The Journal of International Medical Research 1990; **18:** 389 – 399

A Comparison of Butoconazole Nitrate Cream with Econazole Nitrate Cream for the Treatment of Vulvovaginal Candidiasis

H. Ruf [1] and M. Vitse[2]
[1]Belle de Mai Maternity Hospital, Marseille, France; [2]Gynaecology and Obstetrics Clinic, Amiens, France

In a randomized, single-blind, parallel study the safety and efficacy of 2% butoconazole nitrate cream used for 3 days were compared with those of 1% econazole nitrate cream used for 7 days at night in patients with vulvovaginal candidiasis. Patients in both treatment groups had positive potassium hydroxide smears and fungal cultures, and were similar in age, disease duration and history, obstetric history and contraceptive use. Of the 75 patients enrolled, 63 with a *Candida albicans* infection were included in the efficacy analyses. Evaluations were made at the start of the study (visit 1), after 10 – 23 days (visit 2) and after 24 – 45 days (visit 3). Both drugs significantly reduced all signs and symptoms, and at visits 2 and 3 the percentages of patients considered microbiologically, clinically and therapeutically cured were consistently higher for butoconazole- than for econazole-treated patients, although differences were not statistically different. Although both drugs were safe and well tolerated, it is concluded that butoconazole because of its much shorter regimen and superior clinical and microbiological performance was the drug of choice.

Lors d'une étude parallèle randomisée en simple aveugle, l'innocuité et l'efficacité du nitrate de butoconazole crème à 2% appliqué pendant 3 jours ont été comparées à celles du nitrate d'éconazole crème à 1% administré la nuit pendant 7 jours à des patientes présentant une candidose vulvo-vaginale. Les deux groupes présentaient des cultures et des frottis à l'hydroxyde de potassium positifs et étaient comparables au point de vue âge, durée et évolution de l'infection, antécedents obstétricaux et utilisation de contraceptifs. Sur les 75 patientes traitées,

Received for publication 24 May 1990; accepted 1 June 1990.

Address for correspondence: Professor M. Vitse, Chef du Service de Gynécologie Obstetrique, Clinique de Gynécologie Obstetrique, 80000 Amiens, France.

63 présentant une infection à *Candida albicans* ont été incluses dans l'analysis d'efficacité. Des évaluations ont été effectuées au début de l'étude (visite 1), après 10 à 23 jours (visite 2), et après 24 à 45 jours (visite 3). Les deux médicaments ont nettement réduit tous les signes cliniques et les symptômes, et lors des visites 2 et 3 les pourcentages de patientes considérées comme microbiologiquement, cliniquement et thérapeutiquement guéries étaient régulièrement plus élevés chez celles traitées avec le butoconazole que chez celles traitées avec l'éconazole, bien que les différences n'aient pas été statistiquement significatives. Comme les deux produits se sont révélés sans danger et ont été bien tolérés,nous conclusons que le butoconazole, à cause de son effet beaucoup plus rapide et de ses performances cliniques et microbiologiques supérieures, constitue le traitement de choix.

KEY WORDS: Butoconazole; econazole; vulvovaginal candidiasis; *Candida albicans*.

INTRODUCTION

The incidence of vaginal candidiasis, a common persistent infection whose signs and symptoms consist of vulval itching, burning, erythema and vaginal discharge, has risen markedly over the past 30 – 40 years.[1] The species most frequently giving rise to vaginitis is *Candida albicans*, but *C. tropicalis* is another common source of infection; *C. pseudotropicalis, C. krusei, C. parakrusei, C.stellatoidea* and *C. guilliermondii* are rarely involved.[1]

Less than 50% of the patients who harbour *Candida* in the vagina have clinical symptoms requiring treatment. Factors affecting vaginal secretion and thereby the vaginal environment are of prime significance in host susceptibility and the occurrence of symptoms; some of the most important predisposing factors are pregnancy, the hormone pattern that exists just prior to menstruation, use of oral contraceptives or broad-spectrum antibiotics, and diabetes mellitus.[1]

After identifying the cause of vaginal candidiasis, therapy consists of the topical application of candidacidal agents to destroy vulvovaginal *Candida* infections. In the 1930s douches of mercury bichloride were used, whereas later gentian violet was the most effective chemical preparation available. Since 1955 antifungal agents have come into use[1] and the synthetic imidazole antimycotics were introduced in the early 1970s, miconazole nitrate, an arylethylimidazole, and clotrimazole, a (poly)aryl-methylimidazole, being the first imidazole derivatives to appear. Imidazoles, which act by disrupting the cell membrane systems,[2] have proved to be highly effective, providing higher cure rates and lower recurrence rates than previous treatments, and they also have been successful in patients who did not respond to other antifungal agents.

