

Single-dose Sertaconazole Vaginal Tablet Treatment of Vulvovaginal Candidiasis

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Background: Vulvovaginal candidiasis (VVC) is a bothersome disease in women. Poor compliance with the continuous use of antifungal vaginal drugs often results in treatment failure. The aim of the present study was to evaluate the efficacy, acceptability, and safety of single-dose sertaconazole vaginal tablet (500 mg) treatment compared with conventional 3-dose econazole vaginal tablet (150 mg) treatment for VVC.

Methods: In this open, randomized, and comparative study, 40 symptomatic patients with VVC confirmed by the smear method were enrolled. Patients in group A were treated with single-dose sertaconazole vaginal tablet and those in group B were treated continuously with econazole vaginal tablet for 3 days.

Results: The characteristics of the patients in both groups were comparable and without statistical difference. Group A showed a significantly better clearance rate for candidiasis than group B (100% vs. 72.2% on day 7, $p = 0.013$; 100% vs. 77.8% on day 14, $p = 0.030$), based on smear method results. Group A showed a more rapid response for symptom relief than group B on day 7, but there was no difference in overall symptom relief between group A and group B on day 14.

Conclusion: Single-dose sertaconazole proved to be a more convenient and symptom-relieving treatment for VVC. The advantages of such management are worthy of further study in women with relapse VVC. [*J Chin Med Assoc* 2006;69(6):259–263]

Key Words: econazole, sertaconazole, vulvovaginal candidiasis

Introduction

Vulvovaginal (VV) infection is the most frequent gynecologic diagnosis encountered by physicians who provide primary care to women.^{1–6} Many experts believe that more than 90% of VV infections are secondary to bacterial vaginosis, VV candidiasis (VVC), and trichomoniasis.⁶ Among the 3 major causes of VV infections, VVC is the most bothersome, especially in women of childbearing age. Approximately 75% of women experienced at least 1 episode of VVC during their lifetime, and more than half of the women in 1 study experienced a VVC relapse episode.⁷ The treatment of this disease by the great quantity of available drugs

with different recommended treatment duration is not satisfactory.^{8,9} For patients, the long therapeutic schedules can be cumbersome and often lead to bad compliance.^{8–10} The spectrum of activity of various agents becomes an important consideration when evaluating patients who have not responded to initial treatment despite full compliance with therapy. Sertaconazole is a new-generation benzothiazophenazole antifungal derivative, which is suitable for short-term treatment.^{11–13} It acts by inhibiting ergosterol biosynthesis and damaging the cell membrane directly; therefore, it has a powerful fungistatic and fungicidal action.^{12,13} It has been shown that sertaconazole elicits a considerable destructive effect on *Candida albicans* in

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vitro, with evident manifestation after 12 hours.¹⁴ The aim of the present study was to evaluate the efficacy, acceptability and safety of single-dose 500 mg sertaconazole vaginal tablets in women with VVC compared with conventional 3-dose 150 mg econazole vaginal tablets.

Methods

This trial was carried out in accordance with the Declaration of Helsinki (last revised version, Hong Kong 1989), as well as other local guidelines defining the protection of human beings and approved by the Human Ethics Committee of the hospital. This trial was designed as an open, randomized, and comparative study. A total of 40 symptomatic women were enrolled after obtaining their informed consent. All patients had to fulfill the following criteria, including (i) having been clinically diagnosed with VVC and confirmed by a positive microscopic examination; (ii) aged between 18 and 70 years; and (iii) agreeing not to have sexual relations throughout the study. Exclusion criteria included (i) pregnancy or lactating; (ii) suffering from vaginitis with a different etiology; (iii) hypersensitivity to imidazole products administered topically; (iv) previous systemic antifungal treatment within 4 weeks or previous topical antifungal treatment within 1 week; (v) non-controlled diabetes; (vi) consumption of antibiotics or immunosuppressors; (vii) serious chronic diseases; (viii) any other medical condition which the investigator considered sufficiently serious to interfere with the conduct of the study; and (ix) an inability to understand or adhere to the trial protocol. The randomization schedule was drawn up by the sponsor, and was stratified into 4 blocks in order to ensure a balanced distribution of treatment at any time.

The *C. albicans* clearance rate was detected by microscopic examination (smear test) on the second visit (day 7 after treatment) and the third visit (day 14 after treatment). The global evaluation of disease was recorded on day 7 and day 14. The definition in the global assessment were disease status compared with those at the baseline visit, (i) disease presence as the same number or an increased number of symptoms; (ii) initial healing phase as the disappearance of up to 25% of the number of symptoms; (iii) clinical symptomatology in regression as the disappearance of 26–50% of the number of symptoms; (iv) advanced healing phase as the disappearance of 51–75% of the number of symptoms; and (v) complete clinical healing as the disappearance of more than 75% of the number

of symptoms. Six major clinical symptoms, including erythema, maceration, plaque, pruritus, erosion, and foul odor according to a 5-grade scale at the vaginal level (0 for none, 1 for mild, 2 for moderate, 3 for severe, 4 for very severe) were assessed by an investigator in comparison with the results from the first visit (day 0) prior to treatment and the following 2 visits (day 7 and day 14 after treatment, respectively).

