

Research Article

Comparison of Oral Itraconazole and Fluconazole in the Treatment of Severe Vulvovaginal Candidiasis

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Abstract

Objective: To assess the effectiveness and safety of oral itraconazole and fluconazole for Severe Vulvovaginal Candidiasis (SVVC) in nonpregnant women.

Methods: We Randomized Controlled Trials (RCTs) were eligible for inclusion, 289 nonpregnant patients were enrolled for comparing oral itraconazole and fluconazole for the treatment of SVVC in these Randomized Controlled Trials, 98 patients received two dose of oral fluconazole 150 mg, 99 patients received oral itraconazole 200 mg twice daily for 5 days, and 92 patients received 200 mg twice daily for 3 days.

Results: 82.0% (237/289) of cases were caused by *C. albicans*. Non-albicans Candida included *C. glabrata* (11.5%, 33/289), *C. parapsilosis* (3.2%, 9/289) and *C. tropicalis* (0.4%, 1/577), *C. krsei* (0.4%, 1/289), *Candida Lusitania* (0.4%, 1/289), *Candida Famata* (1.4%, 4/289), and *Saccharomyces cerevisiae* (0.7%, 2/577), *Rhodotorula sp.* 0.4% (1/289). The mycological cure rate of the patients at day 7 to 14 were 76.6% (75/98), 77.8% (77/99), and 69.6% (64/92) in fluconazole group, five days itraconazole group and three days itraconazole group respectively, $p > 0.05$. The mycologic cure rate of the patients at day 30 to 35 were 67.4% (66/98), 64.7% (64/99), and 54.4% (50/92) in the above three groups, $p > 0.05$. The mycologic cure rate of the patients with VVC caused by *C. albicans* and non- albicans was 80.6% (191/237) and 48.1% (25/52) at day 7 to 14 after therapy, $p < 0.01$ and 62.2% (157/237) and 44.2% (23/52) at day 30 to 35 after therapy, $p < 0.01$. The mycological cure rate of the patients in susceptible Candia and resistance Candida was 74.5% (187/251) and 44.4% (4/9) at day 7 to 14 after therapy ($p < 0.05$) and 62.2% (156/251) and 33.3% (3/9) at day 30 to 35 after therapy ($p > 0.05$).

Conclusion: The studied demonstrated that itraconazole 200 mg twice daily for 5 days were as effective as two dose of oral fluconazole 150 mg regimen in the treatment of patients with SVVC and could be a choice for therapy of the disorder.

Keywords: Vulvovaginal candidiasis; Itraconazole; Fluconazole

Introduction

It has been estimated that three-quarters of all adult women will suffer from Vulvovaginal Candidosis (VVC) at some time during their lives, and that approximately 40% to 50% of these women will have a second episode. *Candida albicans* is the major causative agent of VVC which accounts for 85% to 90% of positive vaginal fungal cultures [1,2].

Bulik et al. [3] studied 250 randomly selected isolates from VVC for the time period of 1986 to 2008 and found that the MIC₉₀ of fluconazole, itraconazole, and amphotericin B were increased.

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Itraconazole consists of a triazole core and a long lipophilic end, which provides the compound a strong lipophilic character and high affinity to keratin. After oral administration, especially high tissue concentrations are found in the skin and vaginal mucosa. Tissue concentrations can be many times the plasma concentration [4]. *In vitro* susceptibility test shown that itraconazole was resistant to fluconazole-resistant *C. glabrata* but susceptible to fluconazole-resistant *C. albicans* [5]. Itraconazole is effective and safe in the treatment of vulvovaginal candidiasis [6-9]. Oral itraconazole or fluconazole or Intravaginal Imidazoles seem equally effective in treating acute VVC. Oral itraconazole or fluconazole are likely to be beneficial in preventing recurrence of infection [1,7,10].

In 1998, Sobel et al. [11] classified VVC into complicated VVC and uncomplicated VVC. CDC recommended VVC therapy in sexually transmitted diseases treatment guideline on the base of the classification [7]. Currently, there were few study focused on the efficacy of different itraconazole regiments for severe VVC. The aim of the study is to evaluate the mycological efficacy of itraconazole 200mg twice daily for 3 days and 5 days with two doses of fluconazole for severe VVC.

Patients and Methods

Study design

This clinical trial was an open, randomized, parallel design study conducted at the Gynecological Clinic, Peking University Shenzhen Hospital, from January, 2011, through December, 2012. Prior to initiation of the study, the protocol and informed consent were reviewed and approved by the hospital review board. After informed consent was obtained, patients with SVVC were equally randomized to two doses of oral fluconazole 150 mg group, five days oral itraconazole 200 mg twice daily group and three days oral itraconazole 200 mg twice daily group.

