Miconazole Nitrate Vaginal Suppository 1,200 mg versus Oral Fluconazole 150 mg in Treating Severe Vulvovaginal Candidiasis

Shangrong Fan^{a, c} Xiaoping Liu^b Yiheng Liang^a

Departments of ^aObstetrics and Gynecology and ^bLaboratory Science, Peking University Shenzhen Hospital, and ^cShenzhen Key Laboratory of Gynecological Diagnostic Technology Research, Shenzhen, China

Key Words

Vulvovaginal candidiasis · Miconazole · Fluconazole

Abstract

Aims: Miconazole is a synthetic imidazole antifungal that has a broad spectrum of activity against *Candida albicans* and non-*albicans Candida* species. The aim of this study was to evaluate the efficacy and safety of miconazole nitrate vaginal suppository and oral fluconazole in treating severe vulvovaginal candidiasis (SVVC). **Methods:** In this prospective, randomized case control study, 577 cases of consecutive patients with SVVC were studied at the Gynecological Clinic of Peking University Shenzhen Hospital from January 1, 2009 through December 31, 2010. Patients with SVVC were treated with two doses of miconazole nitrate vaginal suppository 1,200 mg or two doses of fluconazole 150 mg. The patients were followed up for 7–14 and 30–35 days following the second dose of therapy. **Results:** The mycological cure rates of the patients on days 7–14 of follow-up were 75.9% (220/290) and 84.0% (241/287) in the miconazole and fluconazole groups, respectively ($p < 0.05$). The mycological cure rates of

the patients at the second follow-up were 64.8% (188/290) and 69.7% (200/287), respectively, in the two groups ($p > 0.05$). **Conclusion:** The study demonstrated that two doses of miconazole nitrate vaginal suppository 1,200 mg were as effective as two doses of an oral fluconazole 150 mg regimen in the treatment of patients with SVVC.

© 2015 S. Karger AG, Basel

Introduction

Vulvovaginal candidiasis (VVC), which affects up to 75% of women of child-bearing age at least once in their lifetime, is predominantly caused by *Candida albicans* [1]. In 1998, Sobel et al. [2] classified VVC into complicated VVC and uncomplicated VVC. The Centers for Disease Control and Prevention recommended VVC therapy in the treatment guideline for sexually transmitted diseases based on this classification [3]. There has been an increasing tendency to use shorter courses of topical or oral antifungal agents, which are effective in mild to moderate diseases. However, women with severe VVC

(SVVC) may not adequately respond to a single dose treatment [1, 3]. The Centers for Disease Control and Prevention recommend two doses of oral fluconazole 150 mg to treat SVVC [3]. Several studies have demonstrated that uncomplicated VVC responds well to a single dose of miconazole nitrate vaginal suppository 1,200 mg [4–9]. The effect of miconazole nitrate vaginal suppository 1,200 mg on SVVC is not known. In the current report, we provide the therapeutic results of patients with SVVC who were treated with two doses of miconazole nitrate vaginal suppository 1,200 mg or two doses of oral fluconazole 150 mg.

Materials 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 1, 2009 through December 31, 2010. Prior to the initiation of the study, the protocol and informed consent were reviewed and approved by the hospital's review board. After informed consent was obtained, patients with SVVC were equally randomized to either two doses of miconazole nitrate vaginal suppository 1,200 mg (miconazole group) or two doses of oral fluconazole 150 mg (fluconazole group).

Case Definition

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

VVC Classification

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

Vaginal Samples

A sample from the lateral vagina wall was obtained with a sterile cotton-tipped swab. The swab was placed in a 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 a medium containing 2% glucose, 2% pepton and 20% glycerol at -70°C . The strains were identified using a standardized system (API Candida).

Antifungal Susceptibility Test

In vitro antifungal susceptibility was tested using a commercial agar diffusion test obtained from Rosco Laboratory (Rosco A/S, Taastrup, Denmark) [10]. The Neo-Sensitabs tablet assay was performed according to the manufacturer's instructions [11] and M44-A guidelines [12].

