Clinical and mycological efficacy of single-day oral treatment with itraconazole (400 mg) in acute vulvovaginal candidosis

Klinische und mykologische Wirksamkeit der Eintages-Oralbehandlung mit Itraconazol (400 mg) bei akuter Vulvovaginalcandidose

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Summary

This study aimed to investigate the effectiveness of single-day oral treatment with itraconazole in acute vulvovaginal candidosis (VVC). Vaginitis was demonstrated by both detection of yeast cells and pseudohyphae formation on microscopic examination of vaginal discharge and mycological culture as well as by the clinical signs and symptoms. Clinical and mycological examinations of the 52 patients were performed before, 1 week (short-term) and 4 weeks (long-term) after single-day oral treatment with itraconazole 200 mg b.i.d. The causative yeast fungi were: Candida albicans (76.9%), C. glabrata (9.6%), C. kefyr (9.6%) and C. krusei (3.9%), respectively. In short- and long-term examinations, clinical cure rates were found to be 61.5% and 90.4%, and mycological cure rates were 63.5% and 90.4%, respectively. Itraconazole was found to be 95.0% effective with C. albicans and 75.0% with other Candida species. It is concluded that treatment of acute VVC with itraconazole is safe and effective in the long-term.

Zusammenfassung


Key words: Candida, candidosis, vulvovaginitis, antmycotic chemotherapy, itraconazole.

Schlüsselwörter: Candida, Candidosis, Vulvovaginitis, Antimykotische Chemotherapie, Itraconazol.

Introduction

Candida is a yeast that causes vulvovaginal candidosis (VVC) in the external genitalia of women and is responsible for 20–25% of all vulvovaginal infections.1, 2 Although it can be detected in all age groups, its prevalence is higher in the sexually active women.
Three of four women have at least one attack and half of these have at least two or more episodes during their lifetime.\textsuperscript{3–5} 

Candida albicans is the most frequent causative agent of VVC and is isolated in 80–92\% of the patients, followed by C. glabrata which accounts for 5–10\%, by C. tropicalis and by other Candida species.\textsuperscript{2, 6}

The data on the incidence and prevalence of VVC are insufficient all over the world. Since the reporting of the disease is not mandatory, we are only able to deduct the prevalence from the results of various studies. The misuse and/or insufficient use of the readily available antifungal drugs poses a problem for epidemiological studies.\textsuperscript{7} In the treatment of acute VVC topical azoles used for 1, 3 and 7 days or 14 day treatment with non-azole topical drugs is preferred. Oral drugs such as 5 day treatment with ketoconazole and 1 day treatment with fluconazole or 1–3 days treatment with itraconazole are also applied.\textsuperscript{8}

Fluconazole and itraconazole are both members of the triazole group used orally and inhibit the fungal sterol synthesis by their action on cytochrome P-450, thereby inhibiting the formation of the fungal cell membrane. Fluconazole is highly water-soluble and can reach high concentrations in body fluids. On the contrary, itraconazole is strongly lipophilic and reaches its highest concentration in tissues. Although they have different dispersions both drugs have been found to be in high levels in vaginal secretions.\textsuperscript{9, 10}

This study aimed to investigate the effectiveness of single-day oral treatment with itraconazole 200 mg b.i.d. in acute VVC on short- (1 week) and long-term (4 weeks) clinical and mycological cure rates.

**Material and methods**

This study was a single-centre, randomized study. All patients were fully informed (orally and in writing) of the objectives and implications of the study and a written informed consent was obtained from each patient before they were admitted to the study.

**Study population**

Patients with complaints of vaginal discharge, dyspareunia, burning, itching and reddening diagnosed as acute VVC (less than three episodes in a period of 1 year) admitted to the outpatient clinic of Department of Obstetrics and Gynecology at the Faculty of Medicine, Çukurova University between May 1999 and March 2002 were included in the study. All patients were clinically examined and a detailed history was obtained prior to the treatment. Patients with pregnancy, diabetes mellitus, immunodeficiency, history of corticosteroid, antibacterial or antifungal drug use in the past month, patients with clinical findings without positive mycological examination results, patients infected with Trichomonas sp., with recurrent Candida vaginitis or with bacterial vaginosis were excluded from the study. Sixty-four patients with clinically and mycologically proven cases of acute VVC (with direct microscopy and culture) who agreed to participate in our study were included in the study. All patients were between 20 and 47 years of age and married.

