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THREE-DAY TREATMENT OF PATIENTS WITH VULVOVAGINAL CANDIDIASIS: A COMPARISON OF BUTOCONAZOLE INSERTS WITH ECONAZOLE OVULES

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ABSTRACT

The safety and efficacy of butoconazole nitrate 100-mg pessaries was compared with that of econazole nitrate 150-mg ovules in a three-day regimen in nonpregnant patients with vulvovaginal candidiasis. Follow-up visits occurred approximately 11 and 32 days after the completion of treatment. In microbiologic assessments of the elimination of the pathogenic *Candida* sp from vaginal secretions (wet-mount and culture), butoconazole was superior to econazole, both at visit 2 (89% versus 52%, respectively; $P = 0.006$) and at visit 3 (100% versus 67%, respectively; $P = 0.014$). Among patients treated with butoconazole who had a microbiologic cure at visit 2, no cases of relapse were detected a month after treatment ended. In contrast, 33.3% of econazole-treated patients experienced relapse. Clinical cures (absence of vulval and vaginal signs and/or symptoms) were comparable for the two treatment groups at visit 2 (69% for butoconazole and 82% for econazole) and also at visit 3 (80% for butoconazole and 83% for econazole). Therapeutic cures (simultaneous clinical and microbiologic cures) were numerically but not statistically superior for butoconazole at visit 2 (62% versus 48%) and at visit 3 (80% versus 58%). No serious adverse events were reported or observed with the use of either drug.

INTRODUCTION

The incidence of vulvovaginal candidiasis has increased in the last 30 to 40 years,[1] and it is now one of the most common diseases faced in gynecological practice.[2] The increase in candidiasis has paralleled the increase in antibiotic usage[1] and the increase in the use of oral contraceptives, both of which are predisposing factors of the disease.[1]

The major symptoms of vulvovaginal candidiasis are itching (which can be intolerable), dyspareunia, and burning, especially during urination. Clinical signs include erythema (nearly always associated with itching) and excoriations from scratching.

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Until the 1930s the most effective treatments were bichloride of mercury douches. Treatment has progressed through the use of gentian violet, the principal and most effective chemical agent until the mid 1950s and a potent candidicide, which is still used in special instances. Nystatin was introduced in 1955 and became a potent treatment, along with candicidin, proprionic acids, chlordantoin, povidone-iodine, and others.[1] A new treatment era began in the early 1970s with the introduction of the highly effective synthetic imidazoles miconazole nitrate and clotrimazole. The original treatment courses were for 14 days to ensure elimination of the fungus in the vulvovaginal area and to prevent recurrence.

All of the above treatments, although potent, left something to be desired because of inconvenience, messiness, adverse events, or lengthy duration of treatment. Patients consequently have found it difficult to comply with the full course of treatment and often cease to apply the medication as soon as their symptoms abate.[2] The movement, therefore, has been toward shorter treatment courses in the hope that patients will be more willing to follow a shorter regimen. Miconazole 2% cream has been shown to be effective with a seven-day treatment course,[3] and clotrimazole 200-mg vaginal tablets have been effective in three-day treatment regimens.[4]

Econazole nitrate, a synthetic imidazole introduced in the late 1970s, and structurally very similar to miconazole, has proven to be an effective, well-tolerated antifungal agent.[5,6] It was as effective as clotrimazole in trials comparing 200-mg clotrimazole vaginal tablets with 150-mg econazole vaginal ovules in a three-day treatment course.[4]

Butoconazole, a newly developed synthetic imidazole specifically developed to treat vaginal candidiasis, has been found to be particularly effective against candidal infections in mice, even at low concentrations. When compared with other imidazoles, reinfection rates were unusually low after treatment was discontinued.[7] In clinical studies, butoconazole was also shown to be as effective as the other antifungal imidazoles. In two separate studies with three-day courses of treatment, the clinical cure rates of 2% butoconazole cream[8] and 50- or 100-mg butoconazole inserts[9] were equivalent to 200-mg clotrimazole tablets. Microbiologic cure rates were either superior[9] or equivalent[8] to those of clotrimazole. In the study by Brown and coworkers,[9] the 30-day follow-up culture analysis showed a clinically superior cure rate for butoconazole, approaching statistical significance. In a trial comparing butoconazole with miconazole, the 2% cream used for three nights was found to have an equivalent cure rate to miconazole cream used for seven nights.[10] Similarly, in a six-day trial, 1% and 2% butoconazole creams were as efficacious as 2% miconazole cream.[2] In all the above studies, butoconazole was well tolerated.

