

Treatment of recurrent vulvo-vaginal candidiasis with sustained-release butoconazole pessary

Ling Zhi Heng¹, MBBS, Yujia Chen¹, MBBS, Thiam Chye Tan^{1,2}, MBBS, MMed

ABSTRACT Vulvo-vaginal candidiasis (VVC) is a common infection among women. 5% of women with acute infection experience recurrent vulvo-vaginal candidiasis (RVVC). There is currently no optimal or recommended regime for RVVC. Although antifungal agents, such as imidazoles, have been successfully used as a first-line treatment for acute VVC, its effectiveness is limited in RVVC. This could be due to patient factors, drug application (such as leakage) or dosing factors. A sustained-release (SR) bioadhesive vaginal cream (2% butoconazole nitrate) has incorporated VagiSite technology, a topical drug delivery system that allows SR of the drug. We describe its efficacy and the successful use of a butoconazole-SR formulation in the treatment of two cases of RVVC.

Keywords: butoconazole, candidiasis, recurrent vulvo-vaginal
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INTRODUCTION

Candidiasis is a common cause of infective vaginal discharge experienced by women. 75% of women experience at least one episode of vaginitis during their lifetime. Recurrent vulvo-vaginal candidiasis (RVVC) is defined as four or more episodes of symptomatic vulvo-vaginal candidiasis (VVC) in one year. Up to 5% of women of childbearing age have experienced RVVC.⁽¹⁾ Common symptoms include vaginal discharge, vulvar pruritus, dyspareunia and dysuria. On genital examination, the labia and vulva are often swollen, erythematous, with skin fissures commonly associated with it, and often accompanied by a thick, white-coloured vaginal discharge. The pathogenesis of RVVC is multifactorial and the causes may be idiopathic or secondary to a variety of host or microbial factors (Table I).

The *Candida* species may be part of the normal commensal flora in asymptomatic healthy women and often do not result in any long-term sequelae unless there has been a change in the host environment. The *Candida* (*C.*) *albicans* spp. has been known to be the main causative organism of RVVC, accounting for 80%–85% of cases. The remaining cases are due to non-*albicans* species, with *C. glabrata* being the most common. Its frequency has nearly doubled over the last ten years, and it has been shown to account for 5%–15% of RVVC.^(2,3) Other non-*albicans* species also include *C. tropicalis* (< 5%) and *C. krusei* (~ 1%).⁽⁴⁾

There is currently no gold standard for the treatment of RVVC. However, gynaecological experts have concurred that the recommended treatment should include the induction of clinical remission per acute episode, followed by a period of up to six months of maintenance therapy.⁽⁵⁾ This view is supported by a randomised controlled trial conducted by Sobel et al, which proved that maintenance therapy with weekly fluconazole for six months after clinical remission was superior in the reduction

Table I. Risk factors for recurrent vulvo-vaginal candidiasis.

Risk factors	Examples
Microbial	<ul style="list-style-type: none"> • <i>Candida albicans</i> species • Non-<i>albicans Candida</i> species
Host	<ul style="list-style-type: none"> • Uncontrolled diabetes mellitus • Oestrogen excess – oral contraceptive pills, hormone replacement therapy, local oestrogen administration, pregnancy • Antibiotic-induced • Immunosuppression – SLE, HIV, long-term steroid use • Behavioural – receptive orogenital sex

SLE: systemic lupus erythematosus; HIV: human immunodeficiency virus

of clinical recurrence.⁽⁵⁾ The Ministry of Health, Singapore, has recommended induction and maintenance regimens for RVVC.⁽⁶⁾ The recommended induction regimens for RVVC are: (a) fluconazole 150 mg every 72 hours, three doses; and (b) topical imidazole therapy for 7–14 days, according to symptomatic response. The recommended maintenance regimens for RVVC are: (a) oral fluconazole 150 mg once weekly over a period of six months; and (b) clotrimazole 500 mg vaginal suppositories once weekly over a period of six months. 90% of patients are protected from symptomatic recurrence using this maintenance regimen.⁽⁷⁻⁹⁾ However, recurrence of VVC occurs in 30%–40% of women after cessation of the six-month regimens.^(1,5) Relapses are mostly due to the same strain of *Candida* that had caused the original episode of vaginitis, although it may occasionally be due to new strains of *C. albicans* or an entirely new species, which would suggest reinfection instead of a relapse.⁽⁵⁾

Butoconazole 2% sustained-release (SR) has been shown to demonstrate efficacy, compared to other RVVC treatments. As mentioned, there is currently no optimal antifungal regime for RVVC. We thus report the successful empirical use of butoconazole in the treatment of RVVC in two cases.