**Medication**

All patients received a single-day treatment with 400 mg itraconazole, two capsules of 100 mg orally with meal in the morning and two capsules in the evening.

**Mycological examination**

Two specimens of vaginal discharge were taken with sterile swabs by using a dry sterile speculum and placed into a Sabouraud glucose broth with 1 ml of glucose liquid. The specimens were sent to the Mycology Laboratory of the Department of Medical Microbiology, Faculty of Medicine, Çukurova University at the same day. One of the specimens was mixed with a drop of saline on a slide for direct wet-mount microscopy and Gram stain, another specimen was used for culture on two Sabouraud glucose agar (SGA) plates. The media were incubated for 1–2 days in air at 26 and 37 °C. Specimens which yielded yeast cells and pseudohyphae on direct microscopy and resulted in at least 10 yeast colonies in SGA media were accepted positive. Candida species were identified by germ-tube formation in human serum at 37 °C for 2 h, micromorphology on cornmeal agar-Tween 80 according to the Dalmau’s method, and by using the commercial API 20 C (bioMerieux, Marcy Etoile, France) system. The ATCC reference strains C. albicans (ATCC 10231) and C. tropicalis (ATCC 22019) were used as quality controls.\textsuperscript{4, 11}

**Follow-up**

Patients were asked to return twice, 1 week (short-term) and 4 weeks (long-term) after the treatment, and were examined by the same clinician at each visit. Sexual abstinence was advised until the short-term control. The clinical and mycological efficacy of the itraconazole was rated as cure, improvement and failure.
Statistical analysis

Clinical and mycological data were analysed by using a chi-square test to compare results of treatment at short- and long-term control visits. Statistical significance was set at $P < 0.05$.

Results

Twelve (19%) of the 64 patients with acute VVC did not return for the first and/or fourth week re-examination and these patients were excluded from the study leaving 52 (81%) patients in the study group. The mean age of the patients was $34.5 \pm 7.3$ (minimum $= 20$, maximum $= 47$). The causative yeast fungi were found as, 40 (77%) $C. albicans$, five (10%) $C. glabrata$, five (10%) $C. kefyr$ and two (3%) $C. krusei$ from a total of 52 isolates. After the treatment most patients in the study group had greatly diminished clinical signs and symptoms in the first week control, and almost all patients were free of clinical signs and symptoms on the fourth week of control. No side-effects were reported by the patients. The patients' history, clinical and mycological examination with pretreatment, first and fourth week results are given in Tables 1–3.

Clinical cure was greater (90.4%) in the long-term compared with the short-term (61.5%) ($P < 0.05$). Mycological recovery was similarly greater in the long-term (90.4%) than the short-term controls (63.5%) ($P < 0.05$). None of the patients were classified as improved neither in the short-term nor in the long-term controls.

In the study, 19 (37%) of the 52 cases had mycologically positive results in short-term control. The causative yeast fungi in these patients were, $C. albicans$ (79%), $C. glabrata$ (10%) and $C. krusei$ (10%). In the long-term control, five (10%) of the 52 cases had, no mycological response, which were $C. albicans$ (40%), $C. krusei$ (40%) and $C. glabrata$ (20%) isolated. As a result, single-day treatment with itraconazole 47 (90%) of 52 patients cured mycologically. Among them 38 (95%) of 40 $C. albicans$, four (80%) of five $C. glabrata$ and all of five (100%) $C. kefyr$ were cured, while two cases of $C. krusei$ had showed resistance to treatment and this species was detected in both of short- and long-term mycological controls.

Discussion

One of the commonly encountered diseases in Obstetrics and Gynecology is acute VVC. Various drugs are available in different forms with various mechanisms of action. In the past 30 years, there were only a few antifungal drugs available, but in the recent years new drugs have been developed and the variety of antifungal drugs have increased dramatically. This change brought with it a need for better clarification of the indication for each drug. In the past, antifungal drug resistance was not known to exist, but today primary and secondary antifungal drug resistance has been proved by extensive multicentered studies. In 1997, the National Committee for Clinical Laboratory Standards (NCCLS) proposed a standard microdilution technique for yeast fungi. Although in vitro sensitivity of the Candida species does not always mean successful treatment, in vitro resistance almost always means a high rate of failure in the treatment. For this reason in vivo response of the antifungals has earned importance and is the basis of this study.