Case definition

The case definition of VVC comprised the presence of symptoms, the demonstration of blastospores and pseudohyphae in a wet vaginal smear that had been treated with 10% potassium hydroxide, and positive fungal culture. All strains were identified using the API Candida (bioMerieux, France).

VVC classification

The severity of each symptoms and signs such as: itching, burning, discharge, and erythema, was assigned a score on the scale: 0=absent; 1=mild; 2=moderate; 3=severe. Patients with a severity score of 7 or greater were designated severe VVC. Uncomplicated VVC refers to sporadic VVC caused by strains of *Candida albicans*, mild-to-moderate, and normal, nonpregnant women. Recurrent VVC was classified as complicated VVC and was defined as four or more episodes of proved infection during a previous 12-month period [7].

Vaginal samples

A sample from the lateral vagina wall was obtained with a sterile cotton-tipped swab. The swab was placed in tube filled with saline for direct microscopic examination with 10% potassium hydroxide. Culture was performed at the same time for all positive wet vaginal smear cases.

Identification methods

All strains were stored in medium containing 2% glucose, 2% pepton and 20% glycerol at -70. The strains were identified in a standardized system API Candida (bioMerieux, Marcy l'Etoile, France).

Antifungal susceptibility test

The *in vitro* antifungal susceptibility was tested using a commercial agar diffusion test obtained from Rosco Laboratory (A/S Rosco, Taastrup, Denmark). The Neo-Sensitabs tablet assay was performed according to the manufacturer's instructions and M44-A guidelines [12,13]. Quality control isolates *Candida albicans* ATCC 64548 and *Candida albicans* ATCC 64550 were tested in the same manner. Endpoints for the antifungal agents were interpreted according to the manufacturer's instructions and were as follows: for fluconazole, Susceptible (S), zone diameter ≥ 20 mm; Intermediate susceptibility (I), zone diameter 12 mm to 19 mm; and Resistant (R), zone diameter ≤ 11 mm; for itraconazole, S, zone diameter ≥ 15 mm; I, zone diameter 10 mm to 14 mm; and R, no zone.

Admission criteria

Patients admitted to the trial were aged 18 years to 50 years old, generally healthy women with SVVC. Enrolled patients agreed to

abstain from sexual intercourse during the treatment period or use condoms for the remainder of the study period. During the study they also agreed to abstain from using any vaginal product.

Patients were excluded from entry if they: (1) had any other sexually transmitted disease or gynecological abnormality requiring treatment; (2) had a disease known to predispose to candidiasis such as diabetes mellitus, or were receiving antibiotics or corticosteroids; (3) were pregnant; (4) had used antifungal medication in the week before entry; or (5) were expected to menstruate within seven days of the start of treatment. (6) Infected more than one *Candida* species; (7) Uncomplicated VVC and RVVC.

Treatment regimens

Patients who met the study entry criteria were randomized at visit 1 in a 1:1:1 ratio to receive either oral itraconazole 200 mg (Xian-Janssen Pharmaceuticals) per day for 3 days.

140 patients with severe vulvovaginal candidiasis were treated with oral itraconazole 200 mg twice daily for three days or five days or orally Fluconazole 150 mg (Pfizer Pharmaceuticals) at day 1 and day 4. Sexual abstinence was advised until day 35 (30 to 35) follow up.

Follow-up visits

14 (7 to 14) days and 35 (30 to 35) days following second dosing, patients were required to return to the Gynecological Clinic for a follow-up visit. During this visit, the patient was questioned about any adverse events or concomitant medications.

Eradication or failure was referred candida negative or positive on candida culture at follow-up visits.

Statistical analysis

Therapy outcome were analyzed by using a chi-square test to compare reculta of treatment at short and long-term visits. Student's t test was used to compare the difference between the mean ages of the patients. Statistical significance was set at $P < 0.05$.

Results

Patients and candida strains

Of the 289 patients were enrolled and finished the study. The age of patients was 28.74 ± 6.14 (18 to 50) years-old. 82.0% (237/289) of cases were caused by *C. albicans*. Non-albicans *Candida* included *C. glabrata* (11.5%, 33/289), *C. parapsilosis* (3.2%, 9/289) and *C. tropicalis* (0.4%, 1/577), *C. krusei* (0.4%, 1/289), *Candida lusitanae* (0.4%, 1/289), *Candida famata* (1.4%, 4/289), and *Saccharomyces cerevisiae* (0.7%, 2/577), *Rhodotorula sp.* 0.4% (1/289) (Table 1). The resistance rate of *Candida* from the studied patients was 3.5% (9/260), 3.8% (10/260), 1.5% (4/260), 7.3% (19/260), and 0 for fluconazole, itraconazole, clotrimazole, miconazole, and nystatin, Table 2.

