

Intermittent local prophylaxis against recurrent vaginal candidosis

T E C BUSHELL,* E G V EVANS,† J D MEADEN,‡ J D MILNE,§ D W WARNOCK§

From the *Royal West Sussex Hospital, Chichester; the †General Infirmary, Leeds, the ‡Norfolk and Norwich Hospital, Norwich; and the §Royal Infirmary, Bristol

SUMMARY Women with recurrent vaginal candidosis were treated until the infection cleared and were then given one clotrimazole 500 mg vaginal tablet a month or an identical placebo as prophylaxis. Of 21 women who received placebo, 16 developed symptoms or signs within three months, compared with nine of 17 women given active treatment. Women who relapsed were treated and then given active prophylaxis once a month. Of 30 women given such treatment, 13 relapsed within three months. Women who relapsed were treated and then given two clotrimazole 500 mg vaginal tablets a month. Of 17 women given prophylaxis twice a month, four developed symptoms or signs within three months, but 10 remained clear for 12 months. No appreciable difference was seen in the incidence of mycological recurrence between the different regimens; within three months over half the women in all treatment groups had become recolonised.

Most women with vaginal candidosis respond well to local antifungal treatment. In some, however, the infection is recurrent, often developing month after month, whereas others have persistent symptoms that fail to respond to treatment. Antifungal prophylaxis is a potential method of controlling the condition, and the newer single dose topical formulations of azole antifungal drugs, which have proved effective against acute vaginal candidosis,^{1,2} permit much simpler prophylactic regimens to be devised than was possible in the past.

The object of this work was to assess the effectiveness of intermittent prophylaxis with clotrimazole 500 mg vaginal tablets in managing patients with recurrent vaginal candidosis. We intended to maintain the women free of symptoms and signs for 12 months by treating them, as required if they experienced clinical relapse, with three successive prophylactic regimens.

Patients and methods

To be eligible for admission to this trial patients had to have had at least three documented episodes of vaginal

candidosis during the preceding year. We excluded women who were younger than 16, older than 50, pregnant, or had another lower genital tract infection. At admission all patients had symptoms and clinical signs typical of vaginal candidosis, and none had received antifungal treatment within the previous week. All patients were informed about the nature of the trial, and their verbal consent was obtained.

At each visit Gram stained vaginal smears were examined at the clinics, and vaginal swabs were sent for culture. The swabs were inoculated on to glucose peptone agar plates, which were incubated at 37°C for 48 hours. Isolates were identified as *Candida albicans* on the basis of germ tube formation in horse serum after incubation at 37°C for three hours. Germ tube negative isolates were identified with the API 20C AUX yeast identification system (API Laboratory Products, Basingstoke, England).

Two thirds of the patients were first treated with one clotrimazole 500 mg vaginal tablet and the remainder were given six clotrimazole 100 mg vaginal tablets. Patients with vulvitis were also given clotrimazole cream. No attempt was made to treat their sexual partners. Patients were instructed to return to the clinic one week after completing their initial course of treatment, at which time women who had failed to respond were given further treatment with six clotrimazole 100 mg vaginal tablets.

Address for reprints: Dr D W Warnock, Department of Microbiology, Bristol Royal Infirmary, Bristol BS2 8HW

Accepted for publication 20 January 1988

Once clear of infection, the women were randomised to receive prophylactically either one clotrimazole 500 mg vaginal tablet or an identical placebo tablet (prophylaxis regimen A). In both cases, one tablet was to be used each month, one week before the expected onset of menstruation, as symptoms most often recur at that time. The women were requested to return to the clinics for examination each month, two weeks after using their medication. Symptoms (discharge, itching, and burning) and clinical signs (discharge, vulvitis, and vaginitis) were recorded at each visit, and specimens were taken for mycological investigation.

If, during the 12 month period of prophylaxis, a woman developed symptoms or clinical signs of candidosis, she was temporarily withdrawn from the trial and given further active treatment with six clotrimazole 100 mg vaginal tablets. Once clear of infection, patients who were willing to continue with the trial were given one clotrimazole 500 mg vaginal tablet a month for up to 12 months (prophylaxis regimen B). As with regimen A, this treatment was administered one week before menstruation, and the woman was instructed to return for examination two weeks later.

Patients who developed symptoms or clinical signs of candidosis during that 12 month period of prophylaxis were again withdrawn from the trial and given further active treatment. Once clear of infection, those who wished to continue were given two clotrimazole 500 mg vaginal tablets as prophylaxis each month (regimen C). The first was to be used one week before menstruation and the second at the end of menstruation. Each woman was assessed at monthly intervals, about two weeks after the second tablet had been used.

