

Intermittent prophylactic treatment of recurrent vaginal candidiasis by postmenstrual application of a 500 mg clotrimazole vaginal tablet

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Abstract

The therapeutic efficacy of intermittent, monthly, postmenstrual prophylaxis with a single 500 mg clotrimazole vaginal tablet ($n = 33$) was compared with placebo tablets ($n = 29$) in 62 women (age 28.1, SD 7.2 years) with recurrent vulvovaginal candidiasis. The number of episodes of acute vulvovaginal candidiasis experienced during the year prior to inclusion was 6.3, SD 1.9. The cumulative recurrence frequency after 6 months intermittent prophylaxis with clotrimazole (30.3%) was lower ($p < 0.001$) than that recorded for the women who received placebo (79.3%). After an additional 6 months observation period without treatment there was no significant difference in the cumulative recurrence frequency between the groups (clotrimazole 84.9%; placebo 86.2%). The vagina was recolonised with *Candida albicans* in 70% of the women after 6 months prophylactic treatment with clotrimazole and in 86% of the women who had received placebo. Thus, this study has demonstrated that postmenstrual prophylactic treatment with a single 500 mg clotrimazole vaginal tablet, applied monthly, prevents recurrence of symptoms, although it does not eliminate yeasts from the vagina.

Introduction

Candida vulvovaginitis is one of the most common infections encountered by obstetricians and gynaecologists.¹

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It has been estimated that 75% of all adult women will at some time in their life suffer from at least one episode of candida vulvovaginitis.² The majority of women experience infrequent, isolated episodes of genital candidiasis that respond readily to a variety of topical antimycotic agents.^{3,4} However there is a small group of women who experience repeated episodes of candida vulvovaginitis.⁵

Several studies have been performed aimed at eliminating or reducing the frequency of clinical recurrences by prophylactic, local or systemic application of antimycotics. Various forms of prophylaxis have been used with varying degrees of success.⁵⁻⁸ Bushell and coworkers⁷ evaluated intermittent, local, premenstrual prophylaxis with a 500 mg clotrimazole vaginal tablet given at monthly intervals against an identical placebo regimen. The difference in recurrence rates after 3 months between premenstrual prophylaxis with a 500 mg clotrimazole vaginal tablet (53%) and placebo (76%) was not significant. However, Sobel and coworkers⁸ demonstrated a moderate protection from recurrence by prophylactic treatment with clotrimazole.

The incidence of acute vaginal candidiasis reaches a maximum shortly before the onset of menstruation which may partially be due to changes in the cellular immune response to *Candida albicans* occurring during the menstrual cycle.⁹ Vaginal yeast counts have been shown to be directly related to the development of symptoms and clinical signs of candidiasis.¹⁰ Yeast counts are at a minimum directly after menstruation and acute vaginal candidiasis is less commonly encountered in the immediate postmenstrual period. Thus, it would be reasonable to assume that prophylaxis given postmenstrually would be potentially more effective as the number of candida organisms is then at a minimum.

The aim of the present study was to assess the efficacy of intermittent postmenstrual prophylaxis with a single 500 mg clotrimazole vaginal tablet in women with recurrent vaginal candidiasis.

Patients and methods

Sixty four otherwise healthy women (age 28.1 SD 7.2 years), with a history of at least four episodes of

vulvovaginal candidiasis during the last 12 months were invited to participate in this study. The study was approved by the Ethical Committee, Faculty of Medicine, Gothenburg University. The women were recruited when they presented with an acute episode of vulvovaginal candidiasis, defined as (1) symptoms of irritation, burning and vaginal discharge; (2) signs of inflammation of the vaginal mucosa and microscopical identification of pseudohyphae; (3) cultural isolation of *Candida albicans*. The culture specimens were promptly inoculated on to standard media and growing yeasts were identified as *C. albicans* by the formation of chlamydo spores and the germ tube test. Pregnant patients and women likely to become pregnant during the course of this study were not included. Women who had received antifungal or antitrichomonal treatment during the previous 14 days were excluded. Cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and microscopical examination to exclude *Trichomonas vaginalis* were performed at the initial assessment; in this respect, only women with negative cultures and microscopy were admitted to this study.

