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

Shangrong Fan, Xiaopingliu Liu, Yiheng Liang

Departments of Obstetrics and Gynecology and Laboratory Science, Peking University Shenzhen Hospital, and Shenzhen 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). 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.

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...
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).

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 ≥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 χ² 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).

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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 \textit{C. albicans}. Non-albicans \textit{Candida} species included \textit{C. glabrata} (6.9%, 40/577), \textit{C. parapsilosis} (0.9%, 5/577), \textit{C. tropicalis} (0.3%, 2/577), \textit{C. krusei} (1.0%, 6/577), \textit{C. lusitaniae} (0.2%, 1/577), \textit{C. famata} (0.3%, 2/577), and \textit{Saccharomyces cerevisiae} (0.9%, 5/577). The \textit{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 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 \textit{C. albicans} and non-albicans \textit{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 \textit{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.


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

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

<table>
<thead>
<tr>
<th>Therapeutic efficacy</th>
<th>95% CI</th>
<th>χ², p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>miconazole group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluconazole group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>228</td>
<td>243</td>
</tr>
<tr>
<td>Improvement</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Failure</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Mycologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>201/252, 79.8%</td>
<td>228/263, 86.7%</td>
</tr>
<tr>
<td><em>Non-albicans Candida</em></td>
<td>19/38, 50.0%</td>
<td>13/24, 54.2%</td>
</tr>
<tr>
<td>Subtotal</td>
<td>220/290, 75.9%</td>
<td>241/287, 84.0%</td>
</tr>
<tr>
<td>Day 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>235</td>
<td>240</td>
</tr>
<tr>
<td>Improvement</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Failure</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Mycologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>171/252, 67.9%</td>
<td>187/263, 71.1%</td>
</tr>
<tr>
<td><em>Non-albicans Candida</em></td>
<td>17/38, 44.7%</td>
<td>13/24, 54.2%</td>
</tr>
<tr>
<td>Subtotal</td>
<td>188/290, 64.8%</td>
<td>200/287, 69.7%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Therapeutic efficacy</th>
<th>Total</th>
<th>95% CI</th>
<th>χ², p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>miconazole group</td>
<td></td>
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</tr>
<tr>
<td>fluconazole group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Days 7 – 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>7/9</td>
<td>2/4</td>
<td>9/13, 69.2</td>
</tr>
<tr>
<td>S</td>
<td>158/206, 76.7%</td>
<td>188/220, 85.5%</td>
<td>346/426, 81.3</td>
</tr>
<tr>
<td>Days 30 – 35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>5/9</td>
<td>1/4</td>
<td>6/13, 46.2</td>
</tr>
<tr>
<td>S</td>
<td>136/206, 66.1%</td>
<td>153/220, 69.6%</td>
<td>289/426, 67.8</td>
</tr>
</tbody>
</table>

S = Susceptible and intermediately susceptible; R = resistant.
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.

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Disclosure Statement
The authors have no conflicts of interest to disclose.

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