Admission Criteria

The patients admitted to the trial were generally healthy women with SVVC aged 18–50 years. Uncomplicated VVC and recurrent VVC were excluded from the study. Enrolled patients agreed to abstain from sexual intercourse during the treatment period or to use condoms for the remainder of the study period. During the study, they also agreed to abstain from using any other vaginal product. Patients were excluded if they fulfilled any of the following criteria: (1) having any other sexually transmitted disease or gynecological abnormality requiring treatment; (2) having a disease known to predispose to candidiasis, such as diabetes mellitus, or receiving antibiotics or corticosteroids; (3) being pregnant; (4) having used antifungal medication in the week before entry; (5) expected to menstruate within 7 days of the start of treatment, or (6) infected with more than one *Candida* species.

Treatment Regimens

Patients who met the study entry criteria were randomized at visit 1 in a 1:1 ratio to receive either the miconazole nitrate vaginal suppository 1,200 mg (Xian-Janssen Pharmaceuticals Ltd., Xian, China) at bedtime on days 1 and 4 or oral fluconazole 150 mg (Pfizer Pharmaceuticals Ltd., Dalian, China) on days 1 and 4. Sexual abstinence was advised until day 35 (30–35) of follow-up.

Follow-Up Visits

At 7–14 and 30–35 days following the second dosing, all patients were required to return to the Gynecological Clinic for follow-up visits. During these visits, the patients were questioned about any adverse events or concomitant medications. The signs and symptoms were scored, recorded, and compared with the baseline severity assessment using the same scoring system. Clinical cure was defined as the resolution of signs and symptoms present at baseline with a total severity score of ≤ 2 . Improvement was defined as considerable reduction in the severity of baseline signs and symptoms with a decrease in total score by $\geq 50\%$. Patients who were not clinically cured and improved were considered clinical failures. Mycological eradication or failure was referred to as *Candida* negative or positive on *Candida* culture at follow-up visits [1–3, 12]. Figure 1 shows the algorithm of the admission, treatment and follow-up of the patients.

Statistical Analysis

Therapeutic outcomes were analyzed by using a χ^2 test to compare the results of treatment at the short- and long-term visits. Student's *t* tests were used to compare the differences between the mean ages of the patients. Statistical significance was set at $p < 0.05$. The statistical analysis of the data was performed using SPSS 10.0 (SPSS Inc., Chicago, Ill., USA).

Fig. 1. Admission, treatment and follow-up of the patients. STD = Sexually transmitted disease; CIN3 = cervical intraepithelial neoplasia grade 3.

Results

Patients and Candida Strains

A total of 577 patients completed the study, with a mean age of 29.81 (19–45) years. Overall, 89.4% (516/577) of cases were caused by *C. albicans*. Non-albicans *Candida* species included *C. glabrata* (6.9%, 40/577), *C. parapsilosis* (0.9%, 5/577), *C. tropicalis* (0.3%, 2/577), *C. krusei* (1.0%, 6/577), *C. lusitaniae* (0.2%, 1/577), *C. famata* (0.3%, 2/577), and *Saccharomyces cerevisiae* (0.9%, 5/577). The *Candida* species in the two groups were comparable (table 1).

Efficacy

The mycological cure rates of the patients on days 7–14 were 75.9% (220/290) and 84.0% (241/287) in the

Table 1. *Candida* species in the fluconazole and miconazole groups

<i>Candida</i> species	Miconazole	Fluconazole
<i>C. albicans</i>	252 (86.9)*	264 (92.0)
<i>C. glabrata</i>	27 (9.4)	13 (4.5)
<i>C. parapsilosis</i>	3 (1.0)	2 (0.7)
<i>C. krusei</i>	6 (2.0)	0
<i>C. tropicalis</i>	0	2 (0.7)
<i>S. cerevisiae</i>	2 (0.7)	3 (1.1)
<i>C. famata</i>	0	2 (0.7)
<i>C. lusitaniae</i>	0	1 (0.3)
Total	290 (100.0)	287 (100.0)

Figures in parentheses are percentages.