The women were treated with a single 500 mg clotrimazole vaginal tablet and re-examined after one week. Women who were symptom-free after treatment and who had a negative culture for *C. albicans* were invited to participate in this double-blind trial. Intermittent prophylactic treatment with a 500 mg clotrimazole vaginal tablet or placebo was administered postmenstrually for 6 months. The active and placebo vaginal tablets were indistinguishable. The containers were prepacked and randomised so that neither the clinician, mycologist, nor the patient knew which treatment was being given. The women were clinically and mycologically assessed one week after menstruation for a period of 6 months during which they received either a single 500 mg clotrimazole vaginal tablet or placebo which was inserted by the examining gynaecologist (fig 1). After 6 months of intermittent treatment the women were observed for an additional period of 6 months during which clinical and mycological assessments were performed at 9 and 12 months respectively. The women were instructed to contact their gynaecologist at any time if and when they experienced signs and symptoms suggestive of an acute episode of vulvovaginal candidiasis. An acute clinical and mycological assessment was then accordingly performed. Women with signs and symptoms of an acute vulvovaginal candidiasis confirmed by culture were considered to be failures.

The randomisation to clotrimazole or placebo was stratified according to the frequency of the recurrent episodes of vulvovaginal candidiasis. Women with four or five episodes of vulvovaginal candidiasis per year and women with six or more episodes per year were randomised separately. Prior to inclusion in this

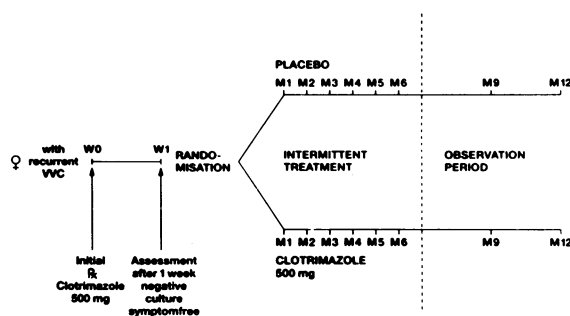


Figure 1 Diagrammatic representation of study design.

study the women were informed that they were not allowed to begin, cease or change contraceptive methods during the course of this study. No attempt was made to treat the sexual partner. Possible concomitant local or systemic medication of any kind was recorded.

Statistical analysis

The results are given as mean, SD unless otherwise stated. The results of prophylactic treatment with clotrimazole and placebo were compared using life-table analysis.¹¹ Wilcoxon's signed rank test was used for the evaluation of statistical significance between groups ($p < 0.05$ was considered to be statistically significant).

Results

Sixty two of the sixty four women who fulfilled the requirements for admission to this study subsequently completed the study. One woman was excluded because of a recurrence of symptoms before prophylactic treatment was commenced. One woman was excluded because of a pregnancy that was diagnosed after the second prophylactic treatment. Prophylactic treatment with clotrimazole was received by 33 women, while the remaining 29 women received placebo. There were no significant differences between groups regarding basic clinical characteristics (table).

Table Comparison of the patients treated intermittently with a 500 mg clotrimazole vaginal tablet or placebo

	Placebo group n = 29	Clotrimazole group n = 33
Age (yr, mean, SD)	27.2, 7.8	29.0, 6.9
Number of previous episodes of vaginal candidiasis during last 12 months (mean, SD)	6.5, 1.8	6.2, 1.9
Duration of current episode, days (mean, SD)	3.6, 1.6	3.7, 1.7
Contraceptive pill	14	14
Intrauterine contraceptive device	5	9
Barrier method of contraception	8	6

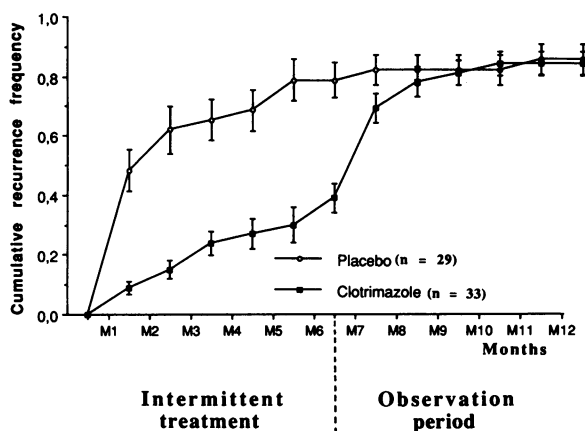


Figure 2 Cumulative recurrence frequency in the women grouped according to type of prophylactic treatment. Significance of difference after 6 months prophylactic treatment with clotrimazole (500 mg) vaginal tablets and placebo vaginal tablets, $p < 0.001$.