Efficacy

The mycological cure rate of the patients at day 7 to 14 were 76.6% (75/98), 77.8% (77/99), and 69.6% (64/92) in fluconazole group, five days itraconazole group and three days itraconazole group respectively, $p > 0.05$. The mycologic cure rate of the patients at day 30 to 35 were 67.4% (66/98), 64.7% (64/99), and 54.4% (50/92) in the above three groups, $p > 0.05$. The mycologic cure rate of the patients with VVC caused by *C. albicans* and non- albicans was 80.6% (191/237) and 48.1% (25/52) at day 7 to 14 after therapy ($\chi^2=23.8$, $p < 0.01$) and 62.2% (157/237) and 44.2% (23/52) at day 30 to 35 after therapy

Table 1: Strains of three groups.

Groups	Non-albicans									Sub-total
	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. parapsilosis</i>	<i>C. krsei</i>	<i>C. tropicalis</i>	<i>Saccharomyces cerevisiae</i>	<i>Candida famata</i>	<i>Candida lusitanae</i>	<i>Rhodotorula sp.</i>	
Itraconazole 3 days	76(82.6)	15(16.3)	1(1.1)	0(0)	0(0)	0(0)	0(0)	0(0)	0	16(17.4)
Itraconazole 5 days	80(80.8)	8(8.1)	5(5.1)	1(1.0)	1(1.0)	2(2.1)	1(1.0)	0(0)	1(1.0)	19(19.2)
Fluconazole	81(82.7)	10(10.2)	3(3.1)	0	0	1(1.1)	2(2.1)	1(1.1)	0	17(17.4)
Total	237(82.0)	33(11.5)	9(3.2)	1(0.4)	1(0.4)	2(0.7)	4(1.4)	1(0.4)	1(0.4)	52

Table 2: Resistance rate of Candida from three groups.

Groups	Resistance rate				
	fluconazole	itraconazole	clotrimazole	miconazole	nystatin
<i>C. albicans</i>					
fluconazole (n=73)	2(2.8)	4(5.5)	1(1.4)	7(9.6)	0(0)
itraconazole 5 days (n=79)	0(0)	0(0)	0(0)	1(1.3)	0(0)
itraconazole 3 days (n=62)	2(3.3)	3(4.9)	0(0)	9(14.6)	0(0)
Total(n=214)	4(1.9)	7(3.3)	1(0.5)	17(8.0)	0(0)
<i>C. glabrata</i>					
fluconazole (n=14)	2(14.3)	1(12.5)	1(7.2)	1(7.2)	0(0)
itraconazole 5 days (n=7)	0(0)	0(0)	0(0)	0(0)	0(0)
itraconazole 3 days (n=8)	2(25.0)	1(12.5)	1(12.5)	0(0)	0(0)
Total (n=29)	4(13.8)	2(6.9)	2(6.9)	1(3.5)	0(0)
Other than <i>C. glabrata</i> non-albicans					
fluconazole (n=5)	0(0)	0(0)	0(0)	0(0)	0(0)
itraconazole 5 days (n=11)	1(9.1)	1(9.1)	1(9.1)	1(9.1)	0(0)
itraconazole 3 days (n=1)	0(0)	0(0)	0(0)	0(0)	0(0)
Total (n=17)	1(5.9)	1(5.9)	1(5.9)	1(5.9)	0(0)

($\chi^2=8.8$, $p<0.01$), Table 3. The mycological cure rate of the patients in susceptible Candida and resistance Candida was 74.5% (187/251) and 44.4% (4/9) at day 7 to 14 after therapy ($p<0.05$) and 62.2% (156/251) and 33.3% (3/9) at day 30 to 35 after therapy ($p>0.05$), Table 4.

Safety

A skin rash occurred in one patient who had received itraconazole 400 mg. The patient discontinued itraconazole therapy and remove from the study. Her skin rash cleared when she treated with an antihistamine agent Loratadine.

Another patient complained of dizziness when she had received itraconazole 800 mg (two days dosages). Her dizziness disappeared when she stopped taking itraconazole. No side effect was reported at fluconazole group.

Table 3: Comparison of therapeutic efficacy of itraconazole and fluconazole in different Candida species.

