

Original article

Safety and efficacy of a new imidazole fungicide, *Sertaconazole*, in the treatment of fungal vulvo-vaginitis: a comparative study using *Fluconazole* and *Clotrimazole*

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Background: *Sertaconazole* is a new imidazole fungicide introduced for vulvo-vaginal candidiasis. It has an azole group with benzothiofene that inhibits biosynthesis of ergosterol and brings about a massive leak of cytoplasm with consequent fungal cell death.

Objective: Assess the safety and efficacy of *Sertaconazole* in the treatment of fungal vulvo-vaginitis for comparison with *Fluconazole* and *Clotrimazole*.

Subjects and methods: One-hundred eighty-eight outpatients with fungal vulvo-vaginitis were recruited at Siriraj Hospital, Thailand between August 31, 2004 and January 30, 2006. The patients were given *Sertaconazole*, *Fluconazole*, or *Clotrimazole*, and received vaginal swab and culture for fungus at seventh and 28th days after treatment.

Results: Out of 188 cases, 177 cases were followed-up completely. *Sertaconazole* group included 66 cases where 35 cure, 20 fail, and 7 recurrent cases. *Fluconazole* group included 60 cases and had 37 cure, six fail, and 20 recurrence cases. *Clotrimazole* group included 55 cases and had 32 cure, nine fail and 11 recurrent cases. There were risk factors of fungal vulvo-vaginitis, including frequent micturition and small toilet shower flushing.

Conclusion: *Sertaconazole* had similar effectiveness and less side-effect as compared with *Fluconazole* and *Clotrimazole*. It appeared to work well with lowest recurrence.

Keywords: *Clotrimazole*, efficacy, *Fluconazole*, fungal vulvo-vaginitis, recurrence, risk factors, *Sertaconazole*

Since *Clotrimazole* has been used in vulvo-vaginal candidiasis (VVC) for decades, fungal resistance against drugs seems to be increasing. It causes more difficulty in treatment, but also affects healthcare expenditure. The incidence of resistance in patients with candidiasis is still high [1, 2]. However, oral *Fluconazole* and *Clotrimazole* vaginal tablet have been used as the current standard treatments of VVC [3].

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Recently, a new imidazole fungicide has been introduced for VVC indication, named *Sertaconazole* [4, 5]. This is an azole group of antifungal with benzothiofene structure similar to tryptophan in fungal plasma membrane, which facilitates the incorporation of *Sertaconazole* into fungal cells. Inhibition of biosynthesis of ergosterol by inactivating 14- α -demethylase enzyme results in formation of pores, bringing about a massive leak of cytoplasm and adenosine triphosphate (ATP) with consequent cell death. *Sertaconazole* also exerts a direct toxic effect on the fungal membrane. With the properties of new structure of this imidazole derivative [6, 7], we may come to the solution for VVC treatment.

Many clinical researches have been conducted on VVC with antifungal agents for the past ten years. However, there are few studies on new antifungal agents. In this study, we made a comparative study of three drugs (*Sertaconazole*, *Fluconazole*, and *Clotrimazole*) in the treatment of VVC in Thailand. The efficacy, safety and tolerability of *Sertaconazole* were evaluated for comparison with *Fluconazole* and *Clotrimazole* in Thai patients.

Subjects and methods:

A computer-randomized comparative study was conducted in VVC patients between August 31, 2004 and January 30, 2006. This study was approved by the Ethics Committee of Faculty of Medicine, Siriraj Hospital.

One hundred and eighty eight patients with age range of 15-50 years were recruited from patients who were treated at Outpatient Gynecologic Department of Siriraj Hospital, Bangkok. We included: 1) patients who are clinically compatible with VVC infection, 2) cases who are confirmed by laboratory examination (direct and/or culture) for *Candida species*, 3) patients who consented to participate in the study and comply to follow-up and evaluation program, and 4) patients who agreed to discontinue any antifungal agents at least two weeks before enrollment. The following patients were excluded: 1) patients with history of hypersensitivity to azole drugs, 2) pregnancy, 3) patients who did not meet any of the inclusion criteria.