* Compared with the fluconazole group, $p > 0.05$, 95% CI, 0.963–2.834.

miconazole and fluconazole groups, respectively ($p < 0.05$). The mycological cure rates of the patients on days 30–35 were 64.8% (188/290) and 69.7% (200/287), respectively, in the two groups ($p > 0.05$). The clinical cure rates were similar to the mycological cure rates (table 2).

The mycological cure rates of the patients on days 7–14 were 83.3% (429/515) and 51.6% (32/62), respectively, in the *C. albicans* and non-albicans *Candida* groups ($p < 0.01$). The mycological cure rates of the patients on days 30–35 were 69.5% (358/515) and 48.4% (30/62), respectively, in the two groups ($p > 0.05$; table 2).

An antifungal susceptibility test was conducted on the 440 strains of *Candida* from patients with SVVC. The mycological cure rates of the patients on days 7–14 were 81.3% (346/426) and 69.2% (9/13), respectively, in the susceptible (including intermediate susceptibility) and resistant groups ($p > 0.05$). The mycological cure rates of the patients on days 30–35 were 67.8% (289/426) and 46.2% (6/13), respectively, in the two groups ($p > 0.05$; table 3).

Safety

Two patients experienced aggravated vaginal burning pain, vulval edema and vulval itching after having used the miconazole nitrate vaginal suppository. One patient had symptom relief after the drug was removed, and another after receiving antianaphylactic treatment. Two patients appeared hypomenorrheic in the fluconazole group. One patient developed gastrointestinal reactions, including nausea, in the fluconazole group.

Table 2. Comparison of the therapeutic efficacy in the fluconazole and miconazole groups

	Therapeutic efficacy		95% CI	χ^2 , p value
	miconazole group	fluconazole group		
<i>Day 14</i>				
Clinical				
Cure	228	243	0.980–2.301	3.52, >0.05
Improvement	28	26	0.653–2.017	0.06, >0.05
Failure	34	18	1.106–3.665	5.23, <0.05
Mycologic				
<i>C. albicans</i>	201/252, 79.8%	228/263, 86.7%	1.033–2.645	4.44, <0.05
Non-albicans <i>Candida</i>	19/38, 50.0%	13/24, 54.2%	0.424–3.291	0.10, >0.05
Subtotal	220/290, 75.9%	241/287, 84.0%	1.101–2.523	5.91, <0.05
<i>Day 35</i>				
Clinical				
Cure	235	240	0.778–1.835	0.66, >0.05
Improvement	13	5	0.932–7.565	3.58, >0.05
Failure	42	42	0.642–1.624	0.00, >0.05
Mycologic				
<i>C. albicans</i>	171/252, 67.9%	187/263, 71.1%	0.801–1.697	0.64, >0.05
Non-albicans <i>Candida</i>	17/38, 44.7%	13/24, 54.2%	0.523–4.075	0.52, >0.05
Subtotal	188/290, 64.8%	200/287, 69.7%	0.880–1.767	1.55, >0.05

Failure designated on day 35 represents a total cumulative failure occurring at any time during the follow-up.

Table 3. Comparison of the therapeutic efficacy of miconazole and fluconazole in susceptible and resistant *Candida* strains

	Therapeutic efficacy		Total	95% CI	χ^2 , p value
	miconazole group	fluconazole group			
Days 7–14					
R	7/9	2/4	9/13, 69.2	0.023–3.523	0.12, >0.05
S	158/206, 76.7%	188/220, 85.5%	346/426, 81.3	1.088–2.927	5.35, <0.05
Days 30–35					
R	5/9	1/4	6/13, 46.2	0.019–3.653	0.17, >0.05
S	136/206, 66.1%	153/220, 69.6%	289/426, 67.8	0.782–1.782	0.61, >0.05

S = Susceptible and intermediately susceptible; R = resistant.