¹Department of Obstetrics and Gynaecology, KK Women's and Children's Hospital, ²Duke-NUS Graduate Medical School, Singapore

Correspondence: Dr Tan Thiam Chye, Consultant Obstetrician & Gynaecologist, Department of Obstetrics and Gynaecology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899. drtctan@me.com

CASE REPORTS

Case 1

A 31-year-old sexually active Chinese woman presented to our centre with symptoms of vulvar itching and vaginal discharge, which she had been experiencing for two years. She self-medicated with over-the-counter antifungal pessaries. However, there was no resolution of the symptoms. She had almost monthly recurrences of vaginal discharge and itch for the past two years. Clinical examination showed erythema of the vulva and vagina with the classical 'cheesy' vaginal discharge of VVC. We performed a vaginal swab of the lateral vaginal walls, which grew *C. albicans* spp. The patient was treated with butoconazole-SR pessary 2% (5 g) intravaginally twice a week for two weeks and followed up weekly for another three weeks. At the patient's three- and six-month follow-ups, she was asymptomatic and the vaginal swab was negative for *Candida*.

Case 2

A 52-year-old perimenopausal Chinese woman with a history of recurrent VVC in the past year had been treated with topical antimycotic azole agents by various doctors. She presented with another episode of vaginal itching and discharge. On examination, she had vaginal erythema and a whitish vaginal discharge typical of candidiasis. The vaginal swab was positive for *C. albicans* spp. She was first started on weekly butoconazole-SR pessary 2% (5 g) for two weeks, followed by maintenance treatment of weekly dose for the next three weeks. The patient's symptoms resolved and she remained asymptomatic for the next six months.

DISCUSSION

C. albicans causes the majority of VVC. Studies have shown that these strains are highly susceptible to all available topical azoles.⁽⁷⁾ However, while long-term maintenance azole treatment is effective in preventing the exacerbation of symptomatic disease, it still fails to eliminate low numbers of putatively sensitive *C. albicans* because of the fungistatic nature of azoles. Hence, the reservoir of subsequent recurrence could be due to the vaginal persistence of these small numbers of *C. albicans*.

The fact that *Candida* persists in only a small number of women suggests that either the vaginal environment is favourable for its persistence or *Candida* has unique microbial characteristics that allow for adaptation even in the presence of azoles.⁽¹⁰⁾ In the last decade, a rising incidence of other non-*albicans* species such as *C. glabrata* and *C. krusei* has been noted. This is an important clinical problem, as these *Candida* spp. are associated with a 10–30-fold reduced sensitivity to fluconazole, as well as lower susceptibility to other oral azoles (e.g. ketoconazole, itraconazole).⁽⁸⁾ Eradication of *C. glabrata* and *C. krusei* is often difficult, although one study has shown it can be accomplished with adequate treatment using butoconazole, clotrimazole or miconazole. This study also demonstrated that butoconazole was superior to miconazole and clotrimazole, with a low minimal inhibitory concentration of 90 at 24 and 48 hours against all species (0.01,

0.01).⁽⁷⁾ With the rise in resistant strains, there is a high rate of recurrences after using the present recommended remission induction treatment regimens with topical clotrimazole, or with imidazole and oral fluconazole.^(1,5) Butoconazole has long been recognised as a treatment for acute and complicated vaginitis. It is fungicidal and presumed to function like other imidazole derivatives via the inhibition of steroid synthesis. It also inhibits the conversion of lanosterol to ergosterol, which results in a change in the lipid composition of the fungal cell membrane. This structural change alters cell permeability and ultimately results in either the osmotic disruption or growth inhibition of fungal cells. The difference between butoconazole and other imidazoles is that the latter play a major role in topical treatment and are therefore developed first for dermatologic use, which are then subsequently applied to VVC. In contrast, butoconazole is a rare exception because it is specifically developed for the treatment of VVC.⁽¹¹⁾

Brown et al⁽¹²⁾ and Seidman et al⁽¹³⁾ have demonstrated the efficacy of butoconazole treatment for VVC in clinical trials, proving that a single dose of SR butoconazole is effective and safe.⁽¹³⁾ Two well-controlled clinical trials have also shown the efficacy of butoconazole when a three-day regimen was adopted. This regimen is comparable to conventional therapies that are longer in term (i.e. seven-day miconazole or fluconazole) and resulted in faster relief of symptoms.^(12,13) Although imidazoles are generally known to be effective first-line treatments of VVC, various factors, such as patients' compliance, ease of use and the side-effect profile, have prevented successful therapy in as many as 50% of women. In order to eradicate such factors, extensive research has been done to develop an easy-to-use imidazole formulation that improves treatment compliance and provides an effective, rapid relief of symptoms. This has resulted in the development of a single-dose, bioadhesive butoconazole nitrate 2% site release vaginal cream available in a prefilled single-use applicator (Gynazole-1).⁽¹³⁾ This formulation utilises VagiSite, a unique and proprietary topical drug delivery system that acts as a delivery platform for the topical drug to be administered in the vaginal cavity.

