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Placebo-Controlled Trial of Itraconazole for Treatment of Acute Vaginal Candidiasis

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Itraconazole is a new orally active triazole antifungal agent with enhanced activity against *Candida* species. In the clinical trial described in this paper, we compared the efficacy and safety of itraconazole capsules with those of clotrimazole vaginal tablets and placebo oral capsules for women with acute vulvovaginal candidiasis. Ninety-five patients were randomized in a 2:1:1 fashion to receive itraconazole (200 mg/day), clotrimazole (200 mg/day), or placebo (two capsules per day) for 3 consecutive days. Clinical success rates (cure and improvement) were similar for women who received itraconazole (96%) and clotrimazole (100%) 1 week posttreatment. These response rates were statistically superior to those obtained with placebo treatment (77%, $P < 0.05$). Negative mycological cultures were found in 95, 73, and 32% of the patients treated with clotrimazole, itraconazole, and placebo, respectively ($P < 0.005$ [active treatments versus placebo]). By 4 weeks posttreatment, the clinical failure rate for itraconazole was less than that observed for clotrimazole (17 versus 30%), but this difference did not reach statistical significance ($P > 0.05$; $\beta = 0.81$). Mycological response rates for itraconazole and clotrimazole were also similar. No patients enrolled in this study discontinued treatment because of an adverse event. Minor side effects were reported by 35, 4, and 41% of patients who received itraconazole, clotrimazole, and placebo, respectively. The most common side effects associated with itraconazole therapy were nausea and headache. In summary, itraconazole was found to be as effective and safe as clotrimazole in women with acute candida vaginitis. Moreover, oral therapy was highly favored over intravaginal treatment in our survey of patients.

The introduction of potent imidazole and triazole antifungal agents has significantly altered the duration of treatment of acute vaginal candidiasis (16). Short courses of therapy with various topical formulations are highly effective and produce few adverse effects (7, 26, 31). Oral agents, such as fluconazole, are also well tolerated and are as effective as local treatments (19, 25). Moreover, patients with candida vaginitis express a strong preference for oral therapy (1, 29).

Itraconazole is a new orally active triazole antifungal drug (21). This agent appears to be an attractive alternative for the treatment of vaginal candidiasis because of its enhanced activity against *Candida* species and its low incidence of untoward effects (8). In an experimental model of candidal vaginitis, itraconazole was shown to be more efficacious than ketoconazole in eradicating vaginal infection with *Candida albicans* (24).

In patients treated prior to hysterectomy, itraconazole was found to be detectable in vaginal tissue by 1 h after a 200-mg oral dose and tissue itraconazole concentrations above the MIC for *Candida* species were maintained for at least 15 h (11). On the basis of these findings, various dosage regimens of itraconazole in open studies of women with acute vaginal candidiasis were investigated (2, 4, 22). The overall data suggest that the best clinical and mycologic results would be obtained with 200 mg of itraconazole once daily for 3 days (6).

The clinical trial that we describe was designed to compare the efficacy and safety of a 3-day course of itraconazole with those of clotrimazole and placebo treatment of women with acute vulvovaginal candidiasis.

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MATERIALS AND METHODS

Nonpregnant women who were 18 years of age or older and who had clinical signs and symptoms of vulvovaginal candidiasis (pruritis, burning, and discharge) and pseudohyphae present on microscopic examination of a KOH smear were considered for enrollment in this study. Women with any of the following conditions were excluded from the study: women who had abnormal Papanicolaou smear cytology, allergy to azole drugs, or chronic vaginal candidiasis; women who were known to have diabetes or immunosuppression; women receiving antifungal chemotherapy; women who were known to have impaired renal or hepatic function; and women who had a concurrent bacterial, viral, or trichomonal vaginal infection.