At the second and third visits, patients were asked about the acceptability of the drug treatment (0 for unsatisfactory result, 1 for acceptable, 2 for satisfactory, 3 for very satisfactory).

Safety and tolerability concerns included the incidence of all adverse events at the local level, their relationship to the trial drugs, and the abnormality of laboratory parameters. All patients were informed that participation was voluntary and they could withdraw from the study at any time without prejudice. The investigator was to withdraw a patient from the trial when: (i) the patient failed to comply with the treatment regimen; (ii) a severe adverse event occurred; or (iii) there was a major violation of the protocol.

Statistical analysis

Data are presented as mean \pm standard deviation (SD). The demographic information and patient characteristics were summarized for each treatment group and also compared between groups using the χ^2 test for categorical variables and analysis of variance (ANOVA) for quantitative variables. The results for all assessments were summarized for each treatment group at each visit. Fisher's exact test was used to compare the difference between the 2 treatment groups. Safety assessment was based on an adverse event analysis. The comparative incidence of adverse events between the 2 treatment groups was evaluated by Fisher's exact test. In addition, the evaluation of acceptability between the treatment groups was assessed by Fisher's exact test. A *p* value < 0.05 was considered statistically significant.

Results

Forty women were enrolled originally in the trial, and 37 completed the study. Patients in group A were treated with single-dose 500-mg sertaconazole vaginal tablet and patients in group B were treated continuously with 150-mg econazole vaginal tablet for 3 days. Two patients in group B were excluded due to therapeutic failure (*n* = 1) and being lost to follow-up (*n* = 1), and one patient in group A was excluded due to being lost to follow-up.

Patient characteristics

Patient age was 44 ± 10 years, ranging from 21 to 63 years. Body height was 159 ± 5 cm, ranging from 150 to 172 cm, and body weight was 57 ± 10 kg, ranging from 38 to 85 kg. The duration between the appearance of the symptoms or signs and the admittance consultation was 12.7 ± 8.2 days, ranging from 2 to 30 days. No significant statistical differences were observed between the groups.

Microscopic evaluation

The percentage of patients with negative smear test for *C. albicans* significantly increased ($p \leq 0.001$) with time after the treatment in both groups. The clearance rate of *C. albicans* was 100% in group A, compared with 72.2% in group B on day 7 after treatment ($p = 0.013$). The clearance rate was maintained at 100% in group A, but increased to 77.8% in group B on day 14 after treatment ($p = 0.03$).

Global evaluation

The global evaluation of the disease, 7 and 14 days after the initial treatment in group A and group B are summarized in Table 1. On day 7, nearly 95% of patients in group A but only 39% of patients in group

B had complete or advanced healing, which reached a statistically significant difference ($p = 0.004$). Although there was no difference in the overall global efficacy between the 2 groups, patients (89.5%) in group A showed statistical significance in their complete healing compared with those (55.6%) in group B. Patients (63.2%) in group A had significantly more improvement in erythema than those (33.3%) in group B on day 7. Other assessments of clinical symptoms, including maceration, plaque, pruritus, erosion, and fetid odor, also indicated a better response in group A (Table 2). Moreover, the symptom intensity also showed more rapid improvement for erythema in group A than in group B (data not shown). When evaluating the common clinical symptoms of the patients suffering from VVC, the results demonstrated that both treatment groups made significant improvement at the follow-up time points compared with baseline. When assessing the results by individual symptoms and by total symptoms, based on the sums of scores, no statistically significant differences were observed between the groups. One patient in group A paradoxically showed a symptom flare-up. The possible cause was not clear, but re-infection may have been the reason.

Table 1. Global efficacy in patients with vulvovaginal candidiasis treated with sertaconazole or econazole

Global evaluation	Day 7		Day 14	
	A n (%)	B n (%)	A n (%)	B n (%)
Number of patients	19 (100)	18 (100)	19 (100)	18 (100)
Persistence	0 (0)	4 (22.2)	0 (0)	2 (11.1)
Initial healing	0 (0)	4 (22.2)	0 (0)	1 (5.6)
Regression	1 (5.3)	3 (16.7)	0 (0)	0 (0)
Advanced healing	7 (36.8)	5 (27.8)	2 (10.5)	5 (27.8)
Complete healing	11 (57.9)	2 (11.1)	17 (89.5)	10 (55.6)
<i>p</i> *	0.004		0.108	

*Fisher's exact test.