Groups	Therapeutic efficacy			
	day 7 to 14 after therapy		day 30 to 35 after therapy	
	Cure cases	%	Cure cases	%
<i>C. albicans</i>				
Fluconazole (n=81)	66	81.5	58	71.6
itraconazole 5 days (n=80)	66	82.5	53	66.3
itraconazole 3 days (n=76)	59	77.6	46	60.6
X2	1.7		2.15	
P-value	>0.05		>0.05	
<i>C. glabrata</i>				
fluconazole (n=10)	5	50	5	50
itraconazole 5 days (n=8)	4	8-Apr	4	8-Apr
itraconazole 3 days (n=15)	4	26.7	3	20
X2	1.86		3.18	
P-value	>0.05		>0.05	
Non albicans other than <i>C. glabrata</i>				
fluconazole (n=7)	4	7-Apr	3	7-Mar
itraconazole 5 days (n=11)	7		6	
itraconazole 3 days (n=1)	1	1-Jan	1	1-Jan
X2	0.69		1.18	
P-value	>0.05		>0.05	
Non albicans				
Fluconazole (n=17)	9	53	8	47.1
itraconazole 5 days (n=19)	11	57.9	11	57.9
itraconazole 3 days (n=16)	5	31.3	4	25
X2	1.95		3.77	
P-value	>0.05		>0.05	
fluconazole (n=98)	75	76.6	66	67.4
itraconazole 5 days (n=99)	77	77.8	64	64.7
itraconazole 3 days (n=92)	64	69.6	50	54.4
Total (n=289)	216	74.8	180	62.3
X2	1.96		3.78	
P-value	>0.05		>0.05	

Table 4: Comparison of therapeutic efficacy of itraconazole and fluconazole in susceptible and resistance Candida.

Groups	Therapeutic efficacy			
	Day 7 to 14 after therapy		Day 30 to 35 after therapy	
	Cure cases	%	Cure cases	%
Susceptible				
Fluconazole (n=82)	62	75.6	55	67.1
itraconazole 5 days (n=96)	75	78.1	63	65.6
itraconazole 3 days (n=73)	50	68.5	38	52.8
Total (n=251)	187		156	
Resistance				
Fluconazole (n=4)	2	4-Feb	1	4-Jan
itraconazole 5 days (n=1)	1	1-Jan	1	1-Jan
itraconazole 3 days (n=4)	1	4-Jan	1	4-Jan
Total (n=9)	4	9-Apr	3	9-Mar
X2	4.03		3.04	
P-value	<0.05		>0.05	

Discussion

Nurbhai et al. [14] showed that there was no significant difference regarding the effectiveness between oral and intra-vaginal treatment of uncomplicated vulvovaginal candidiasis, but there was a trend of preference by the patients of the oral route, regardless of the possible more systemic adverse events that could be noted. Pitsouni et al. [15] reported a Meta analysis including six RCTs. There were 1092 enrolled patients with acute uncomplicated vaginal/vulvovaginal candidiasis. There was no difference between itraconazole and fluconazole regarding clinical cure and improvement at the first and second scheduled visit assessments and mycologic cure at the first and second scheduled visit assessments.

At present study, the mycological cure rate of the patients at day 7 to 14 were 76.6%, 77.8%, and 69.6% in fluconazole group, five days itraconazole group and three days itraconazole group respectively. The mycologic cure rate of the patients at day 30 to 35 were 67.4%, 64.7%, and 54.4% in the above three groups. Although the mycological cure rate was no statistical significant difference of in the three groups, the mycological cure rate of the patients treated with three days itraconazole group was lower than that of fluconazole group and five days itraconazole group. We could conclude that five days itraconazole were as effective as two dose of oral fluconazole 150 mg regimen in the treatment of patients with SVVC and could be a choice for therapy of the disorder. The efficacy of three days itraconazole should be further study.

The mycologic cure rate of the patients with VVC caused by *C. albicans* and non-albicans was 80.6% and 48.1% at day 7 to 14 after therapy and 62.2% and 44.2% at day 30 to 35 after therapy. The result suggested fluconazole and itraconazole could not be chosen for treating VVC caused by non-albicans. Non-azoles antifungal agents could probably be used for treating VVC caused by non-albicans [16-19].

The mycological cure rate of the patients in susceptible Candida and resistance Candida was 74.5% and 44.4% at day 7 to 14 after

therapy and 62.2% and 33.3% at day 30 to 35 after therapy. The result suggested that VVC caused by fluconazole resistant Candida or itraconazole resistant Candida when treated with the fluconazole or itraconazole may had a statistical significant low mycological cure rate. The resistance rate of Candida to fluconazole, itraconazole, clotrimazole, and miconazole, and nystatin, however, was only 3.5%, 3.8%, 1.5% and 0. The most of the therapeutic failure cases were caused by antifungal susceptible Candida. Antifungal resistance is not the main cause of therapeutic failure [20-22].

In conclusion, itraconazole 200 mg twice daily for 5 days were as effective as two dose of oral fluconazole 150 mg regimen in the treatment of patients with SVVC and could be a choice for therapy of the disorder.

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