Single-Dose 500-mg Clotrimazole Vaginal Tablets Compared with Placebo in the Treatment of *Candida* Vaginitis

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In a double-blind controlled clinical trial, 29 practitioners randomized 55 women with culture-proven Candida *vaginitis to treatment with single-dose 500-mg clotrimazole vaginal tablets, and 40 to placebo. At a follow-up visit 7 to 10 days after treatment,* Candida *was present in 21 (38%) of those treated with clotrimazole and in 30 (75%) in the placebo group (*P < .05*). Symptoms had improved or disappeared in 38 (69%) treated with clotrimazole, compared with 22 (55%) in the placebo group (*P > .05*). In 10 (23%) of the mycologically cured women, symptoms were unchanged or worse, whereas symptoms had improved or disappeared in 26 (51%) in whom* Candida *was isolated at the follow-up visit (*P = .015*). Questionnaires sent to the 95 women 4 weeks after the follow-up visit were returned by 62. Vaginal symptoms were reported by 50% in both groups. Further clinical trials including placebo are needed in general practice in the evaluation of the treatment of* Candida *vaginitis.*
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Vaginal discharge and pruritus are frequent reasons for encounter in general practice,[1] and *Candida* vaginitis is the most frequent diagnosis made in these patients.[2] Numerous studies have evaluated different treatment regimens for vaginal candidiasis, and boric acid, nystatin, natamycin, and a range of different imidazole derivatives have all proved effective in the eradication of *Candida*.[3–6] Most clinical trials have compared different drugs or different dosages of the same drug. In a review, Odds[7] concluded that imidazole derivatives gave higher cure rates than polyenes (eg, nystatin), but in the individual studies no statistical difference was usually found. Placebo-controlled studies are infrequent, and only little is known about the natural history of *Candida* vaginitis.

Since imidazole was introduced in the early 1970s, local treatment with imidazole derivatives has been the first choice for vaginal candidiasis. The duration of treatment has gradually been reduced from 1 week to 3 days without a decline in the cure rates,[5,8,9] and single-dose treatment with vaginal tablets is now recommended in uncomplicated cases.[10,11]

Most studies on *Candida* vaginitis have been conducted in hospitals or venereal disease clinics. Women seen in general practice differ from such populations, however,[12] and results obtained in those studies cannot be applied to a general practice population without consideration.

The aim of the present study was to compare single-dose 500-mg clotrimazole vaginal tablets with placebo in the treatment of *Candida* vaginitis in general practice.

METHODS

This multipractice study included 29 general practitioners in the county of Aarhus, Denmark. The study was approved by the county's ethics committee. Each general practitioner was asked to enroll 15 consecutive patients with increased vaginal discharge, pruritus, or malodor. After giving their informed consent, the women underwent a standardized procedure, including history and pelvic examination. Patients were excluded for the following reasons: age less than 18 years, pregnancy, menstruation

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or expected menstruation within the next 8 days, and treatment with antibiotics within the previous 14 days.

A total of 361 women with a mean age of 28.7 years (SD 8.8 years) was included in the study. All the women, except 129 with bacterial vaginosis according to the definition of Amsel et al,[13] were randomly assigned to treatment with single-dose 500-mg clotrimazole vaginal tablets or placebo. The analysis excluded 95 women in whom no *Candida* was found by either of the two culture methods, as well as 38 in whom *Neisseria gonorrhoeae, Chlamydia trachomatis,* or *Trichomonas vaginalis* were isolated. The treatment trial hereafter comprised 99 women with *Candida* found by at least one of the two culture methods. In one patient randomized to treatment with clotrimazole and in three patients treated with placebo, information about culture result or symptoms after treatment was missing, and subsequent analysis comprised 55 women randomized to treatment with clotrimazole and 40 to placebo.

Seven to 10 days after the first visit, a follow-up visit was performed following the same format as at the first visit, including culture for *Candida,* and 4 weeks later a questionnaire was sent to all the women asking about the presence of vaginal symptoms. The study was conducted on a double-blind basis. The history was obtained and clinical examination and microbiological investigations were performed without knowledge of the treatment given.

