Combined topical flucytosine and amphotericin B for refractory vaginal Candida glabrata infections

D J White, A R Habib, A Vanthuyne, S Langford, M Symonds

Patients with vaginitis due to highly azole resistant Candida glabrata can be particularly difficult to treat. We describe three cases of longstanding vaginal candidiasis due to C glabrata. These had failed to respond to local and systemic antifungals. Flucytosine (1 g) and amphotericin B (100 mg) formulated in lubricating jelly base in a total 8 g delivered dose, was used per vagina once daily for 14 days with significant improvement, both clinically and microbiologically. (Sex Transm Inf 2001;77:212–213)

Keywords: amphotericin; flucytosine; Candida glabrata

Introduction

Candida glabrata is the second most common yeast recovered from the genital tract of women with vaginitis and accounts for about 5% of vaginal infections. A substantial minority of C glabrata isolates are azole resistant and further resistance may be selected out by non-curative treatment. Although infections with this organism are not always associated with symptoms and clinical signs some affected women have discharge and/or vulvitis and a poor response to antifungal therapy.

We describe three cases of persistent vaginal candidiasis due to C glabrata, unresponsive to conventional antifungal therapy including boric acid. Flucytosine tablets 500 mg (Center Specialites Pharmaceutiques Cournon Cedex, France) and amphotericin B BP1998 1 mg = 859IU (Bufa BV Uitgeest Holland) were combined in lubricating jelly, Aqualogel (Adams Healthcare, UK). This was used per vagina with clinical and microbiological cure. Treatment was delivered by a unit dose vaginal applicator containing amphotericin 100 mg + flucytosine 1 g based in Aqualogel in a total 8 g delivered dose. This preparation has an unknown shelf life and is obtainable from the pharmacy manufacturing unit, North Staffordshire Hospital, Stoke on Trent ST4 6QG, UK. It was prepared at the pharmacy using an accuracy control system and was thoroughly mixed before packing. Each person was given one applicator containing 8 g jelly for 14 days.

Table 1: Antifungal sensitivities (NCCLS method Bristol PHLS mycology reference laboratory) before treatment with topical flucytosine/amphotericin B in lubricating gel

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<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tr>
<td>Amphotericin B</td>
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<td>Flucytosine</td>
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<td>Fluconazole</td>
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<td>Nystatin</td>
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S = sensitive, R = resistant.

Case 1

A 42 year old woman presented with “recurrent vaginal thrush” since the age of 19. At referral she had had several recent swabs showing heavy growths of candida species in Gram stain microscopy despite 3 months’ treatment with itraconazole 100 mg twice daily for 2 days every week, two Depo-provera (Pharmacia & Upjohn) injections, and a number of other unspecified antifungal treatments including courses of nystatin pessaries. None of these produced any symptomatic response.

Vaginal swabs were positive by Gram stain. A 42 year old woman was treated with itraconazole 100 mg daily combined with clotrimazole 500 mg vaginal pessaries for 7 nights, intravaginal painting with gentian violet 0.5% aqueous solution for 3 days, and boric acid 600 mg in gelatine capsules once daily for 14 nights.

Intravaginal amphotericin B and flucytosine in lubricating jelly was given at night for 14 days. Her symptoms improved and Gram stain and cultures were negative 2 and 5 weeks following treatment.
months later she presented with a 4 week history of discharge. Microscopy of a Gram stained slide was positive for spores and a non-
albicans yeast (not further speciated) was isolated in culture. She responded symptomati-
cally and microbologically to nystatin pessa-
ries at night for 14 nights.

**Case 3**

A 42 year old woman presented with intracta-
ble symptoms of “vaginal thrush” which had started since a hysterectomy 1 year earlier, fol-
lowing which she had started unopposed oestrogen hormone replacement therapy.

Microscopy of a Gram stained vaginal slide showed spores and C glabrata was isolated from those which persisted despite dydrogesterone 10 mg daily for 28 days combined with nystatin pessaries and oral itraconazole 400 mg daily for 7 days, and vaginal boric acid 600 mg daily for 14 days.

Intravaginal amphotericin B and flucytosine in lubricating jelly was given at night for 14 days. Her symptoms improved and microscopy and cultures were negative 2 and 5 weeks following this treatment.

**Discussion**

By comparison with C albicans, C glabrata is intrinsically less sensitive toazole antifungals and, because this organism is haploid (unlike C albicans which is diploid) selection of drugs resistant strains may occur. Persistent vaginal C glabrata is more likely to be found in patients who are clinically not or partially responsive toazole antifungals, older patients, diabetics, and women who have had hysterectomies. Symptoms are, however, not a reliable guide to the causative organism. It is therefore important to speciate isolates from patients presenting with problem vaginal candidosis. Because of the relatively small numbers of patients presenting with this condition, treatment of persistent C glabrata vaginitis is not evidence based but remains largely anecdotal. Most clinicians would start treatment with intravaginal nystatin (the only licensed alternative to azoles in the United Kingdom) and then proceed to either high dose oral itraconazole together with high dose intravaginal azole pessaries or nystatin. Following this with intravaginal boric acid 600 mg at night for 14 days. If this fails however there has previously been no further treatment available. Intravaginal amphotericin/ flucytosine offers a possible treatment for such patients.

Topical flucytosine has been used for vaginal infections caused by both C albicans and anti-
fungal resistant non-albicans candidiasis but a suitable formulation has not been available in the United Kingdom. Although it is the only available fungicidal agent, there are reservations about its topical use because of the potential development of flucytosine resis-
tance, which occurs by mutation of a single gene. The risk of such resistance developing is thought to be reduced by combination with polynucleosides such as amphotericin B with which flucytosine is synergistic in vitro.

Our three cases demonstrate that flucytosine and amphotericin in lubricating jelly may be effective in chronic vaginal C glabrata infection where all other available agents have failed. This treatment was well tolerated in all patients with no or minimal side effects.

We would like to thank Professor Frank Odds for his initial advice and Dr Elizabeth Johnson for help with the results of the antifungal sensitivity tests. Choices: DJW, ARH, and AV collected the patients and wrote the paper. DJW had the idea of using flucytosine and amphotericin intravaginally; MS and SL developed the formul-
ation of amphotericin and flucytosine in lubricating jelly.

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