Discussion

Effectiveness of SVVC Therapy

Watson et al. [13] reviewed the effectiveness of oral versus intravaginal antifungal treatments for uncomplicated VVC and found no difference. Sobel et al. [14] studied 398 patients with complicated VVC, 197 of whom were randomized to a single-dose fluconazole and 201 of whom received two sequential doses. The authors found

that women with SVVC achieved superior clinical and mycological eradication with a 2-dose fluconazole regimen. The 2-dose oral fluconazole regimen currently becomes a standard regimen for the treatment of complicated VVC [3]. Miconazole can be used to treat VVC and recurrent VVC [1, 3, 15]. The miconazole nitrate suppository 1,200 mg consists of 1,200 mg of miconazole nitrate and inactive ingredients. Barnhart [9] studied the efficacy of bedtime versus daytime administration of one

dose of miconazole nitrate vaginal suppository 1,200 mg to treat VVC. The mycological cure rates were 74.5 and 73.6% in the daytime and bedtime groups, respectively. Menon et al. [16] evaluated the effect of ambulation on the vaginal distribution of miconazole nitrate 1,200 mg and found that this activity does not hinder the spread of the insert.

The present study showed that the mycological and clinical cure rate of the patients with SVVC on days 7–14 and 30–35 were comparable in the miconazole and fluconazole groups. These results suggest that 2-dose miconazole nitrate vaginal suppository 1,200 mg may represent a potential future regimen for the treatment of SVVC. The current study further supported that patients with SVVC should use more doses of the antifungal for clinical and mycologic eradication [3, 14].

Non-albicans *Candida* species, mainly *C. glabrata*, have increasingly been identified as the cause of VVC. Infections with non-albicans *Candida* species frequently do not respond to standard azole treatments [17]. In the current study, the mycological and clinical cure rates of patients in the non-albicans *Candida* group were lower than those in the *C. albicans* group on days 7–14 and 30–35, but no statistically significant differences were found.

Failure to respond to antifungal therapy can occur due to either microbiological resistance or clinical resistance. Previously, it has been shown that there may be a discrepancy between the results of the fungal susceptibility tests and therapeutic outcomes [18, 19]. In the current study, the mycological and clinical cure rates of the patients in the susceptible *Candida* group were higher than those in the resistant *Candida* group on days 7–14 and 30–35, but without statistically significant differences.

Safety

Stevens et al. [20] found low systemic absorption of miconazole nitrate from the miconazole nitrate vaginal suppository 1,200 mg from either single or multiple applications. The authors reported the adverse drug reaction of miconazole nitrate vaginal suppository 1,200 mg including burning, pruritus, and irritation [8, 9, 20]. In the present study, the adverse drug reaction rate of miconazole nitrate 1,200 mg vaginal ovule insert and oral fluconazole 150 mg was low. Only 2 patients experienced aggravated vaginal anaphylaxis symptoms after using the miconazole nitrate vaginal suppository. The side effects of oral fluconazole were hypomenorrhea and gastrointestinal reactions in this study.

We conclude that the 2-dose miconazole nitrate vaginal suppository 1,200 mg is safe and effective in the treatment of SVVC. The miconazole nitrate vaginal suppository and oral fluconazole have a lower cure rate for VVC caused by non-albicans *Candida* species than by *C. albicans*. Azole-resistant *Candida* species have a low cure rate when treated with miconazole nitrate vaginal suppository or orally fluconazole, and this topic demands further study.