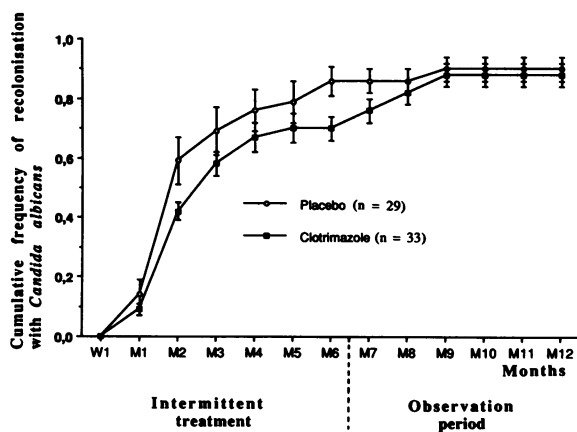


Figure 3 Cumulative frequency of recolonisation with *Candida albicans* in the women grouped according to type of prophylactic treatment. There was no significant difference in the cumulative recolonisation rate between prophylactic treatment with clotrimazole (500 mg) vaginal tablets and placebo vaginal tablets.

The results of life table analysis of prophylactic treatment are shown in fig 2. The cumulative recurrence frequency after 6 months intermittent prophylaxis with a 500 mg clotrimazole vaginal tablet (30.3%) was lower ($p < 0.001$) than that that recorded for the women who received placebo (79.3%). After the 6 months observation period without treatment there were no significant differences in the cumulative recurrence frequency between the groups (clotrimazole 84.9%; placebo 86.2%).

After 6 months prophylactic treatment with

clotrimazole 70% of the women were recolonised with *Candida albicans* (fig 3). The corresponding figure for women who received placebo was 86%. After the 6 month observation period the cumulative recolonisation rates for *Candida albicans* were 88% and 90% respectively for prophylactic treatment with clotrimazole and placebo.

No side effects or complications resulted from prophylactic treatment with either clotrimazole vaginal tablets or placebo vaginal tablets.

Discussion

Although recurrent vaginal candidiasis afflicts only a small proportion of the fertile female population it is of considerable clinical importance.⁵ Frequent episodes of vulvovaginal candidiasis with ensuing pruritis, vaginal discharge and soreness not only affects the individual concerned but may even place a severe strain on normal marital relations. Numerous schedules for the management of recurrent vaginal candidiasis have been advocated.¹²

Several studies have been performed aimed at preventing recurrences by prophylactic, local or systemic application of antimycotics.⁵⁻⁸ In 1978 Davidson and Mould⁵ evaluated the efficacy of prophylactic treatment using local application of 100 mg clotrimazole for 6 days at monthly intervals. This prophylactic treatment regimen kept symptoms below a critical level but did not affect the return of yeasts to the vagina. Sobel⁶ studied the prophylactic use of oral ketokonazole in patients suffering from recurrent vulvovaginal candidiasis. Intermittent prophylaxis with ketokonazole was only partially successful as 24% of the women developed symptoms of vulvovaginal candidiasis during treatment and 57% developed symptoms within an additional 3 months after the cessation of treatment. Bushell and coworkers⁷ evaluated intermittent, local, premenstrual prophylaxis with a 500 mg clotrimazole vaginal tablet given at monthly intervals against an identical placebo regimen. The difference in recurrence rates after 3 months between premenstrual prophylaxis with a 500 mg clotrimazole vaginal tablet (53%) and placebo (76%) was not significant. However, Sobel and coworkers⁸ demonstrated a moderate protection from recurrence by prophylactic treatment with clotrimazole.