Clinical Observation and Investigation

During the pelvic examination, the appearance of the vaginal discharge was noted, and its pH was measured with a paper indicator (Merck, narrow range 4.0 to 7.0). A 10% potassium hydroxide (KOH) solution was then added to the discharge left on the withdrawn speculum, and the presence of a fishy odor was registered (amine test). A wet mount was examined by bright field microscopy at ×400 magnification for the presence of *T vaginalis* and clue cells (vaginal epithelial cells studded with coccobacilli). A diagnosis of bacterial vaginosis was made if at least three of the following four criteria were present: (1) a homogeneous vaginal discharge of thin appearance, (2) a pH > 4.5, (3) a fishy amine odor on addition of 10% KOH to the discharge, and (4) the presence of clue cells.[13]

Microbiological Methods

Cervical specimens for the detection of *C trachomatis* were obtained with cotton-tipped swabs, transported in a sucrose-phosphate medium to the Institute of Medical Microbiology, University of Aarhus, and cultured on cycloheximide-treated McCoy cells.[14]

Specimens for culture for *N gonorrhoeae* were obtained by charcoal cotton-tipped swabs from the cervix, and transported in Stuart's medium to the State Serum Institute (SSI), Copenhagen. *N gonorrhoeae* was isolated and identified according to standard laboratory procedures.[15]

Specimens for culture of *T vaginalis* and *Candida* were obtained by charcoal cotton-tipped swabs from the posterior fornix of the vagina and transported in Stuart's medium to SSI, Copenhagen. The swab for detection of *T vaginalis* was incubated in Diamond's medium, and isolation and identification of *T vaginalis* were performed according to procedures previously described.[16]

The swab for detection of *Candida* was plated onto Sabouraud maltose agar and incubated at 36°C for 3 days. Individual morphologically different colonies were streaked on cornmeal agar and incubated for 3 days at 25°C.[17] The plates were examined daily for the occurrence of chlamydospores, differentiating *Candida albicans* from other yeast species. The term *Candida* in this report includes all yeasts found.

One swab with vaginal secretion from the posterior fornix of the vagina was used for culture of *Candida* in the general practitioner's laboratory. The swab was inoculated in a liquid medium containing trypticase to which sheep serum, penicillin, and streptomycin were added. After incubation at 37°C for 24 hours, *Candida* was demonstrated by microscopy at ×400 magnification. Species identification was not possible.

Statistics

Statistical analyses were performed with Pearson's chi-square test to compare the following in the two treatment groups: the characteristics of patients (Table 1), the presence of *Candida* after treatment (Table 2), the patients' evaluation of symptoms after treatment (Table 3, Table 4) and the patients' evaluation of symptoms in relation to the presence of *Candida* after treatment (Table 5). In the evaluation of symptoms after treatment (Table 3, Table 4) power calculation was performed to determine the type II error (beta) according to Feinstein.[18]

RESULTS

Candida was isolated in the general practitioner's laboratory in 74 patients and at the bacteriological laboratory in 83 patients and by one or both methods in 95 women.

The characteristics of the patients are shown in Table 1. All characteristics were comparable in the two treatment groups ($P > .05$).

At the follow-up visit (Table 2), 34 (62%) women

TABLE 1. CHARACTERISTICS OF PATIENTS WITH *CANDIDA* ISOLATED AT THE INITIAL VISIT, STRATIFIED BY TREATMENT

	Treatment Group		
	Clotrimazole No. (%)	Placebo No. (%)	χ^2
Age (y)			
Mean (SD)	27 (6.9)	28.5 (7.9)	
Range (y)	16–42	18–53	
Duration of symptoms			
0–2 weeks	29 (53)	24 (60)	
>2 weeks	26 (47)	16 (40)	0.50, NS
Contraceptive use			
Oral contraceptive	13 (24)	13 (33)	
Intrauterine device	13 (24)	11 (28)	
Other	19 (35)	6 (15)	
None	10 (18)	10 (25)	4.67, NS
Symptoms			
Discharge	50 (91)	33 (83)	1.48, NS
Itching	45 (82)	35 (88)	0.56, NS
Signs			
Discharge	32 (58)	24 (60)	0.03, NS
Vaginal inflammation	30 (55)	18 (45)	0.84, NS
pH			
4.0–4.5	27 (49)	17 (43)	
>4.5	28 (51)	23 (58)	0.40, NS
Candida species isolated			
Candida albicans	41 (89)	21 (75)	
Other species	5 (11)	7 (25)	2.56, NS
No identification	9	12	

NS—Not significant (P > .05)

treated with clotrimazole were culture negative for *Candida,* compared with 10 (25%) in the placebo group (95% confidence interval [CI], +18% to +55%).

No difference in the mycological cure rate was found when patients with *Candida* isolated in the general practitioner's laboratory and at the bacteriological laboratory were analyzed separately.

