

Comparison of vaginal flora after treatment with a clotrimazole 500 mg vaginal pessary or a fluconazole 150 mg capsule for vaginal candidosis

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Abstract

The effect of antifungal therapy on the vaginal microbial flora was studied in 23 patients suffering from culture-positive, symptomatic vaginal candidosis. They were randomly allocated to receive either a 500 mg clotrimazole vaginal pessary or a 150 mg fluconazole capsule. Quantitative microbiological examination was carried out on samples of vaginal secretions obtained prior, and at intervals up to 10 days after, treatment. No significant difference was found in the vaginal flora before or after therapy in individual patients or between the treatment groups. In patients with *C glabrata* or *C krusei*, the yeasts persisted longer in the vagina with poorer response to either of the medications.

Introduction

The traditional therapy for symptomatic vaginal candidosis, an antifungal vaginal preparation, is both effective and has minimal toxicity. However, many patients and in particular those suffering from recurrent candidosis find this method of treatment inconvenient. Oral fluconazole, a water soluble bis-triazole, has been shown to be at least as effective as topical clotrimazole in the treatment of acute vaginal candidosis.¹ Fluconazole concentrations in the vagina were greater than the MICs for most strains of *Candida albicans* for at least 3 days.² Its effects on the other vaginal microbes have, so far, not been investigated. We report here on our findings of the vaginal flora in patients before and at different time intervals after treatment of culture-positive symptomatic vaginal candidosis by either topical clotrimazole or oral fluconazole.

Patients and methods

The study was carried out in the Genitourinary Medicine Clinic, at St Stephen's Hospital, London. Patients with culture-positive and symptomatic vaginal candidosis gave written, informed consent to partake in the study. Patients were excluded if they were pregnant, lactating, menstruating, had underlying disease or any other urogenital infection during the study period. They were also excluded if there was a history of antifungal or antibacterial therapy in the preceding ten days or a history of allergy to imidazoles or triazoles. The participants agreed to observe sexual abstinence during the study.

All patients underwent a medical and genitourinary examination. Blood samples were obtained for haematological and biochemical tests and syphilis serology. Genital specimens were obtained for the diagnosis of sexually transmitted diseases: cervical and urethral gonorrhoea, chlamydial cervicitis, vaginal candidosis and *Trichomonas vaginalis* infection. Urine samples were obtained for urinalysis and a pregnancy test.

According to a predetermined code of randomisation, patients enrolled in the study received either a vaginal pessary of clotrimazole 500 mg or an oral capsule of fluconazole 150 mg under nursing supervision in the clinic. Before treatment and on the 2nd, 4th, 6th and 10th day after treatment, a sample of vaginal secretion was obtained under direct vision from the posterior fornix by the use of swabs which had previously been weighed and stored in a CO₂ container. A second swab was taken into the transport medium for the isolation of *Mycoplasma hominis* and *Ureaplasma urealyticum*.

The weighed swabs were processed in the microbiology department within 30-60 minutes of collection. After reweighing to determine the weight of secretions obtained, the swab was broken off into a small sterile plastic bottle containing 1 ml prerduced supplemented brain-heart infusion broth (PRSBHI). The specimen was then rigorously mixed with the vortex apparatus for approximately 15 minutes. Quantitative culture was carried out after serial dilutions with PRSBHI on a range of cultural plates. For the isolation of aerobes, plates containing Columbia blood agar (Oxoid, UK), MacConkey agar

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(Oxoid), and Sabouraud dextrose agar with chloramphenicol were aerobically incubated for 24 to 48 hours. For the isolation of microaerophilic organisms, plates containing vancomycin chocolate agar (Difco, USA), Mitis-Salivarius agar (Difco), Gardnerella-selective agar (Oxoid) and brain-heart infusion blood agar (Oxoid) were incubated for 48 to 72 hours in an atmosphere with an additional 5–7% of CO₂. For the isolation of anaerobes, Bifidobacterium agar (Difco) plates and two types of brain heart infusion agar plates containing 10 µg/ml nalidixic acid and 0.02% Tween 80 (ICI America, Wilmington, DE), or 100 µg/ml kanamycin and 7.5 µg/ml vancomycin were incubated for 5 days in 85% N₂, 5% CO and 10% H₂. At the end of the incubation period, all plates were examined. The total viable counts (cfu/g) were calculated accordingly. Bacterial isolates were identified by routine bacteriological procedures and biochemical test kits, such as API 20E, API50CH and MicroScan (Micro Scan, USA). For mycoplasmas, the method described by Taylor-Robinson and Furr was used for initial titrated isolation in urea-containing and arginine-containing media. Ureaplasma was identified by subcultures onto Shepard's manganese-urea agar. Presumptive identification of *M hominis* was made by subcultures onto mycoplasma growth agar (Oxoid).³

Results

Twenty three patients with culture-positive and symptomatic vaginal candidosis were enrolled. The result of one patient was excluded as no follow-up sample was available. Of the 22 patients studied, 11 received a single dose of topical clotrimazole, and 11 a fluconazole capsule.

The average weight of secretion examined was 0.02 g, with a range of 0.012 to 0.032 g. The identification and concentration of the yeasts isolated during the study are shown in the fig. The yeast count varied from 10 to 10⁹ cfu/g of secretions in the pretreatment samples. *C glabrata* was isolated in three patients, two in the fluconazole group and one in the clotrimazole group; *C krusei* was isolated from one patient in each group. Of the 18 patients from whom *C albicans* was isolated before treatment, 17 patients had a negative culture by the 9th to 12th day after treatment.