The subjects were computer-randomized in to three groups according to the medication as follows.

Group A (Fluconazole): Patients took oral *Fluconazole* 150 mg (50 mg x3) single dose [8],

Group B (Clotrimazole): Patients were trained to insert *Clotrimazole* 100 mg vaginal tablet once a day for six consecutive days at bedtime [9],

Group C (Sertaconazole): Patients were trained to insert single *Sertaconazole* 500 mg vaginal tablet at bedtime [5].

Procedures

Confirming that patients were clinically compatible with VVC using microscopic examination and/or culture, we requested them to give their written consent. Data were collected on the case report form. Then, pharmacist randomly dispensed medication with the recorded code. Clinical assessments were recorded at week 1 for efficacy

and safety. Mycological examinations were performed [10]. Repeated-assessment was performed at week 4 to evaluate for recurrence. Finally, patients were requested to fill-up the evaluation form at the end of follow-up period.

Mycological assessment and yeast identification

The specimens were collected from the patient's vagina by clinicians on site using sterile cotton swabs. Swabs were transferred in sterile normal saline tubes at room temperature. They were determined for yeast pathogens as follows [11].

Direct microscopic examination. Swab was directly examined under a microscope with wet preparation smear on glass slide. The morphological characteristics of budding yeast, pseudohyphae, and hyphae were recorded.

Yeast identification. Swabs were directly streaked on Candi Select® media (Sanofi Diagnostic, Pasteur, Marnes-La-Coquette, France) [12] that is a selective media to promote the growth of yeast and to inhibit bacterial contamination. After incubation at 37°C for 24-48 hours, *C. Albicans* was identified as blue colony appearance, as recommended by the manufacturer. White colony indicated non-*C. Albicans* species.

All those, identified presumptively as *C. Albicans*, were screened for *C. Dubliniensis* [13, 14] by cultivation on slant of *Saboraud Dextrose Agar* (SDA) and incubation at 45°C for 48 hours. The isolate that could not grow at this condition, was suspected to be *C. dubliniensis*. This was further confirmed by polymerase chain reaction (PCR). Yeasts that are negative in *C. Albicans* testing were identified to species level using urea hydrolysis carbohydrate assimilation and fermentation tests. The isolates were tested with each sugar, such as dextrose, maltose, sucrose, lactose, galactose, trehalose cellobiose, and soluble starch [15].

All culture positive isolates were tested at their minimum inhibition concentrations (MICs) and minimum fungicidal concentration (MFCs) [5].

The MIC testing was performed for *Sertaconazole*, *Fluconazole*, and *Itraconazole* [16], *Clotrimazole* and *Ketoconazole* by a broth microdilution method, according to the recommendations of The National Committee for Clinical Laboratory Standards (NCCLS). The testing medium was RPMI (Royal Park Memorial Institute, Thailand) media (pH 7.0).

The MIC was defined as the lowest concentration that reduces growth by 80% relative to that of the growth control. The 80% inhibition endpoint was estimated by diluting the drug-free growth control tube 1:5 with test medium. The MFCs of the drugs was tested by determination of growth ability of the isolates in MIC testing wells after subculture on SDA media, and incubated 37°C for 24-48 hours. The MFC was defined as the lowest concentration to show no yeast growth on the media [17]. This included

55 *Clotrimazole*, 66 *Sertaconazole*, and 67 *Fluconazole* cases.

Results

Out of 188 patients enrolled in the study, 177 patients had completed follow-up for four weeks, while 11 cases were lost to follow-up. For three groups of treatment (*Sertaconazole*, *Fluconazole*, and *Clotrimazole* groups), characteristics and follow-up of patients are summarized in **Table 1** and **2**, respectively.