This study was approved by the University Committee on Research in Human Subjects at Michigan State University, and before admission to the study, written, informed consent was obtained from each patient. Medical histories were recorded, and physical and gynecological examinations, including Papanicolaou smears, were performed at each initial visit. Signs (erythema, erosion, and discharge) and symptoms (pruritis, burning, and discharge) were scored by the investigators according to the following scale: none (one point), mild (two points), moderate (three points), or severe (four points). Two high vaginal swabs were obtained and cultured on sheep blood and Nickerson's agar. Plates were incubated at 37°C and read at 18 to 24 h and at 48 h. A diagnosis was confirmed by the presence of *Candida* species. The germ tube test was used for presumptive identification of *C. albicans*. For all patients, blood chemistry

studies (SMAC 20), complete blood counts, and urinalyses were also performed.

The patients were randomized in a 2:1:1 fashion by a predetermined code to receive two 100-mg capsules of itraconazole (Janssen, Piscataway, N.J.), two oral placebo capsules, or two 100-mg vaginal tablets of clotrimazole for three consecutive nights (6, 20). Each patient was instructed not to use any other types of vaginal medication, including vaginal contraceptives and douches, during the entire study period. The patients were supplied with condoms and were advised to have their partners use them during sexual intercourse.

The patients were reexamined at 1 week after completion of treatment. Clinical signs and symptoms were assessed, and diagnostic smears and yeast cultures were taken. In addition, the patients were asked about drug-related side effects, and blood and urine laboratory tests were repeated. The patients were also surveyed as to preference of type and duration of therapy by using a self-administered questionnaire (29). Patients who showed improvement in clinical symptoms and whose cultures were negative for *Candida* species were asked to return for a second follow-up examination. These patients were reevaluated in 3 weeks, unless symptoms recurred or worsened before this scheduled visit.

Clinical responses to treatment were evaluated at each visit and recorded as cure (complete resolution of signs and symptoms), improvement (considerable resolution of presenting signs and symptoms), or failure (no improvement). Mycological evaluations were based on the presence or absence of *Candida* species from cultures at each visit. All patients enrolled were included in the evaluation of drug-induced side effects. The outcome results from the two active treatment groups were expected to be similar and superior to those from the placebo group. Our findings were statistically compared by Fisher's exact test. A P value of <0.05 was considered significant.

RESULTS

Ninety-five women were enrolled in this clinical trial. Disease severity was similar for the different treatment groups. The majority of women presented with mild to moderate signs and/or symptoms. Other demographic and epidemiologic parameters of these patients were also comparable for three treatment groups (Table 1). Because of a negative initial culture for *Candida* species, five patients were excluded from the efficacy evaluation. A total of 48 patients who received itraconazole, 20 who received clotrimazole, and 22 who received the placebo met the requirements for clinical and microbiological evaluations.

The clinical success rates for women who received itraconazole and clotrimazole were similar. Of the 48 patients treated with itraconazole, 46 (96%) were asymptomatic or had improved significantly by the first follow-up visit (Table 2). All 20 patients treated with clotrimazole were clinically cured or had improved. In contrast, only 17 (77%) of 22 women who received placebo capsules improved with treatment. This success rate is statistically inferior to those with the active treatment regimens ($P < 0.05$). At the first posttreatment visit, negative mycological cultures were observed for 19 (95%) patients treated with clotrimazole, 35 (73%) patients treated with itraconazole, and 7 (32%) patients treated with the placebo. There was no difference in mycological cure rates for the active treatment regimens, but both therapies were statistically superior to the placebo ($P < 0.005$).

TABLE 1. Profile of patients in the three treatment groups

Characteristic	Treatment with:		
	Itraconazole	Clotrimazole	Placebo
No. enrolled	50	23	22
Mean age (in yr) (range)	23 (18–43)	23 (18–33)	24 (18–39)
No. with previous yeast infection during past 12 mo (%)	29 (58)	11 (48)	12 (54)
No. taking oral contraceptives (%)	27 (54)	11 (48)	13 (59)
No. who received an oral antibiotic during the previous mo (%)	10 (20)	6 (26)	5 (23)
Mean duration (days) of symptoms (range)	7 (2–60)	8 (2–14)	11 (1–30)
Mean baseline sign/symptom score (SD)	16.0 (3.1)	15.6 (3.1)	16.5 (3.0)
No. of cultures positive for *Candida* species (%):			
C. albicans	46 (92)	20 (87)	21 (96)
Non-*C. albicans* species	2	0	1
No. of negative cultures	2	3	0