Table 1 Signs and symptoms of 52 patients with acute vulvovaginal candidosis before treatment and follow-up.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Pretreatment (day 0)</th>
<th>Short-term (1 week)</th>
<th>Long-term (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[n (%)]</td>
<td>[n (%)]</td>
<td>[n (%)]</td>
</tr>
<tr>
<td>Discharge</td>
<td>52 (100.0)</td>
<td>19 (36.5)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>34 (64.5)</td>
<td>15 (28.8)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Burning</td>
<td>29 (55.8)</td>
<td>4 (7.7)</td>
<td>–</td>
</tr>
<tr>
<td>Itching</td>
<td>26 (50.0)</td>
<td>15 (28.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Reddening</td>
<td>24 (46.2)</td>
<td>8 (15.4)</td>
<td>–</td>
</tr>
</tbody>
</table>

$^1$Column presenting: $\chi^2 = 10.32$, d.f. = 1, $P < 0.05$.

Table 2 Clinical efficacy of itraconazole in patients with acute vulvovaginal candidosis.

<table>
<thead>
<tr>
<th>Clinical examination</th>
<th>Short-term (1 week)</th>
<th>Long-term (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%$^1$</td>
</tr>
<tr>
<td>Cure</td>
<td>32</td>
<td>61.5</td>
</tr>
<tr>
<td>Failure</td>
<td>20</td>
<td>38.5</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$^1$Column presenting: $\chi^2 = 9.15$, d.f. = 1, $P < 0.05$.

Table 3 Mycological efficacy of itraconazole in patients with acute vulvovaginal candidosis.

<table>
<thead>
<tr>
<th>Mycological examination</th>
<th>Short-term (1 week)</th>
<th>Long-term (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%$^1$</td>
</tr>
<tr>
<td>Negative</td>
<td>33</td>
<td>63.5</td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>36.5</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$^1$Column presenting: $\chi^2 = 9.15$, d.f. = 1, $P < 0.05$. 
Itraconazole is a safe, recently developed antifungal drug with a wide spectrum and gained an important place in the treatment of VVC. An important factor for the *in vitro* sensitivity of the *Candida* species is that each species has an *in vitro* profile for sensitivity, thus enabling a high probability of a guess for sensitivity for both fluconazole and itraconazole. If a species is known, *Candida albicans*, *C. tropicalis*, *C. parapsilosis* and *C. lusitaniae* are sensitive to both fluconazole and itraconazole. *Candida glabrata* can be sensitive or resistant to both of these drugs, dose dependently. Isolates of *C. krusei* are assumed to be intrinsically resistant to fluconazole. The studies done on the sensitivity of *C. krusei* strains resistant to fluconazole and itraconazole showed cross-resistance for itraconazole. *C. tropicalis*, in five (15%), *C. parapsilosis* in two (6%) and *C. krusei* in two (6%) vaginal and anal smears of the same cases. They examined by E-test method the *in vitro* resistance was less than fluconazole and that resistance for itraconazole could be related to previous resistance for fluconazole. Johnson *et al.* reported that from a total of 690 *Candida* strains resistant to fluconazole, 32% had cross-resistance for itraconazole.

Candido *et al.* evaluated 17 VVC cases and isolated a total of 33 *Candida* species; as *C. albicans* in 24 (73%), *C. tropicalis* in five (15%), *C. parapsilosis* in two (6%) and *C. krusei* in two (6%) vaginal and anal smears of the same cases. They examined by E-test method the *in vitro* sensitivity of these species to ketoconazole, fluconazole, and itraconazole. Among all 24 isolates of *C. albicans* studied no isolates were resistant to fluconazole, while 21% and 54% of isolates were resistant to ketoconazole and itraconazole, respectively. They also reported that among nine non-*albicans* *Candida* isolates only one *C. krusei* showed resistance to ketoconazole. Otherwise, 100% of the *C. tropicalis* and *C. krusei* isolates were resistant to itraconazole. Also no isolates of *C. tropicalis* and *C. parapsilosis* showed resistance to fluconazole.