At the end of the study, with the exception of one patient with *C glabrata* and one with *C krusei*, all patients reported improvement or cure of symptoms. One patient in the fluconazole group remained positive for *C albicans* and another patient positive for *C glabrata* although both were asymptomatic.

The vaginal flora isolated at each visit is listed in the table. No significant difference was found in the vaginal flora quantitatively or qualitatively before or after either antifungal regimen for individual patients or between the two treatment groups.

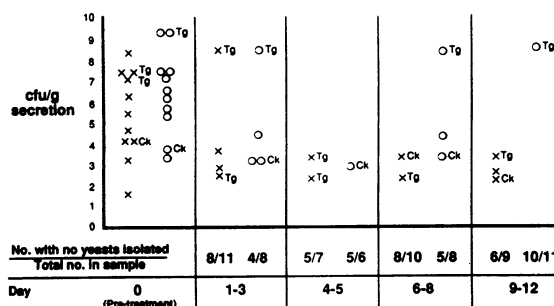


Figure Concentration (cfu/g secretion) of *C albicans* and other yeasts isolated at different time intervals after treatment. Key to fig: T, *C glabrata*; CK, *C krusei*; O, clotrimazole group; X, fluconazole group.

Discussion

It is interesting to note that there was a wide variation in the yeast counts in the vaginal secretion, although all patients were presenting with symptomatic infections. The yeast concentrations in four of the 22 patients studied were < 10⁴ cfu/g before treatment. Such low concentration of yeasts may not be reliably detected by a cursory swabbing technique. This highlights the importance of always making sure that an adequate amount of secretion is routinely sampled for the diagnosis of vaginal candidosis. Odds, *et al*, however, observed that unequivocal clinical evidence of candidosis was strongly associated with high concentrations of vaginal yeasts.⁴ They suggested that isolation of fewer than 10 yeast colonies from a vaginal swab was unlikely to indicate an infection requiring treatment.

The results of our study confirm those of previous studies demonstrating the efficacy of a fluconazole 150 mg tablet in the treatment of culture positive, symptomatic vaginal candidosis attributed to *C albicans*.^{1,2} The antifungal activity of fluconazole is due to the inhibition of ergosterol biosynthesis, an essential sterol found in the membranes of yeasts and other fungi. Fluconazole inhibits the activation of cytochrome P-450-dependent enzymes and like other azoles, has a high affinity for cytochrome P-450-dependent enzymes. However, fluconazole has a much lower affinity for mammalian cytochrome P-450 enzymes than other azoles.⁵ It is postulated that fluconazole with the specific high binding affinity for fungal cytochrome P-450-dependent enzymes, is unlikely to exert any significant effect on the other microbial species present in the vagina. The results of our study substantiate this.

Our experience in treating the small number of patients suffering from non-albicans infection appeared to agree with the observation by Landers that patients with *C glabrata* and *C tropicalis* infection did not respond as well as patients with *C*

Table The number of patients positive for the microbial species shown at different time intervals after treatment

	Days after treatment									
	0		1-3		4-5		6-8		9-12	
Total number of patients	11	11	11	8	7	6	10	8	9	11
Treatment	c*	f*	c	f	c	f	c	f	c	f
Microbes (cfu/g secretion)										
<i>G vaginalis</i> ≥ 10 ⁶	2	5	3	2	2	2	2	1	1	3
Gp B <i>Streptococcus</i> ≥ 10 ⁴	1	0	1	0	1	1	0	1	0	1
Coliforms ≥ 10 ⁴	0	2	0	0	0	0	0	0	0	0
Lactobacilli ≥ 10 ⁶	11	8	11	8	7	6	9	7	9	9
Non-haemolytic strept ≥ 10 ⁴	2	2	3	3	0	0	0	0	0	1
Ureaplasma	3	5	4	6	3	3	3	4	2	5
<i>Mycoplasma hominis</i>	0	1	0	0	0	0	0	0	0	0

*c = clotrimazole group; f = fluconazole group.

albicans infection.⁶ The reliability of in vitro sensitivity testing of *Candida* spp against anti-fungal agents generally is uncertain. Nevertheless, MICs of clotrimazole and fluconazole against *C glabrata* were shown to be higher than those against *C albicans*.^{7,8} Furthermore, Kerridge and Nicholas suggest that *C glabrata*, unlike *C albicans*, is haploid, with no reported sexual stage in its life cycle and the frequency with which drug-resistant strains might be expected to occur will be higher than for diploid yeasts.⁹

C glabrata and *C krusei* are infrequently isolated from patients suffering from vaginitis; both contributed to about 7.5% of cases in one series.¹⁰ However, as fungal vaginitis occurs in so many women, quite a few may be suffering from an infection which is unlikely to respond to the standard dose of therapy. It is therefore important to identify the yeast if the patient has not responded to the routine therapy. It remains to be studied whether a more prolonged course of therapy will be more efficacious for these infections.

In conclusion, both clotrimazole and fluconazole therapy eradicated *C albicans* from the vagina in 17/18 patients with culture positive, symptomatic vaginal candidosis. They were less efficacious in the small number of patients studied in our study who suffered from vaginal infection caused by *C glabrata* or *C krusei*. The vaginal bacterial flora remained unaltered after either therapy.

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Accepted for publication 28 January 1991.