy analysis up to point of withdrawal.

Patient diary cards were poorly completed in this study but available, interpretable data were analysed for the day on which symptoms first resolved.

#### Results

A total of 262 patients were entered into the study. Forty-eight of these patients were excluded from the analysis owing to negative mycology at entry (47) and concomitant use of other antifungal drugs (1). Of the remaining 214 patients, 109 were allocated to receive itraconazole and 105 to receive clotrimazole. Nineteen patients (10 itraconazole, 9 clotrimazole) were lost following the entry assessment and a further 48 (28 itraconazole, 20 clotrimazole) were lost following the short term assessment. Thirty-seven of these patients

were simply lost to follow up and the remainder were withdrawn owing to use of other anti-fungal drugs (20); lack of efficacy/progression of the disease (6); intercurrent illness (2); or withdrawn patient consent (2). There was no significant difference between treatment groups for trial outcome (Chi square test,  $p = 0.436$ ).

There was no significant difference between treatment groups for age or number of days since last monthly period.

Despite the fact that some assessments were performed outside the predefined ranges of 5–10 and 30–40 days, the mean number of days between entry and short and long term follow up visits for all patients eligible for inclusion in the analysis was in fact 8.14 and 8.37 days and 40.25 and 40.45 days for itraconazole and clotrimazole groups respectively.

In both treatment groups the percentage of patients scoring four on the severity scale was reduced from entry to short term follow up and from entry to long term follow up for each sign/symptom. For example in the itraconazole group 22% of patients had severe pruritus on entry but by the short term follow up assessment only 1% of patients scored severe for this symptom. These results were identical in the clotrimazole group for this symptom and similar in both groups for the other signs/symptoms. When compared using the Mann-Whitney U test, there were no significant differences between treatment groups for sign/symptom severity at entry, at short term or at long term follow up.

The short term cure rates in the itraconazole and clotrimazole groups respectively were 74% and 72%. At long term follow up, in the itraconazole and clotrimazole groups, 43% and 37% of patients were completely cured, 8% and 13% had delayed cure, 30% and 29% relapsed and 19% and 20% were classified as mycological failures. The overall cure rate at long term assessment was therefore 51% for itraconazole and 50% for clotrimazole. Analysis demonstrated no statistically significant differences between the treatment groups for mycological cure at short term follow up, for outcome at final visit or for overall cure rate ( $p > 0.05$ ).

The table details the response when patients were asked their opinion of the study medication. Significantly more patients in the group receiving itraconazole preferred this to previous treatments received ( $p = 0.001$ ).

Six percent of itraconazole treated patients admitted to use of a bland cream as a soothing agent between entry and the short term follow up compared to 16% of clotrimazole treated

Table Patients' opinion of treatment

	Itraconazole % patients (n = 92)	Clotrimazole % patients (n = 88)
No previous treatment	10	11
Better than previous treatment	60	28
No different to previous treatment	18	49
Worse than previous treatment	10	3
Unable to answer	2	9

patients. This difference was not significant ( $p = 0.064$ ).

The time to first resolution of symptoms as recorded in the patients' diary cards was a mean of 3.8 days for the itraconazole group compared to 5.5 days for the clotrimazole treated patients. This difference was not significant ( $p = 0.069$ ).

### Discussion

The results of this study demonstrate that oral itraconazole ( $2 \times 100$  mg capsules b.d.) is as effective as clotrimazole vaginal pessary ( $1 \times 500$  mg) in the treatment of vaginal candidosis in a population of women presenting to genitourinary medicine clinics with this condition.

The treatment produced a similar reduction in the severity of signs and symptoms of vaginal candidosis in this group of patients.

Mycological cure rates at short term follow up were 74% for itraconazole and 72% for clotrimazole. At long term follow up the overall mycological cure rate was 51% and 50% respectively for the two treatments with 30% and 29% of patients demonstrating a mycological relapse by this time. Mycological failure rate was 19% and 20% respectively for itraconazole and clotrimazole.

Previously reported studies have demonstrated that mycological cure rates following itraconazole therapy are lower in women with recurrent compared with acute vaginal candidosis.<sup>4,5</sup> As approximately 90% of patients in the present study had received previous treatments for vaginal candidosis and considered their condition sufficiently severe or troublesome to attend a genitourinary medicine clinic, it is likely that the majority could be regarded as recurrent sufferers. However, no record was made of the number of episodes of candidosis experienced in the previous year to confirm this assumption.

If this assumption is correct, then the mycological cure rates seen for itraconazole in the present study are in agreement with previous findings.

The lower mycological cure rates following clotrimazole therapy in this study compared with those in previous reports<sup>6,7</sup> may again be a reflection of the severity/chronicity of the condition in this patient population.

As a relatively large proportion of patients in both groups did not return for the final assessment the percentage mycological cure rates calculated at this time may reflect an underestimate of the true "cure" and should therefore be interpreted with caution. Patients failing to return for long term follow up may do so because they are asymptomatic and do not wish to undergo a further vaginal examination. This always poses a problem in such clinical studies.

In conclusion, both treatments proved equally effective for vaginal candidosis with significantly more patients receiving oral itraconazole, than topical clotrimazole, expressing a preference for this therapy compared with previous treatments they had received.

The authors acknowledge the contribution of Professor W C Noble, who conducted the mycology for this study, and thank the following investigators: A Alawattagama, I Alexander, C J Bignall, G R Kinghorn, E Curlless, J Davidson-Parker, W W Dinsmore, A Edwards, M J Godley, Dr Khan, M Shahidullah, H S K Singha, P G Watson, M Shahmanesh, A R Wisdom.

- 1 Clayton YM. Antifungal drugs in current use: a review. *Proc R Soc Med* 1977;70 Suppl 4:15-17.
- 2 Mayhew SR, Suffield WE. Candidal vaginitis—a study of the efficacy of a reduced duration treatment with miconazole nitrate. *Practitioner* 1979;222:564-7.
- 3 Balsdon MJ. Comparison of miconazole coated tampons with clotrimazole vaginal tablets in the treatment of vaginal candidosis. *Br J Venereal Dis* 1981;57:275-8.
- 4 Cauwenbergh G. Itraconazole: the first orally active antifungal for single-day treatment of vaginal candidosis. *Curr Ther Res* 1987;41:210-4.
- 5 Cauwenbergh G, Legendre R, Blatchford N. Itraconazole, a novel oral antifungal: its efficacy and safety profile. *Proceedings of the Bolivian and Columbian Congress of Dermatology, Bogota* 1988 April 12-22.
- 6 Fleury F, Hughes D, Floyd R. Therapeutic results obtained in vaginal mycoses after single dose treatment with 500 mg of clotrimazole vaginal tablets. *Am J Obstet Gynecol* 1985;152:968-70.
- 7 Hughes D, Kriedman T, Hodgson C. Treatment of vulvovaginal candidiasis with a single 500 mg clotrimazole vaginal tablet compared with two 100 mg tablets daily for three days. *Curr Ther Res* 1986;39:773-7.