Extensive clinical trials have been carried out comparing topical clotrimazole, miconazole and econazole, all of which are available as a cream or as vaginal tablets, for the treatment of vaginal candidiasis. This method of treatment has the advantage that systemic absorption from the vaginal mucosa is negligible (ranging from 0.017% to 0.09% of the applied dose per litre of plasma) after topical application in either animals[3] or humans.[4]

Since many women frequently discontinue treatment as soon as they feel better, they tend to suffer relapses of the disease and there are also women who, for whatever predisposing factors, suffer from recurrent vulvovaginal candidiasis. The ideal approach, therefore, would be to have a short-term treatment that would quickly eliminate the *Candida* organism. Treatment has traditionally involved a 14-day regimen; however, an increase in the dosage has allowed shorter periods of treatment and studies have shown that 7 – 10 days' treatment can result in equivalent cure rates[5] and even shorter treatment periods have been reported to be successful.[6,7]

Econazole nitrate, an imidazole antifungal agent introduced in the mid 1970s, is structurally very similar to miconazole.[8] Applied as a 1% vaginal cream it has been compared with 100 mg clotrimazole vaginal tablets, each used once daily for 7 days.[9] These two fungicides when followed up for 1 month were equivalent in their mycological cure rates and in relieving the clinical symptoms related to vulvovaginal candidiasis.

Butoconazole nitrate (Femstat®) developed specifically as an anticandidal agent, is a new potent vaginal antifungal agent based on 1-(phenylbutyl)imidazole.[10] In animal studies, butoconazole has displayed a greater affinity for *C. albicans* than for dermatophytes[10] and *in vivo* assays comparing it with known agents have indicated its marked superiority in combating *C. albicans*.[11] In experimentally induced *Candida* infections in animals, butoconazole was distinctly superior to miconazole and clotrimazole, both in terms of quickly clearing infections and preventing relapse.[10]

In humans, butoconazole has provided consistently high cure rates even after short treatment periods, with a minimal recurrence of infection after the treatment has ended: 8 days after completion of treatment negative fungal cultures were obtained from 98% of patients who had been treated with 2% butoconazole nitrate vaginal cream once daily for 6 days and use of a 1% butoconazole nitrate cream resulted in negative cultures from 91% of patients.[12] When treated with 2% miconazole nitrate, 83% of patients were culture-negative after 8 days. Even after 30 days negative cultures were found in 80% of those treated with either 1% or 2% butoconazole cream and in 68% of the miconazole treatment group, with rapid relief of clinical symptoms accompanying the microbiological cure. A cream containing 2% butoconazole nitrate applied to the vagina for only 3 days gave results that were practically identical to those achieved after 7 days' treatment with a 2% miconazole nitrate cream.[13] A comparison of 2% butoconazole nitrate cream treatment for 3 days with 200 mg/day clotrimazole vaginal tablets given for 3 days showed that the butoconazole cream was at least as effective as the clotrimazole vaginal tablets.[4]

The purpose of the present study was to assess the safety and efficacy of a 2% butoconazole nitrate cream applied to the vagina for 3 days and to compare it with a 1% econazole nitrate cream used for 7 days.

PATIENTS AND METHODS

Patients

Patients exhibiting the objective signs and symptoms compatible with vulvovaginal candidiasis were eligible. To be included in the trial it was necessary to demonstrate conidia and filaments of *Candida* by microscopic examination of vaginal material mixed with potassium hydroxide and also to detect growth of *Candida* on an appropriate mycobiotic medium.