Of the 35 itraconazole-treated patients evaluated up to 4 weeks posttreatment, 27 (83%) remained asymptomatic or had improved (Table 2). In the clotrimazole-treated group, only 12 (67%) of 18 patients were still clinically cured or had improved. The attrition rate was high for those women who received placebo. Of the seven patients that remained in the study, four (57%) were still asymptomatic and three (43%) were clinical failures. Clinical responses among treatment groups were not statistically different at the second visit. The mycological response at the 4-week posttreatment visit was

TABLE 2. Efficacy evaluation of the three treatment groups

Posttreatment response	No. of patients (%) for the following treatment groups:		
	Itraconazole	Clotrimazole	Placebo
1 wk			
Total no. of patients	48	20	22
Clinical response			
Cure	35 (73)	13 (65)	10 (45)
Improvement	11 (23)	7 (35)	7 (32)
Failure	2 (4)	0 (0)	5 (23)
Mycological response			
Culture negative	35 (73)	19 (95)	7 (32)
4 wk[a]			
Total no. of patients	35	18	7
Clinical response			
Cure	27 (77)	11 (61)	4 (57)
Improvement	2 (6)	1 (6)	0 (0)
Failure	6 (17)	6 (33)	3 (43)
Mycological response			
Culture negative	31 (89)	15 (83)	4 (57)

[a] Based on patient being culture negative at 1 week.

similar for the two active treatment regimens but significantly different from that observed for the placebo group ($P < 0.05$). Negative cultures, on the basis of the patient being culture negative at 1 week, were observed for 31 (89%), 15 (83%), and 4 (57%) patients treated with itraconazole, clotrimazole, and placebo, respectively. Non-*C. albicans* species were isolated from only two women with positive cultures for *Candida* species.

Overall, clinical failures were observed for 8 (17%) of 48 patients who received itraconazole compared with 6 (30%) of 20 patients who received clotrimazole. The converse was observed for mycologic responses. Negative cultures were found in 31 (65%) of 48 patients in the itraconazole group compared with 15 (75%) of 20 patients in the clotrimazole group. A statistical analysis of these findings revealed no difference in overall clinical or mycological outcomes for these active treatment regimens, albeit the probability of making a type II error is large because of our small sample size ($\beta = 0.81$).

Medication-related side effects were reported by 17 (35%) patients who received itraconazole. These adverse experiences were usually minor and included nausea (seven patients), headache (six patients), dizziness (three patients), and bloating (three patients). One patient developed an increased level of transaminase enzyme (serum glutamic oxalacetic transaminase), which returned to normal within the following week. By comparison, only one (4%) patient in the clotrimazole group reported an untoward event. This patient complained of dyspareunia following therapy. Nine (41%) patients treated with placebo complained of adverse effects. Headache and nausea were reported most frequently. No patient enrolled in this investigation discontinued treatment because of an adverse event.

DISCUSSION

Over the past 2 decades, the imidazoles (miconazole, clotrimazole, ketoconazole, butoconazole, and tioconazole) have become the most widely used drugs for the treatment of vaginal candidiasis. With the exception of ketoconazole, these agents are used topically for treatment durations of 1 to 7 days with similar success rates (16). Local applications of these antifungal preparations are usually without untoward effects, but most patients still prefer oral therapy (17). Ketoconazole is an effective oral agent, but it has not been widely utilized for the treatment of candida vaginitis because of the higher risk of systemic toxicity.

A new class of azole antifungal agents, the triazoles, has recently been introduced into clinical practice. These drugs appear to offer both microbiological and clinical advantages over the imidazoles. Terconazole, the prototype agent, exhibits potent in vitro activity against *C. albicans* as well as other *Candida* species (28, 30). In addition, terconazole has also been shown to be more effective than imidazoles in the treatment of vaginal candidiasis in rats (30). In clinical trials, various topical preparations of terconazole achieve cure rates equal or superior to those with imidazole antifungal agents (31). The increased incidence of non-*C. albicans* species causing vaginal candidiasis may become an important impetus for the use of triazoles (9). However, data assessing the efficacy of terconazole versus imidazoles in women infected with non-*C. albicans* species are lacking.