Experimental VC in rats has been treated with a single oral dose of itraconazole and the drug has been shown to inhibit the penetration of the fungus into the vaginal squamous epithelium, with the ability of the drug to reach structurally and alter intracellularly located fungal elements. The single dose drug has a prolonged effect leading to complete eradication of the fungus from the vagina within 3 days. Itraconazole 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 4 days after a single-day treatment with 200 mg b.i.d. Pharmacokinetic properties show that this long acting drug is ideal for short-term treatment protocol. However, there are a few recent studies focusing on the oral treatment of acute VVC with itraconazole. These studies reported that 1–3 days oral treatment with itraconazole in short- and long-term controls clinical cure rates of 80–96% and, mycological cure rates of 70–96% were achieved, respectively. Cauwenbergh studied different treatment schedules of itraconazole including 200 mg b.i.d. for 1 day, 200 mg once daily for 2 days and 200 mg once daily for 3 days and followed up 1 week and 1 month for clinical and mycological efficacy. Author reported in short- and long-term controls clinical cure was 82–89%, and mycological cure was 79–84% with no statistically significant difference between groups. He also reported the drug was well-tolerated, minor and reversible side-effects had been seen in 19 (3.4%) of 552 patients such as abdominal pain, nausea and headache.

Roongpisuthipong *et al.* evaluated 17 VVC cases and isolated a total of 33 *Candida* species; as *C. albicans* in 24 (73%), *C. tropicalis* in five (15%), *C. parapsilosis* in two (6%) and *C. krusei* in two (6%) vaginal and anal smears of the same cases. They examined by E-test method the *in vitro* resistance was less than fluconazole and that resistance for itraconazole could be related to previous resistance for fluconazole. Johnson *et al.* reported that from a total of 690 *Candida* strains resistant to fluconazole, 32% had cross-resistance for itraconazole. Otherwise, 100% of the *C. tropicalis* and *C. krusei* isolates were resistant to itraconazole. Also no isolates of *C. tropicalis* and *C. parapsilosis* showed resistance to fluconazole.

Roongpisuthipong *et al.* reported the oral treatment with itraconazole 200 mg b.i.d. for 1 day in 59 cases of acute VVC. The first week and the first month controls showed clinical cure of 89% and 90%, mycological cure of 83% and 69%, respectively. This has been explained by the author with the fact that the drug is three to 10 times more concentrated in genital organs than the plasma and because of a long half-life of 20 h in humans.

Stein and Mummaw compared the efficacy of oral treatment with itraconazole 200 mg once daily and clotrimazole vaginal tablet (200 mg/day) for 3 days and clinical cure rates were found to be 96% and 100% in the first week and, 83% and 70% in the fourth week, respectively. Mycological cure was found to be 73% and 95%, respectively in the short-term control and was similar in the long-term. Minor and reversible side-effects such as nausea and headache were seen in 35% of the cases where itraconazole was used. Although side-effects for clotrimazole was reported to be 4%, the authors reported itraconazole to be as safe as clotrimazole for the treatment of acute VVC.

Woolley and Higgins compared three treatments groups as: topical treatment with clotrimazole (500 mg vaginal pessary and 1% cream), oral treatment with itraconazole (200 mg b.i.d. for 1 day) and oral treatment with fluconazole (150 mg once daily for 1 day) in acute VVC and reported clinical cure of 80%, 80%, 62%, respectively, and mycological cure of 95%, 96%, 83%, respectively 7–10 days after treatment. The authors reported clinical and mycological cure rates in the fluconazole group significantly lower than those in the itraconazole group or clotrimazole group.

Beyer and Voorhoeve-den Hartog treated 17 cases of acute VVC with itraconazole 200 mg once daily for 2 days and after the end of the therapy they investigated clinical and mycological cure rates for 5 days every day. On the fourth day, they detected mycological cure on all
patients. In the first day, all of the 17 patients complained of leucorrhoea and 16 patients complained of pruritis vulvae, in the third day leucorrhoea and pruritis vulvae were present only to a mild degree in five patients, in the fifth day four patients had mild leucorrhoea, two cases mild eritema and one patient had mild pruritis vulvae. No side-effects were seen in any of the patients.

In our study in short-term controls clinical and mycological cure rate was found to be 61.5% and 63.5%, and in long-term clinical and mycological cure rate was 90.4% and 90.4%, respectively. The single-day treatment with itraconazole (400 mg) had significance when first and fourth week results were compared for clinical cure (Table 2). The mycological cure rate was found to be significantly higher in long-term controls (Table 3). Clinical and mycological cure rates found in this study is lower in the first week and higher in the fourth week when compared with the other studies.\\n
In conclusion, single-day treatment with itraconazole in acute VVC has been found to be safe and effective with high cure rates. The treatment for acute VVC should begin with mycological diagnosis and confirmation, identification of the causative fungi, also evaluation and if possible control of the predisposing factors. We believe whether topical or systemic, all therapies should be accompanied by in-depth information given to the patient about the vaginal and general body hygiene and all of the patients should be followed up clinically and mycologically after treatment.

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