Table 1. Patient's characteristics.

		<i>Fluconazole</i> (number)	<i>Clotrimazole</i> (number)	<i>Sertaconazole</i> (number)
Age (years)	<15	-	-	-
	15-19	2	1	5
	20-24	9	7	8
	>24	56	47	53
Marital status	Yes	58	44	53
	No	9	11	13
Occupation	Labour	28	22	27
	House wife	21	9	15
	Profession	5	4	7
	Trader	11	15	9
	Student	2	5	8
Income (Baht/month)	<5,000	25	24	23
	5,000-10,000	21	15	25
	>10,000	21	16	18
Sexual partner(s)	1	59	45	63
	2	1	7	3
	3	7	3	-
Sexual intercourse (times/week)	0-1	38	26	40
	2-3	23	24	21
	≥4	6	5	5
Contraception	No	16	24	19
	Tub sterilization	18	12	12
	Condom	12	7	8
	Oral Pill	20	13	27
	Implant	-	-	-
Education	Primary	21	20	25
	Secondary	22	14	19
	College	8	6	10
	Bachelor degree	16	15	12

Table 2. Patients' follow-up in each group.

	<i>Sertaconazole</i>	<i>Fluconazole</i>	<i>Clotrimazole</i>
Complete follow-up (177)	62	63	52
Loss to follow-up (11)	4	4	3
Total	66	67	55

The results of treatment by the three drugs (*Sertaconazole*, *Fluconazole*, and *Clotrimazole*) are shown in **Table 3**.

Sertaconazole had some difficulty in dissolution, which might increase the failure rate of medication. This problem could be solved by dipping the drug into clean water for five seconds before vaginal insertion. Then, we evaluated results of treatment for medications by *Sertaconazole* separately in two

cases with partially-undissolved and completely-dissolved drugs. **Table 4** shows results of treatment for medications by *Sertaconazole* in fraction, where no.1-66 and no.67-188 might include undissolved drugs and completely-dissolved drugs, respectively.

As risk factors of fungal vulvo-vaginitis, factors of frequent micturition, vulvar cleaning, and associated sexually transmitted diseases were summarized in **Table 5**.

Table 3. Results of treatment for each medication in the study.

	Cure number (%)	Fail number (%)	Recurrent number (%)	NA number (%)
<i>Sertaconazole</i> (66 cases)	35 (53.0)	20 (30.3)	7 (10.6)	4 (6.1)
<i>Fluconazole</i> (67 cases)	37 (55.2)	6 (9.0)	20 (29.9)	4 (6.0)
<i>Clotrimazole</i> (55 cases)	32 (58.2)	9 (16.4)	11 (20.0)	3 (5.5)

NA: not available

Table 4. Results of treatment in fraction for *Sertaconazole*.

	Cure Number (%)	Fail Number (%)	Recurrent Number (%)	NA Number (%)
<i>Sertaconazole</i> (total, 66 cases)	35 (53.0)	20 (30.3)	7 (10.6)	4 (6.1)
<i>Sertaconazole</i> (no.1-66, 13 cases)	4 (30.8)	7 (53.9)	1 (7.7)	1 (7.7)
<i>Sertaconazole</i> (no.67-188, 53 cases)	31 (58.5)	13 (24.5)	6 (11.3)	3 (5.7)

NA: not available.

Table 5. Risk factors of fungal vulvo-vaginitis.

		<i>Fluconazole</i> (number)	<i>Clotrimazole</i> (number)	<i>Sertaconazole</i> (number)
Frequent micturition (5+/day)	Yes	21	21	20
	No	40	39	47
Vulvar cleansing	Toilet shower	Sometimes 11	14	14
		Everytimes 17	26	16
	Simple water use	Sometimes 20	9	24
		Everytimes 9	9	6
ASTD	Others	3	6	4
	Yes	9	12	14
	No	58	43	52

ASTD: Associated sexually transmitted diseases.