VagiSite has been designed to contain a high internal phase ratio water-in-oil emulsion system. This enables the drug-containing emulsion to act as a bioadhesive film on the mucosal surfaces of the vagina, allowing sustained and controlled delivery of the topical drug for as long as seven days. In this way, the active drug is able to remain in constant contact with the vaginal mucosal tissue, thus enabling continuous treatment of the infection with a single-dose regimen.⁽¹⁴⁾ With such a bioadhesive nature, this also means that leakage is minimal as compared to conventional creams. The patient can also administer the medication at any time of the day without having to be in a supine position for drug application. With conventional creams, nighttime application is vital, as the supine position will help to keep the cream intact within the vaginal cavity. Thus, using the SR formulation will undoubtedly help to improve treatment compliance, as it is less messy and more convenient for patients, resulting in minimal

interruption to their daily routine. Weinstein et al, who analysed the average length of time the butoconazole nitrate 2% SR vaginal cream remained intact within the vaginal cavity, found that the median vaginal retention time of the SR delivery system was 4.2 days, compared to 2.57 days for the conventional butoconazole preparation.⁽¹⁴⁾ Besides its SR properties, it also provides significantly faster relief of severe symptoms on the first post-treatment day.^(12,13)

The combination of bioadhesive and SR properties in butoconazole nitrate 2% site release vaginal cream has enabled the drug to be given in a very low dose, resulting in minimal adverse drug-related effects. Systemic absorption has been shown to be very low (1.7% of a single 100 mg dose) compared to the conventional vaginal cream (5.5%).⁽¹⁴⁾ As it is a topical vaginal cream, systemic effects are fewer compared to oral tablets. So far, no known drug interactions have been reported. Clinical trials have also shown that the butoconazole nitrate 2% SR formulation was well tolerated by 314 patients in one study. 18 (5.7%) patients complained of vulvar/vaginal burning, itching, soreness, swelling, pelvic/abdominal pain or cramping, or a combination of two or more of these symptoms. However, only three (1%) patients considered these complaints to be treatment-related. Two other clinical trials in the United States have also proved that adverse effects of butoconazole are infrequent and mild.⁽¹¹⁾

With oral imidazoles, the main adverse effects are commonly associated with gastrointestinal symptoms such as abdominal pain and headache.⁽¹⁵⁾ They have also been associated with the possible development of resistance, as well as systemic adverse effects affecting the liver and kidney.⁽¹¹⁾ With oral medications, there is also a risk of drug interactions if the patient is taking other medications concomitantly. Therefore, when compared to oral azoles, butoconazole has a much better safety profile.⁽¹¹⁾ Furthermore the rates of recurrence of the numerous current regimens are very high, at 30%–40%.⁽¹⁾

Although the use of butoconazole in acute VVC, compared to other forms of treatment, has long been accepted as superior against all species of *Candida*, its use in RVVC still remains novel. In this report, its use in young, sexually active and perimenopausal women has been successfully demonstrated clinically, as well as mycologically. With the single-dose regimen being highly efficacious with a low side-effect profile, this could well be a novel regimen for the treatment of RVVC. The half-life of butoconazole-SR gel is approximately 4.2 days. Thus, we suggest an induction period of twice weekly for the first two weeks, followed by maintenance treatment of once a week for three to four weeks. In comparison to the six-month regimen, this six-week regimen may encourage greater patient compliance. However, we recommend a larger-scale randomised controlled study to

evaluate the efficacy and side effects of the use of butoconazole in the treatment of RVVC.

In conclusion, RVVC is a highly troublesome and emotionally traumatic condition for women. There is currently no optimal treatment for RVVC. Intravaginal butoconazole 2% SR gel twice weekly for two weeks, followed by weekly maintenance for three to four weeks, was used in the two abovementioned cases with good clinical and mycological cure within six months. Good therapeutic consideration and convenience favour the use of this drug compared to other azole pessaries and oral treatments. However, randomised trials are required to further compare and demonstrate the superiority of butoconazole to other azoles in order to determine its long-term efficacy.

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