

Efficacy of itraconazole versus fluconazole in vaginal candidiasis

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Abstract

Objective: To compare the efficacy of fluconazole 150mg single dose and itraconazole 200mg twice for one day in the treatment of acute vulvovaginal candidiasis.

Methods: The study was carried out at the Department of Dermatology, PNS Shifa Hospital, Karachi, from March, 2008 to February 2009 and comprised 60 women with clinical and mycological diagnosis of vaginal candidiasis. Diagnosis was based on history, clinical examination and relevant investigations. The women were divided into two equal groups. After initial assessment, Group 1 was treated with capsule fluconazole 150mg stat, and Group 2 with capsule itraconazole 200mg twice for one day. They were assessed clinically for cure and relapse on day 7 and 21 respectively. All findings were recorded in the proforma. Data was analysed using SPSS 12.

Results: The overall clinical evaluation showed 70% (n=21) cure rate with itraconazole and 50% (n=15) with fluconazole. In Group-1, 7 (23.33%) and in Group-2 8 (26.6%) showed some improvement, while 2 (6.66%) in Group 1, and 7 (23%) in Group 2 failed to respond. Relapse was observed in 9 (28.5%) and 16 (53%) of the cured cases in Group 1 and Group 2 respectively.

Conclusion: Itraconazole was found to be more effective in the treatment of vulvovaginal candidiasis compared to fluconazole with high cure and low relapse rate.

Keywords: Itraconazole, Fluconazole, Vaginal candidiasis, Efficacy. (JPMA 62: 1049; 2012)

Introduction

Vulvovaginitis is the inflammation of the vagina and the vulva. Candida vaginitis is predominantly caused by strains of *Candida albicans* (>90%).¹ *Candida* species are commonly found in small amount in a healthy vagina. However, when an imbalance occurs, such as change in normal acidity of a vagina or the change in hormonal balance, the *Candida* multiplies and symptoms of candidiasis like non-specific vulvovaginal pruritus, soreness, thick vaginal discharge, vulvar pain and dyspareunia appear.²

Effective management of *Candida* infection depends on accurate diagnosis; selection and administration of specific therapy and good compliance of the patient.³ There are variety of local and systemic antimycotic agents available for the treatment of vulvovaginal candidiasis.⁴ The systemic drugs are more expensive than topical preparations, but the latter can cause irritant contact dermatitis and are sometimes messy. In contrast, systemic therapy is easy to administer and patient compliance is improved.⁵ Furthermore, if the vulva is very inflamed an oral preparation is much less painful to administer.⁶

Fluconazole and itraconazole are both triazole antifungals. They have been licensed for the short-term oral treatment of vaginal candidiasis and have proved to be safer than both amphotericin B and ketoconazole.⁵ Both of them have good safety and efficacy data. The objective of the current study was to provide comparative data of the single-dose regimen of fluconazole versus the single-day dosage of itraconazole in vulvovaginal candidiasis. In the past, antifungal drug resistance was not known to exist, but today primary and secondary antifungal drug resistance has been proved by extensive multicentre studies.⁷ Although in vitro resistance to drug almost always mean a high rate of failure in the treatment, but in vitro sensitivity of the *Candida* species to antifungal drugs does not always mean successful treatment.⁷

In view of the reasons cited above, in vivo response of the antifungal has earned importance and, therefore, was the basis of this study. No local data is available regarding the effect of these antifungals. Asian women are living in hot and humid environment and are more prone to developing these types of infections.

Patients and Methods

The quasi-experimental study was conducted at the Department of Dermatology, PNS Shifa Hospital, Karachi, from March 1, 2008 to February 28, 2009 and comprised 60 women aged 16 years or over with symptomatic acute vulvovaginal candidiasis, and willing to participate in the study. All patients were married. None of them had received topical or systemic antifungal within 1 month before enrollment. Before starting the treatment, they were assessed

for vaginal discharge, itching, burning, erythema and oedema. Pregnant women and women during puerperium were excluded from the study. In all patients, the diagnosis was confirmed by direct microscopy and cultures. After establishing the diagnosis, the subjects were randomly divided into two groups of 30 each. Patients in Group 1 were prescribed capsule itraconazole (200mg twice oral dose for 1 day) and those in Group 2 were given capsule fluconazole (150 mg single oral dose).

After treatment, they were followed up on day 7 and day 21, and each sign and symptom was assessed separately. Clinical effectiveness was recorded as cure, improvement, failure and relapse as follows:

Cure: Complete disappearance of all signs and symptoms; Improvement: Improvement or partial disappearance of signs and symptoms; Failure: No change or worsening of signs and symptoms; and Relapse: Reappearance of signs and symptoms after documented cure had occurred.

Data was analysed using SPSS version 12. Relevant descriptive statistics, frequency and percentages were computed to present symptoms and findings of clinical examination before and after the treatment. Chi square test of proportions was applied to test the hypothesis. Time measurement was presented by mean standard deviation.

