Single-Dose Tioconazole Compared with 3-Day Clotrimazole Treatment in Vulvovaginal Candidiasis

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A total of 80 patients were equally randomized to receive a single dose of 6.5% tioconazole ointment or a 3-day course of 100-mg clotrimazole vaginal tablets for the treatment of vulvovaginal candidiasis. Of the 32 evaluable patients treated with tioconazole, 27 (84%) remained asymptomatic 4 weeks posttreatment, compared with 28 of 33 patients (85%) treated with clotrimazole. A total of 34 patients in each group could be evaluated for mycological response based on culture results 1 and 4 weeks after treatment. Twenty patients (59%) who received tioconazole and twenty-one patients (62%) who received clotrimazole remained culture negative 4 weeks after therapy. Of 40 patients who received tioconazole, 12 (30%) experienced local irritation or itching, compared with 2 of 40 patients (5%) treated with clotrimazole (P < 0.01). Single-dose tioconazole ointment was as effective as a 3-day course of clotrimazole tablets, but significantly more patients in the tioconazole-treated group experienced local side effects.

The duration of treatment for Candida vaginitis has changed dramatically over the past several years. New high-dose imidazole derivatives have produced excellent short-term cure rates with treatment durations as short as 1 to 3 days (1, 3, 4, 13, 16, 21). In addition, 4-week follow-up cultures of patients undergoing short-term treatment have not shown a higher incidence of recolonization by Candida organisms compared with cultures from patients undergoing longer periods of treatment (3, 13, 16, 20, 21). Shorter courses of therapy also encourage compliance and decrease expense and inconvenience (1, 3, 12, 16).

Tioconazole is a new imidazole antifungal agent similar to miconazole and clotrimazole. It has a broad spectrum of activity and is more active than other imidazoles against Candida albicans in vitro (10, 11, 18). In a randomized study of 109 women with vaginal candidiasis, a 3-day course of treatment with 2% tioconazole vaginal cream produced higher cure rates 7 to 10 days (P = 0.01) and 4 weeks (P < 0.05) after therapy than did clotrimazole vaginal tablets (6).

Houang and Lawrence reported a mean vaginal concentration of 21.4 μg/ml 24 h after insertion of a single 300-mg ovule of tioconazole in 10 patients with vaginal candidiasis (8). This concentration is significantly higher than the MIC (1.6 to 12.5 μg/ml) of tioconazole for C. albicans (10). These studies suggest that a single application of the agent could be clinically effective in the treatment of Candida vaginitis.

The study reported here was designed to compare the efficacy and acceptability of a single intravaginal application of 6.5% tioconazole ointment (325 mg) with a 3-day regimen of clotrimazole vaginal tablets in women with vulvovaginal candidiasis.

The study was presented in part at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nev., 24 to 26 October 1984.)

MATERIALS AND METHODS

Nonpregnant women, aged 18 to 65, with clinical signs and symptoms of vulvovaginal candidiasis (pruritis, burning, discharge) and pseudohyphae present on microscopic examination of a KOH smear were considered for the study. Women who were menstruating, known to have diabetes, receiving corticosteroids, sensitive to imidazole drugs, or who had a concurrent bacterial, viral, or trichomonal vaginal infection were excluded.

Before admission to the study, written informed consent was obtained from each patient. A medical history was taken, and a physical and gynecological examination, including a Papanicolaou smear cytology, were performed at the initial visit. Two high vaginal swabs were obtained and cultured on sheep blood, chocolate, MacConkey, Thayer-Martin, and Candida-Mycobacterium bovis BCG agar. Plates were incubated at 37°C and read at 18 to 24 and at 48 h. A diagnosis of vulvovaginal candidiasis was confirmed by the presence of Candida sp. on blood and Candida-BCG agar. The germ tube test was used for presumptive identification of C. albicans. Blood chemistry studies, a complete blood count, and urinalysis were also performed on all patients.