The purpose of this study was to compare and evaluate the safety and

efficacy of butoconazole nitrate* 100-mg pessaries with that of econazole nitrate† 150-mg ovules in a three-day treatment regimen for vulvovaginal candidiasis.

PATIENTS AND METHODS

Seventy-two patients, 34 allocated to butoconazole and 38 allocated to econazole, were enrolled in this study. Patients had to exhibit clinical signs or symptoms of vulvovaginal candidiasis, with microscopic examination confirming this diagnosis prior to the initiation of therapy. They were required to be 18 years or older, and in good general health.

Excluded from the study were women with trichomonas, clue cells, gonococcus, known sensitivity to imidazole derivatives, candidiasis extending beyond the vagina or vulva, diabetes, impaired immune function, or any gynecologic conditions necessitating specific treatment. The study also excluded women who used antibiotics, systemic antimycotics, corticosteroids, or immunosuppressive drugs; women who were treated with oral or intravaginal antifungal medication during the week prior to the start of the study; women who required systemic antifungal treatment; and women who had a partner who used or needed topical antifungal preparations for the genital area. Finally, women were excluded if they were pregnant, lacked sufficient contraception, expected to menstruate during the treatment course, or were unwilling or unable to comply with the requirements of the study.

The study was conducted according to the principles of the Declaration of Helsinki, 1975. Patients gave their informed consent and were fully informed about the aims of the study, the nature of the drugs, possible adverse events, and their right to withdraw at any time and for any reason. The study was approved by each hospital's ethical review committee.

The study was conducted using a randomized, single-blind, parallel-group design. The investigator was unaware of which treatment each patient received until the study was completed. Depending on their designated treatment group, patients were instructed to insert into the vagina either one butoconazole nitrate 100-mg pessary (using the disposable applicators provided) or one econazole nitrate 150-mg ovule every evening for three consecutive days.

Patients were instructed to return to the clinic for one to two follow-up evaluations. Each visit included a physical examination, performed by the same physician each time, and microscopic and fungal culture examina-

* Trademark: Femstat® (Syntex, U.S.A., Palo Alto, California) and Gynomyk® (Casenne Laboratories, Paris, France).
† Trademark: Gyno-Pevaryl 150® (Cilag Laboratories, Paris, France).

tions. The physical examination included evaluation for vulval or vaginal discharge, itching, burning, erythema, swelling, excoriation, and dyspareunia. The severity of each sign or symptom was recorded, on a four-point scale (0 = none to 3 = severe). Wet-mount preparations (using potassium hydroxide [KOH]) and Gram stain preparations were examined for yeast cells and clue cells, trichomonas, and gonococcus. The fungal cultures were sent to an independent laboratory and identified by a microbiologist who was unaware of which drug the patient was taking. If the patient was free of all vulval and vaginal signs or symptoms at either of the follow-up visits, she was judged clinically cured. Patients with both a negative wet-mount preparation and negative fungal cultures were assessed as having a microbiologic cure. Patients who enjoyed both a clinical cure and a microbiologic cure were assessed as having a therapeutic cure. At the end of each examination, the patients were questioned about any unusual or unpleasant symptoms they may have experienced.

The first follow-up evaluation took place 10 to 23 days (preferably 14 days) after the initial visit. If examination showed clinical and wet-mount signs of candidiasis, the patient was excluded from further study. Patients with a satisfactory response to the medication returned for a second follow-up visit 24 to 45 days (preferably 35 days) after the initial visit (Figure 1). If a patient did not return for follow-up visits within the prescribed time frames, or if data were unavailable at a particular visit, that patient was excluded from efficacy analyses for those specific parameters.