The results were analysed with a rank correlation method.³

Results

We admitted to prophylaxis regimen A 42 women aged between 18 and 45. All had presented with *C albicans* infection. We assigned 21 to the active prophylaxis group and the remaining 21 to the placebo group. The composition of these groups was similar regarding age, contraceptive method, and number of episodes of candidosis during the preceding year (table). The proportion of women in each group given the different initial treatments was similar, as was the number of women who required repeat treatment to clear their presenting infection.

Four of the 21 women given active prophylaxis on regimen A defaulted and have been excluded from analysis. Of 34 women receiving regimen A who relapsed and required further treatment, all consented

Table Clinical characteristics of women with recurrent vaginal candidosis (figures are numbers of patients unless otherwise stated)

Characteristic	Active prophylaxis (n = 21)	Placebo prophylaxis (n = 21)
Age range (years)	18-35	18-41
Mean age (years)	26.8	28.9
No of attacks during previous year:		
3-5	7	7
≥ 6	14	14
Mean No of attacks during previous year	6.5	7.3

to further prophylaxis and were admitted to regimen B (once monthly active prophylaxis). Four of these women subsequently defaulted, however, and have been excluded from analysis. Of 21 women receiving regimen B who relapsed and required further treatment, 19 consented to further twice monthly prophylaxis (regimen C). Two of these women subsequently defaulted, however, and have been excluded from the results.

Figure 1 shows the cumulative total percentages of women who developed symptoms or clinical signs while receiving the different prophylaxis regimens. Of the 21 women who received placebo treatment, no fewer than 16 (76%) developed symptoms or signs within three months, and only one remained clear for 12 months. Nine (53%) of the 17 women given regimen A active treatment developed symptoms or signs within three months, as did 13 (43%) of the 30 women receiving regimen B. Three (18%) of the 17 women given regimen A active treatment and nine (30%) of

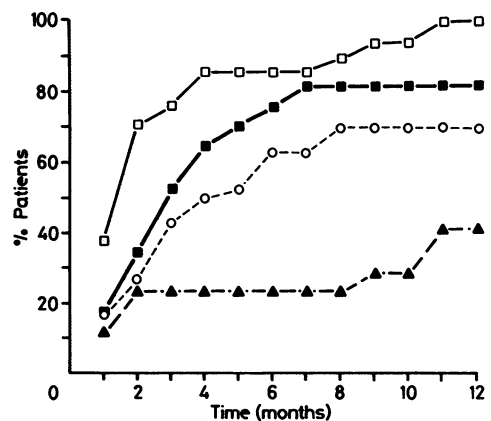


Fig 1 Cumulative total percentages of women showing recurrence of symptoms or clinical signs while receiving different prophylaxis regimens (see fig 2 for details of regimens).

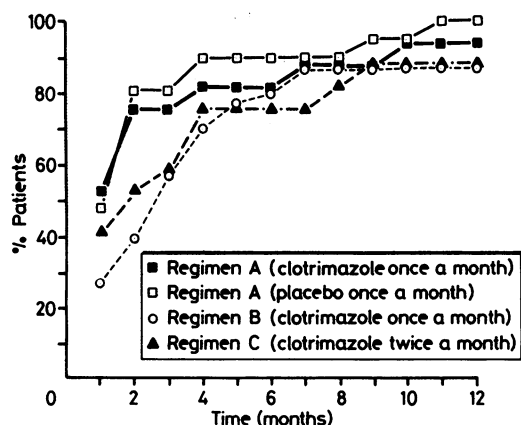


Fig 2 Cumulative total percentages of women showing recurrence of vaginal colonisation with *Candida albicans* while receiving different prophylaxis regimens.

the 30 receiving regimen B remained clear for 12 months. Of the 17 women receiving regimen C, four (24%) developed symptoms or signs within two months, but 10 (59%) remained clear for 12 months. This was significantly ($p < 0.05$) better than the effect of placebo treatment.

Figure 2 shows the cumulative total percentages of women who became recolonised (all with *C. albicans*) while receiving the different prophylaxis regimens. No appreciable difference was seen between the different regimens; over half the women in all groups had become recolonised within three months, and at 12 months over 85% were colonised.