Discussion

The objectives of the present study were to evaluate the antifungal efficacy [18], recurrent rate and safety and tolerability of three drugs (*Clotrimazole*, *Fluconazole*, and *Sertaconazole*). In the present analysis based on of 188 subjects, these drugs had similar effectiveness in treatment of vulvo-vaginal candidiasis. The rate of cure (or effectiveness) fell in the range of approximately 55%, as shown in **Table 3**. However, *Sertaconazole* had some difficulty in dissolution, which could be easily expelled from the patients' vagina. When those subjects with undissolved drugs were excluded, the effectiveness of *Sertaconazole* was increased up to 58.5% from 53.0%, as shown in **Table 4**. This suggests that *Sertaconazole* might be the most effective medication among the three drugs.

In relation to the recurrent rate, *Fluconazole* had the highest rate of relapse of 29.9%, and *Clotrimazole* had consecutively high relapse rate of 20%. On the other hand, *Sertaconazole* had the lowest relapse rate of only 10.6% (**Table 3**). *Fluconazole* has been used in oral form [19]. It also been used commonly among AIDS patients with fungal opportunistic infection. *Clotrimazole* is used as a long-term clinical antifungal agent [20].

In relation to the safety, the present results showed minimal side-effect without adverse event. In clinical practice, *Fluconazole* has advantage due to oral form, and can be used more easily, compared to *Sertaconazole* (500 mg) and *Clotrimazole* (100 mg) in vaginal form [21]. Antifungal vaginal tablet is still favorably used because of the belief that vaginal disease should be treated by vaginal medication. Some Thai females trust the six-day regimen [21] of vaginal tablets more than one-day regimen, although several studies show equal antifungal efficacy between the two regimens. The one-day regimen (500 mg *Sertaconazole* vaginal tablet) [22] seemed to be less popular than the previous six-day regimen (100 mg *Clotrimazole* vaginal tablet).

The duration of infection was 7-14 days in most patients. The number of patients with previously-experienced fungal vulvo-vaginitis is the same with those who had it for the first time. As shown in **Table 1**, most patients never have antibiotics or corticosteroid prior to the infection, and only one-third have oral contraception. In our study, only few patients had history of diabetes mellitus and several cases of low immunity, one case of immune disease, and seven

cases of HIV-infection. In addition, more than one-third of our patients wore tight thick clothing, especially jean trousers or pants (see **Table 5**). Vulvar cleansing after urination by toilet shower or simple water-use increased significantly in Thailand. A small number of patients use antiseptic solution or vaginal douching for vulvar cleansing. To analyze recurrent and not-recurrent fungal infection, we selected data on clothing, toilet vulvar cleansing, and frequent micturition from our patients who came back for four-week follow-up. In the present analysis based on 188 subjects, 65 (34.6%) wear tight and thick clothing, especially jean trouser or pant and 123 (65.4%) wear simple clothing. Forty cases use the toilet shower to clean vulva every time after urination while 53 uses it only some of the time. Thus, the calculated rate of toilet shower use is 90 cases (47.9%). Twenty-eight cases use simple water to clean vulva every time after urination while 42 uses it only some of the time. Thus, 37.2% of the patients used simple water. The other 14.9% of the patients may use toilet tissue paper instead of vulvar cleansing. These data might reflect the fact that vulvar moisture would occur due to such uses of either toilet shower or simple water use in toilet.

Fungal vulvo-vaginitis could be transmitted by sexual intercourse. Generally, fungal vulvo-vaginitis is found after treatment of trichomoniasis because of the change of vaginal pH after such treatment. However, most STD might occur separately.

In some immuno-compromised patients [23] such as cases of HIV-positive and lymphoma on chemotherapy, no recurrent case was observed in the study.

In conclusion, *Sertaconazole* had similar effectiveness and less side-effect with *Fluconazole* and *Clotrimazole*. It appeared to work well with lowest recurrence.

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