At the end of the study, the investigator evaluated the overall clinical condition of all patients receiving treatment. This evaluation was based on the presence or absence of clinical signs or symptoms of vulvovaginal candidiasis. Patients were rated on a scale ranging from no clinical response to very good response. In addition, all patients who returned for second or

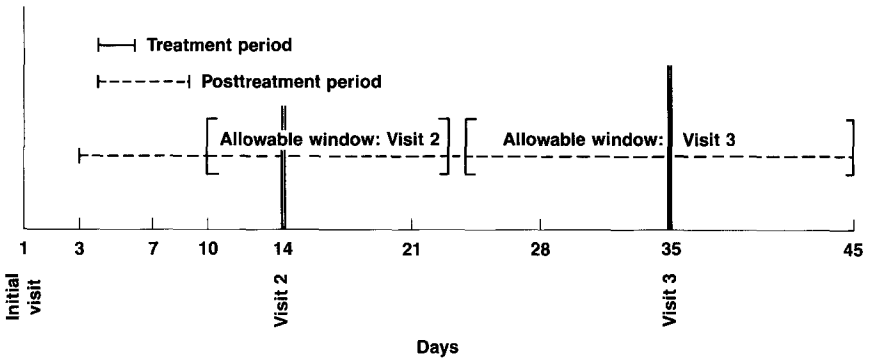

Figure 1. Treatment schedule for patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis, showing periods from treatment completion to follow-up visits.

third visits were judged as cured or not cured in a final-visit analysis. For those patients who were not cured at the second visit, the final visit was their second visit. For all other patients, the final visit was their third.

In the demographic analyses, Student's t test[11] was used for age and duration of vaginitis and the chi-square test[12] for vaginitis and obstetric history. The Wilcoxon rank sum test[12] was used to analyze between-treatment differences in clinical signs or symptoms. The Wilcoxon signed rank test[12] was used to determine significant within-treatment changes in those variables from admission to final visit. Fisher's exact test[12] for significant between-treatment differences was used to analyze the percentage of subjects with positive wet-mount and culture results. The overall clinical response and efficacy scores were analyzed using the Wilcoxon signed rank test.[12]

RESULTS

Patients

Seventy-two patients between 17 and 46 years of age were enrolled in this study. Of the 72 patients enrolled in the study, nine were excluded from both the efficacy and safety analyses: four because of negative wet-mount preparation or negative culture results at baseline, and five because of nonvalid evaluations at follow-up visits. Of the remaining 63 patients, 31 received butoconazole and 32 received econazole. All of these were evaluated for safety and overall clinical response. Because of various protocol violations, eight additional patients (four allocated to treatment with butoconazole and four allocated to treatment with econazole) were excluded from the efficacy analyses of symptomologic and microbiologic response.

The two groups were comparable in age, duration of current vaginitis, and parity; a comparable percentage of patients in each group was experiencing a first episode of vaginitis (Table I). Contraceptive methods were similar in the two groups, with 61.7% of the butoconazole group and 57.9% of the econazole group using oral contraceptives, 26.5% of the butoconazole group and 34.2% of the econazole group using intrauterine devices, and a total of 11.8% and 7.8% in the butoconazole and econazole groups, respectively, using either no birth control, condoms, hysterectomy, or some other method not mentioned above.

Clinical Evaluations

In clinical evaluations for the severity of the signs and symptoms of vulvovaginal candidiasis, response was good within each study group at

Table I. Comparison of the demographics and disease history for patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis.

	Butoconazole	Econazole	Total	*P*-Value
No. of patients	34	38	72	0.6980*
Age (yrs)				
Mean ± SD	27.62 ± 6.34	26.95 ± 8.04	27.26 ± 7.24	
Range	17–39†	18–46	17–46	
Duration of current vaginitis (days)				
No. of patients†	32	38	70	0.1625‡
Mean ± SD	14.56 ± 16.12	21.26 ± 23.37	18.20 ± 20.52	
Range	0–90	2–84	0–90	
First episode of vaginitis	19 (55.9%)	23 (60.5%)	42 (58.3%)	0.6899§
Parity = 0	15 (44.1%)	19 (50.0%)	34 (47.2%)	0.6222§

* *T* test.
† One 17-year-old patient was included in the analysis.
‡ Discrepancy in numbers of patients is due to missing data.
§ Chi-square test.

visit 2 compared with baseline. All of the symptoms and signs evaluated (vulval or vaginal discharge, itching, burning, erythema, swelling, excoriation, and dyspareunia) responded to each drug (Figure 2). Between the second and third visits, clinical response continued to improve or was maintained for all the signs and symptoms evaluated. There were no significant differences between the groups at either visit 2 or visit 3.