Table 2. Percentage of clinical symptoms and signs in patients with vulvovaginal candidiasis treated with sertaconazole or econazole

	Group A			Group B		
	Day 0 n (%)	Day 7 n (%)	Day 14 n (%)	Day 0 n (%)	Day 7 n (%)	Day 14 n (%)
Number of patients	20 (100)	19 (100)	19 (100)	20 (100)	18 (100)	18 (100)
Erythema	20 (100)	7 (36.8)	2 (10.5)	20 (100)	12 (66.7)	5 (17.8)
Maceration	18 (90)	6 (31.6)	2 (10.5)	17 (85)	9 (50.0)	4 (22.2)
Plaque	20 (100)	8 (42.1)	2 (10.5)	18 (90)	11 (61.1)	8 (44.4)
Pruritus	19 (95)	6 (31.6)	2 (10.5)	19 (95)	11 (61.1)	4 (22.2)
Erosion	15 (75)	4 (21.1)	0 (0)	17 (85)	10 (55.6)	4 (22.2)
Fetid odor	17 (85)	2 (10.5)	2 (10.5)	18 (90)	9 (50.0)	5 (27.8)

Patients in group A had a significantly higher acceptability than those in group B ($p = 0.044$), although there was no difference on day 14 (data not shown). No adverse event occurred in either treatment group during the study.

Discussion

VVC is a common gynecologic disease, especially in women of childbearing age.¹⁵ Aged and menopausal women suffer less from VVC, except in those with immunocompromised status or with long-term use of steroids, antibiotics or, of most importance, estrogen. The most common cause of VVC is *C. albicans*, but a significant proportion of yeast vaginitis is produced by non-*albicans* *Candida*.¹⁵⁻¹⁸ Of the non-*albicans* species, the majority are *C. glabrata*.¹⁸ *C. albicans*, and the less common but morphologically similar yeast, *C. tropicalis*, are identical in appearance on a microscopic smear of vaginal secretions, showing typical hyphae, pseudohyphae, and budding yeast. Other non-*albicans* forms of *Candida* show budding yeast only.¹⁵ Yeasts can be identified in a significant proportion of normal, asymptomatic women. One study showed that VVC could be detected in 28.8% of asymptomatic women by the polymerase chain reaction technique and in 6.6% by culture,¹⁸ suggesting that the diagnosis of VVC is sometimes very difficult to confirm and many cases of VVC may be missed. Edwards¹⁵ commented that a diagnosis of VVC on the basis of sudden onset of itching or a patient self-report of yeast infection is sloppy but often correct. Only a patient with recurrent or recalcitrant symptoms deserves the absolute identification of the organism.¹⁵ Usually, this can be achieved on a microscope by an experienced examiner. However, when a patient is symptomatic with a negative smear, or does not respond completely to therapy with a positive smear, a vaginal culture should be performed.¹⁵ This study used very restrictive criteria to enroll the patients – all should have been clinically diagnosed with VVC and confirmed by a positive microscopic examination. Although it may omit many patients with VVC, the results obtained are more uniform and consistent.

More than 3-quarters of patients avoid long-term therapy, either orally or vaginally, in order to reduce the risk of adverse reactions. It is difficult to ensure patient compliance if the symptoms are not serious. In addition, topical antimycotic treatment with antifungal drugs is recommended as the therapy of choice in VVC since oral drugs need to be used with caution due to their potential adverse effects (gastrointestinal toxicities,

hepatotoxicity), some of which are rare but serious (angioedema, Stevens-Johnson syndrome), and their interactions with other drugs.¹⁵⁻¹⁹ Therefore, in this study, we explored 2 different topical antimycotic drugs (sertaconazole and econazole) to study their efficacy, acceptability and safety in women with VVC.

Sertaconazole is the first compound to bring a new chemical structure: benzothioephene 3,7-disubstituted, together with the already known azole matrix.¹¹ Its efficacy, tolerability, and safety have been widely demonstrated in previous preclinical and clinical studies.²⁰⁻²³ Sertaconazole has been shown to have a powerful antifungal activity both *in vitro* and *in vivo* on a broad spectrum of fungi, especially on dermatophytes (*Trichophyton*, *Microsporum*, *Epidermophyton*), pathogenic yeasts (mainly against *C. albicans* and *C. tropicalis*) as well as against *Aspergillus*, *Trichomonas vaginalis*, and *Scopulariopsis*.^{20,24} In previous research from a Spanish group²⁰ and a French group,²² single-dose sertaconazole was recommended as the preferred treatment. The present study also demonstrated that single-dose sertaconazole would provide more rapid results in both mycotic clearance and clinical symptom relief. This is the first study to evaluate its efficacy, acceptability and safety in Asian (Chinese) women with VVC.

In summary, although our study population was small, we still found that single-dose treatment with sertaconazole vaginal tablets provided significantly better global efficacy, more rapid symptom improvement, higher mycotic clearance rate, higher patient acceptability, and an equal and well-tolerated safety profile in women with VVC compared with the 3-dose treatment of econazole vaginal tablets. Single-dose sertaconazole vaginal treatment is the better choice in treating women with VVC because it ensures better compliance. Since no regimen has proved to be effective, safe, and convenient for the management of recurrent VVC,¹⁹ the ease of use, convenience, high acceptability, and high safety profile of single-dose sertaconazole make it a good preventive regimen for the management of recurrent VVC.

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