TABLE 2. THE PRESENCE OF *CANDIDA* SPECIES 1 WEEK AFTER TREATMENT WITH SINGLE-DOSE 500-mg CLOTRIMAZOLE VAGINAL TABLETS OR PLACEBO (N = 95)

Treatment Group	Positive for Candida No. (%)	Negative for Candida No. (%)
Clotrimazole	21 (38)	34 (62)
Placebo	30 (75)	10 (25)

$\chi^2 = 11.19$, P = .00082

TABLE 3. PATIENT'S EVALUATION OF SYMPTOMS 1 WEEK AFTER TREATMENT WITH SINGLE-DOSE 500-mg CLOTRIMAZOLE VAGINAL TABLETS OR PLACEBO (N = 95)

Treatment Group	Improved or Disappeared No. (%)	Unchanged or Worse No. (%)
Clotrimazole	38 (69)	17 (31)
Placebo	22 (55)	18 (45)

$\chi^2 = 1.42$, P = .23

If the analysis was restricted to women harboring the *C albicans* species, 67% (27/41) were culture negative after treatment with clotrimazole, compared with 19% (4/21) given placebo (95% CI, +24% to +68%).

Symptoms had improved or disappeared in 69% treated with clotrimazole, compared with 55% in the placebo group (95% CI, −6% to +34%) (Table 3). Assuming a minimal relevant difference of 30%, the probability of type II error is 5.6%.

Although symptoms 1 week after treatment were more frequently present in women who were still *Candida* positive, 23% of the *Candida*-negative patients still had symptoms, while 51% of the culture-positive patients stated that their symptoms had improved or disappeared (Table 5).

The follow-up questionnaires sent 1 month after treatment were returned by 62 (65%) of the women with complete information (Table 4). In both treatment groups 50% of the women reported that their vaginal symptoms were unchanged or worse (95% CI, −26% to +26%). Assuming a minimal relevant difference of 30%, the probability of type II error is 1.2%.

DISCUSSION

In previous studies of single-dose 500-mg clotrimazole in the treatment of *Candida* vaginitis, *Candida* was eliminated in 74% to 94%.[5,9,10,19] None of the treatment trials was from general practice, and the lower mycologic cure rate in the present study may be due to differences be-

TABLE 4. PATIENT'S EVALUATION OF SYMPTOMS 5 WEEKS AFTER TREATMENT WITH SINGLE-DOSE 500-mg CLOTRIMAZOLE VAGINAL TABLETS OR PLACEBO (N = 62)

Treatment Group	Improved or Disappeared No. (%)	Unchanged or Worse No. (%)
Clotrimazole	20 (50)	20 (50)
Placebo	11 (50)	11 (50)

$\chi^2 = 0.070$, P = .79

TABLE 5. PATIENT'S EVALUATION OF SYMPTOMS IN RELATION TO ISOLATION OF *CANDIDA* SPECIES 1 WEEK AFTER TREATMENT (N = 95)

Clinical Status	Improved or Disappeared No. (%)	Unchanged or Worse No. (%)
Candida positive	26 (51)	25 (49)
Candida negative	34 (77)	10 (23)

$\chi^2 = 5.93$, P = .015

tween the study populations, eg, with regard to the virulence and antibiotic resistance of the *Candida*, differences in sexual transmission, gastrointestinal colonization, and perhaps dietary habits.

The special interests of investigators carrying out a hospital-based study are likely to improve compliance and reduce the number of inappropriate applications of the vaginal tablets. In some studies application was done by the investigator, thereby eliminating any problems with compliance. The present study was carried out by a number of general practitioners under conditions very similar to everyday routine. Low compliance seems less likely in this study because single-dose therapy was used, but inappropriate application of the vaginal tablets could explain the lower mycologic cure rate. Results obtained under these circumstances do, however, reflect reality in general practice rather than what could be obtained under optimal conditions.

From a pharmacologic and microbiologic point of view, the primary goal in the treatment of vaginal candidiasis is to eradicate *Candida*. From a clinical point of view the objective is to relieve symptoms, since the presence of *Candida* is in itself not an indication for therapy.

More than 83% of the patients were free of symptoms 1 week after treatment in previous studies using single-dose clotrimazole 500 mg.[5,9] With the lower mycologic cure rate in the present trial, one would also expect a lower symptomatic cure rate. The use of placebo, however, may also tend to reduce the symptomatic cure rate because the patients' expectations of the outcome of the treatment may have been lower, since they knew that they might receive placebo.