Acknowledgments

This research was supported by Shenzhen Science and Technology Grant 200702108, 200703031, 20120320020, and JCYJ 20140415162338813.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Sobel JD: Vulvovaginal candidosis. *Lancet* 2007;369:1961–1971.
- 2 Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, Reed BD, Summers PR: Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapy considerations. *Am J Obstet Gynecol* 1998;178:203–211.
- 3 Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59:61–63.
- 4 Gummerus M, Timonen H, Kauko M, Kivijärvi A, Saarikoski S, Tuimala R, Venesmaa P, Wilén-Rosenqvist G: Miconazole in the treatment of vaginal candidosis. A multicenter study. *Mycoses* 1988;31:159–162.
- 5 Dinsmore WW, Granger SE: An open study to assess the acceptability and effectiveness of miconazole 1,200 mg single ovule in the treatment of acute vaginal candidosis. *Br J Clin Pract* 1989;43:238–241.
- 6 van Heusden AM, Merkus HM, Corbeij RS, Oosterbaan HP, Stoot JE, Ubachs HM, Verhoeff A: Single-dose oral fluconazole versus single-dose topical miconazole for the treatment of acute vulvovaginal candidosis. *Acta Obstet Gynecol Scand* 1990;69:417–422.
- 7 van der Meijden WI, van der Hoek JC, Staal HJ, van Joost T, Stolz E: Double-blind comparison of 200-mg ketoconazole oral tablets and 1200-mg miconazole vaginal capsule in the treatment of vaginal candidosis. *Eur J Obstet Gynecol Reprod Biol* 1986;22:133–138.
- 8 Upmalis DH, Cone FL, Lamia CA, Reisman H, Rodriguez-Gomez G, Gilderman L, Bradley L: Single-dose miconazole nitrate vaginal ovule in the treatment of vulvovaginal candidiasis: two single-blind, controlled studies versus miconazole nitrate 100 mg cream for 7 days. *J Womens Health Gend Based Med* 2000;9:421–429.
- 9 Barnhart K: Safety and efficacy of bedtime versus daytime administration of the miconazole nitrate 1,200 mg vaginal ovule insert to treat vulvovaginal candidiasis. *Curr Med Res Opin* 2005;21:127–134.
- 10 Rosco Diagnostica A/S: User's Guide for Neo-Sensitabs Susceptibility Testing, ed 18. Taastруп, Rosco Diagnostica A/S, 2005/2006.23.

- 11 Clinical and Laboratory Standards Institute/ National Committee for Clinical Laboratory Standards: Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts: Approved Guideline. Document M44-A. Wayne, Clinical and Laboratory Standards Institute, 2004.
- 12 Sobel JD, Brooker D, Stein GE, Thomason JL, Wermeling DP, Bradley B, Weinstein L: Single oral dose fluconazole compared with conventional clotrimazole topical therapy of *Candida* vaginitis. Fluconazole Vaginitis Study Group. Am J Obstet Gynecol 1995; 172(4 Pt 1):1263–1268.
- 13 Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A: Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): systematic review. BJOG 2002;109:85–95.
- 14 Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, Nyirjesy P, Heine MW, Willems J, Panzer H, Wittes H: Treatment of complicated *Candida* vaginitis: comparison of single and sequential doses of fluconazole. Am J Obstet Gynecol 2001;185:363–369.
- 15 Donders GG, Bellen G, Mendling W: Management of recurrent vulvo-vaginal candidosis as a chronic illness. Gynecol Obstet Invest 2010;70:306–321.
- 16 Menon S, Izquierdo A, Rosen M, Hummel A, Barnhart K: The effect of ambulation on vaginal distribution of miconazole nitrate (1,200 mg). J Womens Health (Larchmt) 2007;16:703–706.
- 17 Hettiarachchi N, Ashbee HR, Wilson JD: Prevalence and management of non-albicans vaginal candidiasis. Sex Transm Infect 2010; 86:99–100.
- 18 Sobel JD, Zervos M, Reed BD, Hooton T, Soper D, Nyirjesy P, Heine MW, Willems J, Panzer H: Fluconazole susceptibility of vaginal isolates obtained from women with complicated *Candida* vaginitis: clinical implications. Antimicrob Agents Chemother 2003;47:34–38.
- 19 Fan SR, Liu XP: In vitro miconazole susceptibility and clinical outcome in vulvovaginal candidiasis. Int J Gynaecol Obstet 2007;97: 207–208.
- 20 Stevens RE, Konsil J, Verrill SS, Roy P, Desai PB, Upmalis DH, Cone FL: Bioavailability study of a 1,200 mg miconazole nitrate vaginal ovule in healthy female adults. J Clin Pharmacol 2002;42:52–60.