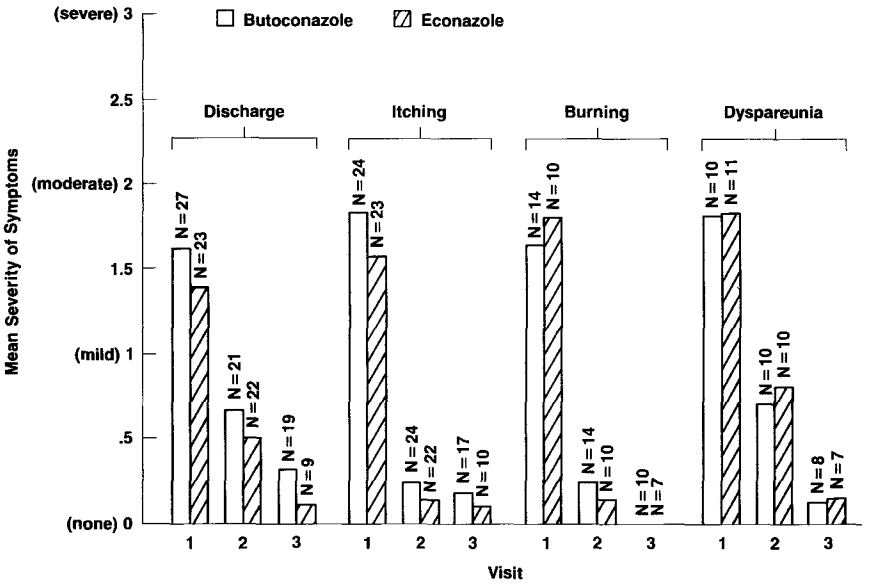

Figure 2. Summary of vaginal and vulval symptoms for patients who exhibited symptoms during the baseline evaluation.

The overall clinical response for the 63 patients who received treatment is summarized in Table II. When considering patients whose signs or symptoms disappeared entirely or remained in mild or residual form (ie, when the very good and good responses were summed), both groups responded well, with 90.3% of the butoconazole patients and 78.1% of the econazole patients falling into those two categories (Figure 3).

Laboratory Evaluations

Examination of wet-mount preparations, when available, using KOH to reveal the fungal hyphae, showed that between baseline and visit 2, 92% (23 of 25) of the patients on butoconazole and 70.4% (19 of 27) of the patients on econazole showed an absence of fungus. At the time of visit 3, all 20 available patients who received butoconazole remained free of the organism in the KOH smear, while 83.3% (10 of 12) of those on econazole did. Thus butoconazole was clinically superior to econazole in preventing relapse, although the between-treatment differences for the KOH smears were not statistically significant (Figure 4).

The culture evaluations, however, did yield a statistically significant difference in favor of butoconazole. At visit 2, *Candida* sp were absent in the vaginal secretions of 88.5% (23 of 26) of the patients on butoconazole and in 55.6% (15 of 27) of those on econazole ($P = 0.0135$). All 20 patients on butoconazole remained free of the organism in the culture during visit 3, while 66.7% (8 of 12) of those on econazole did so ($P = 0.0138$) (Figure 4).

Microbiologic, Clinical, and Therapeutic Cure Rates

The microbiologic, clinical, and therapeutic cure rates are summarized

Table II. Overall clinical response of patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis.

	Butoconazole		Econazole
Very Good*	23 (74.2%)		22 (68.7%)
Good†	5 (16.1%)		3 (9.4%)
Fair‡	2 (6.5%)		4 (12.5%)
No clinical response§	1 (3.2%)		3 (9.4%)
Total	31 (100%)		32 (100%)
P-value‖		0.4839	

* Signs/symptoms disappeared.
† Only mild or residual signs/symptoms remained (none worsened and all improved since baseline).
‡ Moderate residual signs/symptoms remained (most improved and none worsened since baseline).
§ Signs/symptoms remained the same or worsened.
‖ Wilcoxon signed rank test.