Results

All the 60 patients completed the study and there was no dropout. Their ages ranged from 18 to 57 years in Group 1 (mean 35.63 ± 10.72 years) and from 23 to 54 years in Group 2 (mean 34.26 ± 8.91 years). The duration of the disease (enquired through history) varied from 7 to 35 days in the former (mean = 18.76 ± 10.57 days) and from 10 to 42 days (mean = 21.70 ± 11.42 days) in the latter.

Patients were assessed for discharge, itching, burning, erythema and oedema. Vaginal discharge was initially present in all 60 (100%) patients recruited in the study. After one week, 4 (13.3%) patients in Group 1 and 15 (50%) in Group 2 did not respond to therapy. There was marked difference in treatment response between the two groups ($p = 0.002$) (Table).

Itching was initially present in 28 (93%) patients in each group. In Group 1, 2 (6.7%) patients showed treatment

Table: Comparison of symptomatic cure rate after treatment with Itraconazole (Gp 1) and Fluconazole (GP 2).

Symptoms	Itraconazole (Gp 1) (n=30)	Fluconazole (GP 2) (n=30)	p value
Vaginal Discharge	4 (13.3%)	15 (50%)	≤ 0.002
Itching	2 (6.7%)	14 (46.7%)	≤ 0.001
Burning	3 (10%)	5 (16.7%)	≤ 0.70
Erythema	2 (6.7%)	8 (26.7%)	≤ 0.03
Edema	2 (6.7%)	6 (20%)	≤ 0.25

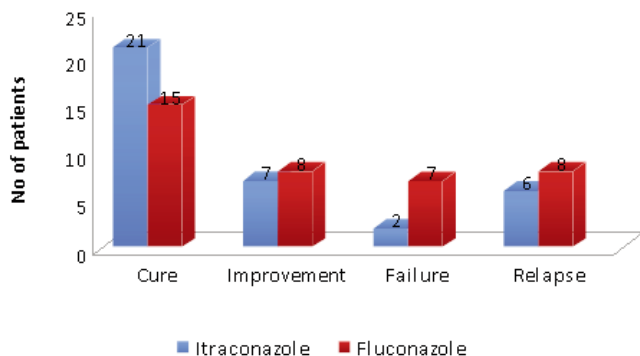


Figure: Comparison of treatment response with Itraconazole (Gp 1) and Fluconazole (GP 2).

failure on the 7th day followup. In Group 2, failure was observed in 14 (46.7%) patients ($p = 0.001$). Burning was initially observed in 18 (60%) patients in Group 1. Three (10%) patients did not respond to the drug. In Group 2, there were initially 16 (53%) patients with burning. On the 7th day followup, 5 (16.7%) still had the symptom ($p = 0.70$). There was no response difference.

Erythema was initially observed in 18 (60%) patients in each group. In Group 1, 2 (6.7%) patients did not respond to the therapy, while in Group 2, 8 (26.7%) patients did not report improvement in symptoms ($p = 0.03$). Initially, 7 (23%) patients in Group 1 and 11 (36%) patients in Group 2 were observed with oedema. Two (6.7%) patients in Group 1 and 6 (20%) patients in Group 2 did not respond well ($p = 0.25$).

At the 7th day followup for all the symptoms, 21 (70%) of the total in Group 1, and 15 (50%) of Group 2 had been cured completely; 7 (23.33%) patients in Group 1 and 8 (26.6%) in Group 2 showed clinical improvement; 2 (6.66%) in Group 1 and 7 (23%) in Group 2 showed no response. Time taken for cure varied from one to six days (Mean 3.67 ± 1.228) in Group 1 and one to seven days (Mean 4.19 ± 1.425) in Group 2. Relapse was seen in 6 (28.5%) of the 21 cured patients in Group 1, and 8 (53%) of the 15 cured patients in Group 2 on day 21. Response to treatment, as such, was significantly better in Group 1 compared to Group 2 (Figure).

Discussion

Itraconazole and fluconazole are safe, broad-spectrum antifungal drugs which have gained an important place in the treatment of vulvovaginal candidiasis. Their safety and efficacy have been evaluated in a number of comparative and non-comparative trials conducted in different areas of the world.^{8,9}

There are various national studies available and we compared our results with the other studies. Eradication rate observed in our study was similar to that in the literature. Our results with itraconazole (70% cures) and fluconazole (50%

cure) are in accordance with an earlier study.¹⁰ It compared three treatment groups as topical treatment with clotrimazole (500mg vaginal pessary and 1% cream), oral treatment with itraconazole (200mg twice a day for one day) and fluconazole (150mg single dose) in separate groups of acute vulvovaginal candidiasis and reported clinical cure of 80%, 80% and 62% respectively for each regimen 7-10 days after the treatment. Clinical cure was significantly lower in fluconazole group than that in the itraconazole group or the clotrimazole group.