In the present study postmenstrual prophylactic treatment with a single 500 mg clotrimazole vaginal tablet was evaluated against placebo in women with recurrent vulvovaginal candidiasis. The women included in this study had experienced an average of 6 episodes of acute vulvovaginal candidiasis during the last 12 months prior to inclusion in this study. The correct diagnosis of the recurrent nature of the patients vulvovaginal candidiasis was confirmed by the fact that 60% of the women who received placebo

experienced a recurrence within 2 months and almost 80% had experienced a recurrence after 6 months prophylactic treatment with placebo. Postmenstrual prophylactic treatment with a single 500 mg clotrimazole vaginal tablet was shown to be successful in preventing the recurrence of an acute episode in women with recurrent vulvovaginal candidiasis.

However, postmenstrual prophylactic application of a single 500 mg clotrimazole vaginal tablet did not reduce the cumulative recolonisation rate with *Candida albicans*. Our findings in this respect are in agreement with the findings of Davidson and Mould⁵ who evaluated the efficacy of prophylactic treatment using local application of 100 mg clotrimazole for 6 days at monthly intervals. This prophylactic treatment regimen kept symptoms below a critical level but did not affect the return of yeasts to the vagina. Vaginal yeast counts have been shown to be directly related to the development of symptoms and clinical signs of acute candidosis.¹⁰ It is not unreasonable to assume that yeast counts are also important for the development of signs and symptoms in women with recurrent vulvovaginal candidiasis, although other factors, for example immunological mechanisms are known to be important.^{9,12} Thus it is possible that prophylactic treatment with local application of clotrimazole at monthly intervals maintains yeast counts at a sufficiently low level that symptoms do not arise, although it does not eliminate yeasts from the vagina.

This study has demonstrated that prophylactic treatment with a single 500 mg clotrimazole vaginal tablet, applied postmenstrually, at monthly intervals prevented recurrence of symptoms. When prophylaxis was terminated after 6 months, symptoms invariably returned. Thus, a continuous prophylactic regimen given at monthly intervals as described here may well provide a simple, effective alternative

for women with recurrent vulvovaginal candidiasis.

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- 1 Mead PB. *Candida albicans*. In: Monif GRG (ed). *Infectious Diseases in Obstetrics and Gynecology*. New York. Harper & Row 1982:323-45.
- 2 Berg AO, Heidrich FE, Fihn SD. Establishing the cause of symptoms in women in a family practice. *JAMA* 1984;251:620.
- 3 Milsom I, Forssman L. Treatment of vaginal candidosis with a single 500 mg clotrimazole pessary. *Br J Venereal Dis* 1982;58:124-6.
- 4 Cohen L. Single dose treatment of vaginal candidosis: comparison of clotrimazole and isconazole. *Br J Venereal Dis* 1984;60:42-4.
- 5 Davidson F, Mould RF. Recurrent genital candidosis in women and the effect of intermittent prophylactic treatment. *Br J Venereal Dis* 1978;54:176-83.
- 6 Sobel J. Management of recurrent vulvovaginal candidosis with intermittent ketokonazole prophylaxis. *Obstet Gynecol* 1985;65:435-40.
- 7 Bushell TEC, Evans EGV, Meaden JD, Milne JD, Warnock DW. Intermittent local prophylaxis against recurrent vaginal candidosis. *Gemittourin Med* 1988;64:335-8.
- 8 Sobel JD, Schmitt C, Meriwether C. Clotrimazole treatment of recurrent and chronic *Candida vulvovaginitis*. *Obstet Gynecol* 1989;73:330-4.
- 9 Kalo-Klein A, Witkin SS. *Candida albicans*: Cellular immune system interactions during different stages of the menstrual cycle. *Am J Obstet Gynecol* 1989;161:1132-6.
- 10 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.
- 11 Cramer DW, Walker AM, Schiff I. Statistical methods in evaluating the outcome of infertility therapy. *Fertil Steril* 1979;32:80-6.
- 12 Forssman L, Milsom I. Treatment of recurrent vaginal candidiasis. *Am J Obstet Gynecol* 1985;152:959-61.

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