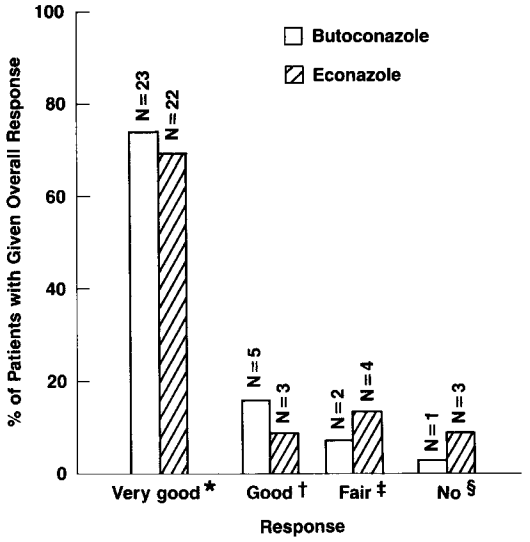

Figure 3. Overall clinical response of patients treated with butoconazole or econazole for vulvovaginal candidiasis. *Signs/symptoms disappeared; †only mild or residual signs/symptoms remained (none worsened and all improved since baseline); ‡moderate residual signs/symptoms remained (most improved and none worsened since baseline); §signs/symptoms remained the same or worsened.

in Table III. At visit 2, 88.5% of the butoconazole-treated patients and 51.9% of the econazole-treated patients achieved a microbiologic cure (both negative wet-mounts and cultures). The differences between the cure rates achieved using these drugs were statistically significant ($P = 0.0063$). All of the butoconazole-treated patients returning for visit 3 maintained this microbiologic cure, while only 66.7% of the econazole-treated patients did; again, the difference was statistically significant ($P = 0.0138$) (Figure 5).

Rates of clinical cure (absence of all vulval and vaginal signs or symptoms) were comparable for patients in both groups. At visit 2, 69.2% and 81.5% of the patients receiving butoconazole and econazole, respectively, were judged clinically cured. Of patients who returned for visit 3, 80.0% who received butoconazole and 83.3% who received econazole were still free of clinical signs or symptoms. None of the differences between the two drug treatments were significant (Figure 5).

At visit 2, a therapeutic cure (both clinical and microbiologic cure) was assigned to 61.5% (16/26) of the patients on butoconazole and to 48.1% (13/27) of those on econazole, while at visit 3, 80.0% (16/20) of those on butoconazole and 58.3% (7/12) of those on econazole were so judged. While these percentages favor butoconazole, none of the differences between the drugs were statistically significant (Figure 5).

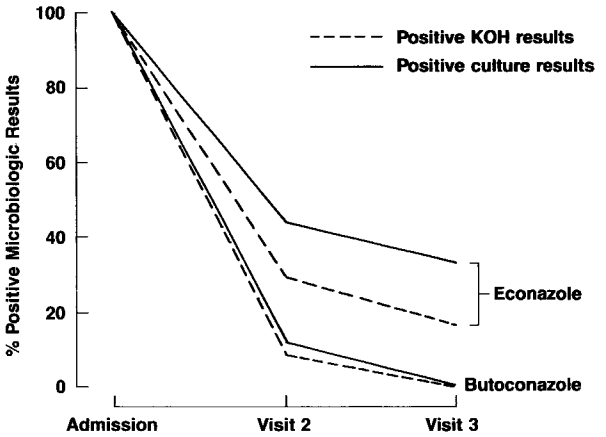

Figure 4. Percentage of patients with positive microbiologic results (excluding patients with baseline data only). Between-drug *P*-values (based on Fisher's exact test, two-tailed): visit 2: potassium hydroxide (KOH), 0.0777; culture, 0.0135; visit 3: KOH, 0.1331; culture, 0.0138.

Table IV summarizes the therapeutic cure evaluation for each patient's last follow-up visit. This parameter perhaps best reflects the overall therapeutic response achieved for patients participating in this study. Among patients who received butoconazole, 70.4% were assigned a therapeutic cure when last seen by the investigator. The corresponding result for patients who received econazole was 35.7%. The difference between the two test drugs was statistically significant ($P = 0.015$) in favor of butoconazole.

Table III. Summary of cure rates of patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis.