Another study established the relationship of clinical outcome of candidal infection and in vitro results by the determination of minimum inhibitory concentration (MIC) of itraconazole and fluconazole.² Clinically, itraconazole was effective in 64.3% of the cases, while fluconazole was effective in 71.0%. The mycological cure rates (negative culture) were 64.3% with itraconazole and 78.9% with fluconazole. In clinical and mycological evaluation, the responses were statistically significant at the end of the treatment for both regimens. There was a reduction in the symptoms of vaginitis and a reduction of *Candida* in vaginal swabs. There was no significant difference in clinical response between these regimens.^{2,3}

We had given the clinical trial of single-day therapy of itraconazole, while an earlier study showed that the treatment with a daily 200mg oral dose of itraconazole for 3 days and a single 150mg oral dose of fluconazole proved to be equally effective in the treatment of vaginal candidiasis.¹¹

The results of these studies are similar to our study results. Clinical cure rate was significantly high in the itraconazole group compared to the fluconazole group. This difference between the efficacy of itraconazole and fluconazole could be explained by the fact that in our local setup, women might be suffering from fluconazole-resistant strain of *Candida* species although, identification of different strains of *Candida* was not included in our study. Literature also suggests that *Candida Glabrata* and *Candida Krusie* are often non-responsive to fluconazole, but are susceptible to itraconazole. However, more local studies are required to be done for the evaluation of therapeutic efficacy of these antifungal drugs.^{12,13}

A meta analysis¹⁴ on various studies conducted on the efficacy of single-day dose of fluconazole comprising 3279 patients, found a positive clinical response in 94% with a range of 88-100% and mycological cure in 85% (range 76-98%) of patients at first followup visit. Furthermore, in a similar European multicentre study, 70% patients were cured clinically during therapy and 24% improved clinically.¹⁴

Our findings do not coincide with the results of above-mentioned studies. This may be because of secondary drug resistance as fluconazole is a commonly prescribed drug in our population for vulvovaginal candidiasis. Similarly,

primary resistance of local candida species to fluconazole cannot be ruled out. The small sample size of our study necessitates further studies to validate the findings.

There are no local studies available regarding the comparison of efficacy of the two drugs, but a number of different non-comparative studies on the efficacy of single-day oral dose of fluconazole and itraconazole have been carried out in different areas. One such study was done on 20 patients to assess the therapeutic efficacy of itraconazole in vaginal candidiasis.¹⁵ In this study, an oral dose of itraconazole 100mg was given twice a day once a week for three consecutive weeks. After receiving the treatment, only 45% patients had mild itching and burning. Mild discharge was observed in 60% and pain in 5%, whereas redness was not seen in any of the patients. In contrast, the patients treated with itraconazole in our study showed much better response. Post-treatment, only 13.3% patients had discharge, 7.14% had itching and 16.6% had burning, whereas erythema was not seen in any of the patients.

The differences between the results of the two studies, could be due to the smaller sample size (20 vs. 60) and the different dose regimen.

In our study, those receiving fluconazole reported low cure rate and clinical improvement, while failure and relapses were quite high compared to an earlier study done locally¹⁶ which assessed the efficacy of single-dose oral fluconazole for vulvovaginal candidiasis at the Holy Family Hospital, Rawalpindi. In that study, 64 patients received fluconazole 150mg. Clinical improvement after the therapy was seen in 89.7% while complete clinical cure was found in 10.2%. None of the patients failed to respond and there was no relapse.¹⁶ Our results regarding high relapse rate with fluconazole compared to itraconazole were also consistent with international data reported earlier.¹⁰ This is probably, because that itraconazole is highly active against most common fungi. It stays in the vaginal mucosa longer than ketoconazole and fluconazole because of its high lipophilicity and high affinity for keratin. It has been found in the vaginal tissue for four days after a single-day treatment with 200mg twice a day. The highly lipophilic character of itraconazole results in favourable tissue blood ratio.¹⁷ Therefore, recurrence rate with itraconazole is low as suggested by a comparative study wherein the recurrence rate after 28 days of treatment was 7% with itraconazole, and 23% with fluconazole.¹⁰

Our study had several limitations. The sample size was not adequately powered to see the efficacy of itraconazole versus fluconazole. Hence, a larger sample size, preferably a trial, should be undertaken. Besides, it was a

single-center study. A multi-centre study is recommended for the future to substantiate the findings of the current study.

Conclusions

As suggested by our study, vaginal discharge was the commonest presenting symptom of vulvovaginal candidiasis. Other common presentations were itching and burning. Cutaneous involvement like erythema and oedema were the least common findings. Itraconazole was found to be more effective in the treatment of vulvovaginal candidiasis compared to fluconazole, and might represent a better choice in treating the condition. Failure and relapse rates were significantly high with fluconazole. Average time for relief of symptoms was less for the itraconazole group compared to the fluconazole group.

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