Patients were equally randomized by a predetermined numerical code to receive either a single 5-g. application of 6.5% tioconazole ointment (325 mg) (Pfizer Inc., New York, N.Y.) at bedtime or two 100-mg intravaginal tablets of clotrimazole for three consecutive nights. Each patient was instructed not to use any other type of vaginal medication, including vaginal contraceptives and douches, during the entire study period. Patients were supplied condoms and were advised to have their partners use them during sexual intercourse.

Patients were re-examined at 1 and 4 weeks after completion of treatment. Clinical signs and symptoms were assessed and diagnostic smears and cultures were taken for yeast. In addition, at the 1-week follow-up visit, patients were asked about drug-related side effects, and blood and urine laboratory tests were repeated. The results of the two treatment groups were statistically compared by using Fisher's exact test.

RESULTS

The 80 patients were randomly divided into the two treatment groups. Because of a negative initial culture or lack of follow-up, four patients treated with tioconazole and

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two patients treated with clotrimazole were excluded from evaluation. All 80 patients completed a course of therapy and were included in the evaluation of medication-related side effects. Demographic and epidemiologic parameters were comparable for the two treatment groups (Table 1).

**Symptomatic response.** The overall clinical success rate was similar for the two treatment groups. Of 36 patients who received tioconazole, 34 (94%) were asymptomatic at the first follow-up. Of 30 clotrimazole-treated patients available for evaluation at the 4-week visit, 27 (90%) remained asymptomatic. In the clotrimazole group, 37 of 38 patients (97%) were asymptomatic at 1 week posttreatment. Of 32 clotrimazole-treated patients evaluated at the 4-week follow-up, 28 (88%) remained asymptomatic (Table 2). In each case of a recurrence of symptoms there was a positive vaginal culture for *Candida* sp.

**Mycological response.** Of the 36 evaluable patients treated with tioconazole, 28 (78%) were culture negative at the 1-week posttreatment follow-up, compared with 34 of 38 evaluable patients (89%) treated with clotrimazole. In the group treated with tioconazole, all but two patients with negative cultures at 1 week received 4-week posttreatment cultures. Of those 26 patients, 20 (77%) were still culture negative. In the clotrimazole-treated group, four patients who were culture negative at 1 week did not receive a second follow-up culture. Of the remaining 30 patients, 21 (70%) were still culture negative for *Candida* sp. (Table 2). Thus, a total of 34 patients in each group were assessable for efficacy evaluation based on culture results 1 and 4 weeks posttreatment. Twenty patients (59%) who received tioconazole and twenty-one patients (62%) who received clotrimazole remained culture negative 4 weeks after treatment (not significant).

**Side effects.** Medication-related side effects were reported by 12 patients (30%) in the tioconazole-treated group. A total of nine patients complained of local pruritis after insertion of the ointment; this symptom lasted an average of 18 h and ranged from mild to severe in intensity. Three patients complained of labial swelling, two had local burning, and one patient complained of vaginal irritation. Of those patients experiencing side effects, two suffered recurrent candidiasis during the follow-up period. They were retreated with a different imidazole antifungal and did not experience an adverse side effect during treatment. By comparison, only two patients (5%) in the clotrimazole-treated group reported an untoward effect from medication. One patient complained of vaginal burning, and one complained of a sensitive clitoris. The difference in adverse reactions between the two treatment groups was statistically significant (P = 0.006). Biochemical and hematological abnormalities were not observed in either group.

**DISCUSSION**

Vaginitis caused by *Candida* sp. has become one of the most troublesome forms of vaginitis because it is so frequently a recurrent problem. Short-term therapy is particularly effective for the treatment of isolated episodes of vulvovaginal candidiasis, but recurrence rates can range from 10 to 40% (2, 17). The reason that some patients present with repeated episodes of *Candida* vaginitis is not known, but several studies suggest a relationship between anorectal and vulvovaginal candidiasis (7, 14, 24). The recurrence of genital infection may also be a consequence of incomplete eradication of the initial vaginal infection (5). Higher incidences of recurrence have also been found in patients with a previous history of candidal vulvovaginitis (13).