Discussion

The prevention of recurrent vaginal candidosis remains a difficult problem, and until we can address the underlying cause(s) of the condition optimum management with antifungals is required. Women with vaginal candidosis often respond to local antifungal treatment, but symptoms then recur within a few weeks. Indeed, 16 (76%) out of 21 women given placebo treatment in this investigation suffered a symptomatic recurrence within two months. Symptoms also recur despite more prolonged local treatment or concomitant treatment of the intestinal tract⁴ or sexual partner.⁵

Davidson and Mould were the first to report the beneficial effect of intermittent local antifungal prophylaxis in women with recurrent candidosis.⁶ Application of clotrimazole vaginal tablets and cream for six consecutive nights during each menstrual cycle, commencing on the fifth night of the cycle, caused an appreciable reduction in the incidence of symptomatic recurrences; 11% of women given active treatment

relapsed within four months compared with 53% given identical placebo treatment. More recently, Sobel has shown that both intermittent and continuous oral treatment with ketoconazole help to prevent symptomatic recurrence of vaginal candidosis,^{5,7} but the reported toxic effects of this drug have resulted in a reluctance to use it for this condition.⁸ This has again focused attention on local prophylaxis.

Our findings show that intermittent local prophylaxis with a single 500 mg dose of clotrimazole administered one week before menstruation led to fewer symptomatic recurrences than experienced with placebo treatment. Most of our patients had a refractory condition, so it was not surprising that this monthly regimen was not an invariable success. Patients with more intractable conditions, who required two 500 mg doses of clotrimazole a month, gave encouraging results and had fewer symptomatic recurrences than those receiving placebo. It is not clear whether this was due to the increased dosage or whether the timing of the second dose was influential.

Overall, of the 29 women who completed the trial, 22 (76%) were kept clear of symptomatic vaginal candidosis for 12 months by the prophylactic use of clotrimazole 500 mg vaginal tablets either once or twice a month. The women for whom treatment failed despite twice monthly treatment would possibly benefit from more frequent prophylaxis.

Although prophylaxis with clotrimazole was helpful in preventing recurrences of symptoms and clinical signs, which was the original object of this work, it did not affect mycological recurrence. Yeasts recurred at almost the same rate, irrespective of the prophylaxis regimen used. Sobel⁵ and Davidson and Mould⁶ have also noted that prophylaxis does not affect recolonisation with *C. albicans*.

Hopwood *et al* have shown a direct relation between vaginal yeast counts and the development of symptoms and clinical signs typical of candidosis.⁹ This would help to account for the symptomatic relief obtained by women given intermittent local prophylaxis. Further investigation, with yeast counts, is required to establish whether successful prophylaxis depends on keeping the vaginal yeast population below the numbers at which symptoms or signs develop.

In conclusion, intermittent local prophylaxis with single dose clotrimazole vaginal tablets has been shown to reduce the recurrence of symptoms in women with recurrent vaginal candidosis. Application of two 500 mg doses of clotrimazole a month produced prolonged symptomatic relief in most women, though it often failed to prevent reacquisition of *C. albicans*. More frequent prophylactic treatment might benefit the women who relapsed while receiving this regimen.

We thank Mr P A Llewellyn for his help with the design of

this investigation, and Bayer UK Limited for financial support.

References

- 1 Cohen L. Single dose treatment of vaginal candidosis: comparison of clotrimazole and isoconazole. *British Journal of Venereal Diseases* 1984;**60**:42-4.
- 2 Milsom I, Forssman L. Treatment of vaginal candidosis with a single 500-mg clotrimazole pessary. *British Journal of Venereal Diseases* 1982;**58**:124-6.
- 3 White C. The use of ranks in a test of significance for comparing two treatments. *Biometrics* 1952;**8**:33-41.
- 4 Milne JD, Warnock DW. Effect of simultaneous oral and vaginal treatment on the rate of cure and relapse in vaginal candidosis. *British Journal of Venereal Diseases* 1979;**55**:362-5.
- 5 Sobel J. Management of recurrent vulvovaginal candidiasis with intermittent ketoconazole prophylaxis. *Obstet Gynecol* 1985;**65**:435-40.
- 6 Davidson F, Mould RF. Recurrent genital candidosis in women and the effect of intermittent prophylactic treatment. *British Journal of Venereal Diseases* 1978;**54**:176-83.
- 7 Sobel J. Recurrent vulvovaginal candidosis. A prospective study of the efficacy of maintenance ketoconazole therapy. *N Engl J Med* 1986;**315**:1455-8.
- 8 Hay RJ. Ketoconazole: a reappraisal. *Br Med J* 1985;**290**:260-1.
- 9 Hopwood V, Warnock DW, Milne JD, Crowley T, Horrocks CT, Taylor PK. Evaluation of a new slide latex agglutination test for diagnosis of vaginal candidosis. *Eur J Clin Microbiol* 1987;**6**:392-4.

Bushell, Evans, Meaden, Milne, Warnock