Active treatment did not significantly improve the symptomatic cure rate compared with placebo 1 week after treatment, and no therapeutic benefit was found after 5 weeks. Unfortunately the large number of women lost to follow-up introduces a bias. It is difficult to evaluate how those responding to the questionnaires differ from nonresponders, but the dropout rate reduces the validity of the long-term evaluation.

Candida is frequently present in women without vaginal symptoms, and it is therefore considered to be an opportunistic pathogenic microorganism.[20,21] *Candida* would also be expected to be present in a proportion of women with vaginal complaints without being the cause of symptoms. In these women the eradication of *Candida* would not affect the symptoms, which might explain that 23% of the women in whom no *Candida* was found after treatment still had symptoms.

Though troublesome, vaginal candidiasis is not a serious condition, and none of the women left the study because of intolerable symptoms before the first follow-up after 1 week. Symptoms improved or disappeared in more than one half of the women on placebo after 1 week, and active treatment was not significantly better than placebo. Further clinical trials conducted in general practice and including placebo therapy are needed to confirm these results and to evaluate other regimens in the treatment of *Candida* vaginitis.

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References

1. Fry J: Common Diseases, Their Nature, Incidence and Care, ed 2. Lancaster, England, Medical & Technical Publishing, 1979
2. Bro F: The diagnosis and treatment of patients with vaginal discharge in general practice. Ugeskr Laeger 1988; 150:1553–1556 (English summary)
3. van Slyke KK, Michel VP, Rein MF: Treatment of vulvovaginal candidiasis with boric acid powder. Am J Obstet Gynecol 1981; 141:145–149
4. Eliot BEW, Howat RCL, Mack AE: A comparison between the effects of nystatin, clotrimazole and miconazole on vaginal candidiasis. Br J Obstet Gynaecol 1979; 86:572–577
5. Robertson WH: A concentrated therapeutic regimen for vulvovaginal candidiasis. JAMA 1980; 244:2549–2550
6. Buch A, Christensen ES: Treatment of vaginal candidosis with natamycin and effect of treating the partner at the same time. Acta Obstet Gynecol Scand 1982; 61:393–396
7. Odds FC: Candida and Candidosis. London, Leicester University Press, 1979
8. Highton BK: A trial of clotrimazole and nystatin in vaginal moniliasis. J Obstet Gynecol 1973; 80:992–995
9. Milsom I, Forssman L: Treatment of vaginal candidosis with a single 500-mg clotrimazole pessary. Br J Vener Dis 1982; 58:124–126
10. Cohen L: Is more than one application of an antifungal necessary in the treatment of acute vaginal candidiasis? Am J Obstet Gynecol 1985; 152:961–964
11. Fleury F, Hughes D, Floyd R: Therapeutic results obtained in vaginal mycoses after single dose treatment with 500 mg clotrimazole vaginal tablets. Am J Obstet Gynecol 1985; 152:968–970
12. Bro F: Patients with vaginal discharge in general practice. Acta Obstet Gynecol Scand 1989; 68:41–43
13. Amsel R, Totten PA, Spiegel CA, et al: Nonspecific vaginitis. Am J Med 1983; 74:14–23

14. Ripa KT, Mardh P-A: Cultivation of *Chlamydia trachomatis* in cycloheximide-treated McCoy cells. J Clin Microbiol 1977; 6:328–331
15. Reyn A: Recent developments in the laboratory diagnosis of gonococcal infections. Bull WHO 1969; 40:245–255
16. Nielsen R: Trichomonas vaginalis. Laboratory investigations in trichomoniasis. Br J Vener Dis 1973; 49:531–535
17. McGinnis MR: Laboratory Handbook of Medical Mycology. New York, Academic Press, 1980
18. Feinstein AR: Clinical biostatistics–XXXIV. The other side of "statistical significance": alpha, beta, delta, and the calculation of sample size. Clin Pharmacol Ther 1975; 18:491–505
19. Goormans E, Bergstein NAM, Loendersloot EW, Branolte JH: One-dose therapy of *Candida* vaginitis. Chemotherapy 1982; 28:106–109
20. Sobel JD: Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. Am J Obstet Gynecol 1985; 152:924–934
21. Gardner HL: Candidiasis. In Gardner HL, Kaufman RH (eds): Benign Diseases of the Vulva and Vagina. Boston, GK Hall Medical, 1981, pp 217–242