	Visit 2		Visit 3	
Type of Cure*	**Butoconazole**	**Econazole**	**Butoconazole**	**Econazole**
Microbiologic				
No. (%) cured	23 (88.5)	14 (51.9)	20 (100)	8 (66.7)
P-value†	0.0063		0.0138	
Clinical				
No. (%) cured	18 (69.2)	22 (81.5)	16 (80.0)	10 (83.3)
P-value†	0.3520		1.0000	
Therapeutic				
No. (%) cured	16 (61.5)	13 (48.1)	16 (80.0)	7 (58.3)
P-value†	0.4117		0.2400	

* Definitions: Microbiologic cure = negative fungal cultures and potassium hydroxide results at follow-up visits; clinical cure = complete cessation of signs and symptoms of vaginal/vulval candidiasis at follow-up visits; therapeutic cure = both microbiological and clinical cures.
† Fisher's exact test (two-tailed).

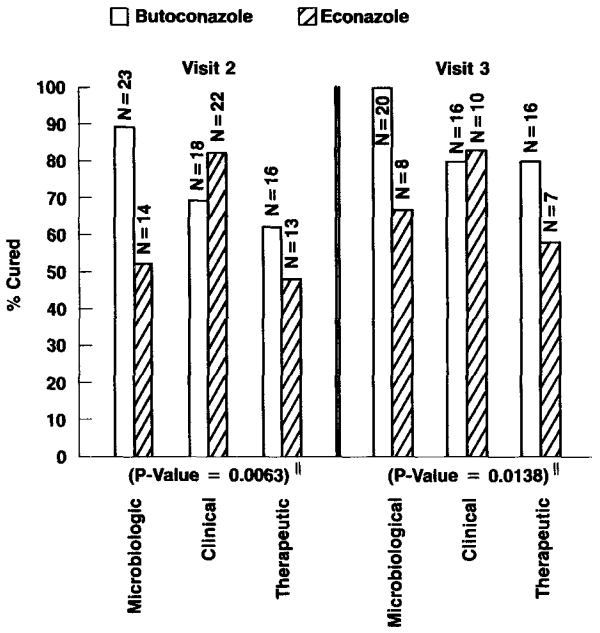

Figure 5. Summary of microbiologic,* clinical,† and therapeutic‡ cure rates for patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis.§ *Negative fungal cultures and potassium hydroxide negative at follow-up visits; †complete cessation of signs and symptoms (excluding discharge) of vulvovaginal candidiasis at follow-up visits; ‡microbiologic plus clinical cure; §Fisher's exact test (two-tailed).

Adverse Experiences

No patient had adverse experiences requiring termination of drug treatment. Only minor complaints were reported. Four patients receiving butoconazole reported leakage, and one reported messiness and spotting. Four patients who received econazole reported leakage, and one reported both spotting and leakage.

Table IV. Therapeutic cure: final patient visit of patients treated with butoconazole inserts or econazole ovules for vulvovaginal candidiasis.

	Butoconazole		Econazole
Patients cured	19 (70.4%)		10 (35.7%)
Patients not cured	8 (29.6%)		18 (64.3%)
Total patients	27 (100%)		28 (100%)
P-value*		0.015	

* Fisher's exact test (two-tailed).

DISCUSSION AND CONCLUSIONS

Early trials favored butoconazole over miconazole and clotrimazole in treating experimentally induced vaginal *Candida albicans* infection in mice. Cultured assays showed that butoconazole was more effective than the other drugs in clearing the infection and that it was also more potent in preventing reinfection.[7] Similarly, in the present study, butoconazole showed a superior microbiologic cure rate in eradicating *Candida* sp from human vaginal secretions and exhibited the power to prevent reinfection (Figure 5).

Low reinfection rates are particularly important when short treatment courses are used; the present trial sought to demonstrate the efficacy of butoconazole in a three-day course of treatment. A shorter treatment course is advantageous because it yields better patient compliance with the treatment regimen. As successful treatment of vulvovaginal candidiasis depends largely on patient compliance, butoconazole's high microbiologic cure rates and low reinfection rates in the present study show a marked advantage of butoconazole over econazole.

Patient compliance may also depend on the convenience of the treatment mode and tolerance for the drugs: both drugs were administered in the form of convenient vaginal inserts or ovules. In addition, there were no adverse experiences, and tolerance for both drugs was nearly equal. Patients reported only a few minor complaints of leaking and spotting.

It may be concluded that a three-day regimen with butoconazole is as safe and well-tolerated as a similar econazole regimen in the treatment of vulvovaginal candidiasis. Furthermore, butoconazole is superior to econazole in efficacy (both microbiologic and therapeutic cure) and in the prevention of relapse.

Acknowledgment

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