The results of this investigation suggest that a single 5 g-application of 6.5% tioconazole ointment is as effective as a 3-day course of clotrimazole vaginal tablets for the treatment of vulvovaginal candidiasis. Although a number of patients experienced an untoward effect with tioconazole, none found the treatment unacceptable. In a small study comparing tioconazole to placebo ointment, 11 patients were randomized to receive 5 g of 6.5% tioconazole ointment or 5 g of the ointment without tioconazole (unpublished data). Local pruritis was observed in two of five patients who received tioconazole, whereas none of the six patients who received ointment alone demonstrated pruritis symptoms. This suggests that the high concentration of tioconazole may be responsible for the local irritation, rather than the vehicle itself.

Over one-half of our patients with positive cultures during follow-up were asymptomatic. Whether to treat women with asymptomatic vaginal colonization with *Candida* sp. is debatable. Some advocate treatment of these patients since there is always some degree of inflammation that follows vaginal colonization by *Candida* sp., and there is no way to predict which women may later develop a symptomatic infection (9, 19). Another approach is to treat only asymptomatic women at increased risk of developing *Candida* vaginitis due to their use of oral contraceptives or broad-spectrum antibiotics. Many practitioners consider it unnecessary to prescribe antifungal treatment in cases in which the patient has no complaints of vaginitis. Furthermore, it is unlikely that asymptomatic colonized patients would undergo a course of treatment, since compliance is often poor even in those with symptoms.

The mechanism for recurrent vulvovaginal candidiasis still remains controversial. Combined oral and vaginal treatment

### TABLE 1. Profile of patients in two treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tioconazole</th>
<th>Clotrimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients enrolled</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>No. initially culture positive for <em>Candida</em> sp.</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Mean age in yr (range)</td>
<td>23 (18–39)</td>
<td>23 (18–46)</td>
</tr>
<tr>
<td>Mean duration (days) of symptoms (range)</td>
<td>12.5 (1–60)</td>
<td>13.5 (1–90)</td>
</tr>
<tr>
<td>No. with previous yeast infection during past 12 mo</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>No. taking oral contraceptives</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>No. receiving antibiotics during previous mo</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean duration (days) of follow-up for all cures (range)</td>
<td>24.9 (7–33)</td>
<td>29.4 (9–46)</td>
</tr>
</tbody>
</table>

### TABLE 2. Efficacy evaluation of two treatment groups

<table>
<thead>
<tr>
<th>Point of follow-up</th>
<th>Ratioa (%) of asymptomatic response</th>
<th>Ratioa (%) of negative mycological response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tioconazole</td>
<td>Clotrimazole</td>
</tr>
<tr>
<td>1 wk</td>
<td>34/36 (94)</td>
<td>37/38 (97)</td>
</tr>
<tr>
<td>4 wk</td>
<td>27/30 (90)</td>
<td>28/32 (88)</td>
</tr>
<tr>
<td>Overallb</td>
<td>27/32 (84)</td>
<td>28/33 (85)</td>
</tr>
</tbody>
</table>

*a* Ratios represent number of patients showing no symptoms (or negative cultures) out of patients tested.

*b* Ratios based on follow-up examinations 1 and 4 weeks posttreatment.
has proved no more effective than local treatment in preventing recurrent infection (15). Single-dose treatment is an effective and safe method of treating acute symptomatic cases of vulvovaginal candidiasis (3, 16). Treatment that can be performed during the patient’s initial visit obviates the problem of compliance and helps reduce the cost of care. For patients with repeated recurrence of symptomatic Candida vaginitis, longer courses of therapy may be of benefit, either with miconazole (23), clotrimazole (12), or ketoconazole (22).

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LITERATURE CITED