The oral triazoles (fluconazole and itraconazole) may ultimately become the treatment of choice for women with vaginal candidiasis (18). Unlike terconazole, these systemically active triazoles have the capability to eliminate rectal carriage of *Candida* species, which may be an important determinant in the relapse or recurrence of vulvovaginal candidiasis (10, 15). In contrast to ketoconazole, these agents are highly effective following short courses of therapy and produce minimal side effects (6, 17, 19, 25). The oral triazoles do not appear to alter vaginal flora and may prove advantageous in the treatment of non-*C. albicans* species (3, 5). Furthermore, patient acceptance of this form of therapy has been highly favorable (1, 29).

Numerous studies comparing newer antifungal agents in the treatment of vulvovaginal candidiasis have been published. Mycological cure rates for the various azole derivatives range from 50 to 100% when assessed within 15 days of completion of treatment (16). The mycological cure rates observed in the present study were similar to those of other clinical trials of azole antifungal agents used in the treatment of vulvovaginal candidiasis and were comparable to those from a previous study that we conducted with this patient population (26). It was not surprising to discover that approximately one-third of our patients who received placebo capsules had cultures that were negative for *Candida* species 1 week following treatment. Similar findings have also been observed in clinical trials with placebo suppositories (31) and placebo oral capsules (23).

Virtually all of our patients treated with active medication showed significant improvements in their signs and symptoms. In contrast, almost one-quarter of the patients who received the placebo were initial clinical failures. Moreover, most of the patients who exhibited initial improvement with the placebo relapsed and required antifungal therapy. Our overall clinical failure rate with itraconazole was less than that observed with clotrimazole (17 versus 30%), but this difference did not reach statistical significance. It is important to note that because of our small sample size, the power ($1 - \beta$) of finding a statistical difference between active treatment regimens would be approximately 0.2. This suggests that a large type II error for detecting a difference between these two drugs exists.

Disparate findings in multicenter trials comparing fluconazole to topical antifungal therapy have been reported. In one study (19), the long-term clinical response rate (27 to 62 days after treatment) was found to be significantly greater following a single 150-mg dose of fluconazole than with clotrimazole ($P = 0.02$). In another trial (25), the clinical response rates 30 to 35 days posttreatment were similar following a 3-day treatment regimen of fluconazole or clotrimazole. Treatment with a single 150-mg dose of fluconazole resulted in a relapse rate 80 to 100 days after therapy similar to that of treatment with a 150-mg intravaginal tablet of econazole (17). Additional clinical trials with larger sample sizes would be of interest to help determine whether systemic therapy with these newer triazoles does indeed lead to fewer clinical relapses.

A course of treatment with an intravaginal preparation of an azole antifungal drug is usually without major adverse effects. Minor side effects, such as burning, irritation, itching, and dyspareunia, can occur with all topical agents (13). The frequency and severity of side effects depends on many factors, including dose, duration of therapy, and individual susceptibility (12, 26). In the present investigation, only one patient treated with clotrimazole reported an untoward effect. In contrast, over one-third of our patients who received itraconazole reported an adverse experience. More importantly, none of these side effects were severe and no patient discontinued therapy. Of note, a similar incidence and spectrum of adverse effects were reported by our patients

who received placebo capsules. We feel that this investigation further substantiates the relative safety of itraconazole for the treatment of vaginal candidiasis that has been observed in placebo-controlled (23) and open studies (2, 22).

In summary, itraconazole was found to be as effective as clotrimazole for the treatment of acute vulvovaginal candidiasis. Although more minor side effects were reported with itraconazole use, no patient discontinued therapy. Itraconazole therapy was highly favored over therapy with clotrimazole in our survey of patients. This finding has also been documented in a similar opinion survey (27). This suggests that this mode of therapy may help overcome the poor drug compliance observed in patients treated for vulvovaginal candidiasis (14).

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