Women with trichomonads or clue cells detected using wet mount microscopy were not eligible for the study, since these

Femstat® is the registered tradename of Syntex Laboratories, Inc, USA.

findings indicated the presence of *Trichomonas vaginalis* and *Gardnerella vaginalis*. Also excluded were women with any gynaeco- logical abnormality requiring treatment with antibiotics, corticosteroids or immunosuppressive drugs; any disease (diabetes mellitus), condition (pregnancy) or drug predisposing the patient to candidiasis; use of antifungal medication in the week prior to the start of the study; menstruation in the first 7 days of the study; candidiasis extending beyond the vulvovaginal area; or sensitivity to imidazole derivatives.

Patients provided verbal consent after being fully informed about the aims of the study and the procedures and medications to be used. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Treatment

Patients were assigned to receive either butoconazole or econazole according to a computer-generated randomization code and to prevent participating investigators from knowing which treatment was being used, medications and applicators were distributed in identical packaging by an assistant. Treatment consisted of inserting an applicator containing 100 mg butoconazole cream into the vagina in the evening for 3 days or an applicator containing 50 mg econazole cream for 7 days.

Evaluation of treatment

The same investigator examined the patient when admitted to the study (visit 1) and again at visit 2. At visits 1 and 2 a vaginal examination was carried out to assess signs of candidiasis, and vulval and vaginal erythema, oedema, excoriation, dyspareunia, ulceration, discharge, itching and burning were evaluated, the severity of signs and symptoms being rated on a scale of 0 – 3 (0, absent; 1, mild; 2, moderate; 3, severe).

Potassium hydroxide smears prepared from vaginal secretions enabled the investigator to identify the presence of the pseudohyphae of *Candida*, which were detected using low- and high-magnification microscopy, and microscopic examination of vaginal material mixed with physiological saline was used to rule out trichomonads or clue cells.

Specimens were taken for fungal cultures and identification of the fungi was carried out by an independent laboratory, without the microbiologist knowing which drug the patient had applied.

Efficacy of the study drugs was evaluated at each visit according to the reduction in severity of the clinical signs and symptoms of vaginitis and according to whether or not fungal cultures and preparations of potassium hydroxide and saline smears from vaginal secretions were negative.

Patients having either an unsatisfactory clinical response or a positive potassium hydroxide smear after 10 – 23 days (visit 2), preferably as close to day 14 as possible, were excluded from further evaluations but those patients who had improved clinically and who a negative potassium hydroxide response at visit 2 were examined again within 24 – 45 days of admission to the trial (visit 3), preferably as close to day 35 as possible (Fig. 1).

At the end of the study, the investigator provided an overall evaluation of the patients' clinical response as follows: 'very good', disappearance of all clinical signs and symptoms of vulvovaginal candidiasis; 'good', some mild signs and/or symptoms remained, although all had improved; 'fair', most signs and symptoms had improved and none had worsened, but some of moderate severity remained; and 'no clinical response', signs and symptoms either remained unchanged or had worsened. Patients free of all signs and symptoms, with the exception of mild discharge, were rated as clinically cured and the simultaneous achievement of a negative potassium hydroxide preparation and a negative fungal culture was classified as a microbiological

cure; patients with concurrent clinical and microbiological cures were rated as having been therapeutically cured.

Patients were requested to notify the investigator about any cutaneous or systemic adverse event and at each visit patients were questioned about adverse events. Any adverse event reported by a patient or observed by an investigator was rated as mild, moderate or severe, and was evaluated as being either 'probably related' or 'probably not related' to the medication, or as having an 'unknown' relationship to it.

Statistical analysis

In the demographic analyses, the Student's *t*-test[14] was used for age and duration of vaginitis and the χ^2-test[15] for vaginitis and obstetric history. For the sign and symptom scores the Wilcoxon rank sum test[15] was used to determine the significance of the differences between the two treatments at each of the visits (between-treatment change); the Wilcoxon signed rank test[1] was used for each treatment to compare the severity score at visit 2 with that at admission and the severity score at visit 3 with that at visit 2 (within-treatment change). Fisher's exact test (two-tailed)[15] was used to analyse significant between-treatment differences of wet mount results and percentage of subjects with positive fungal cultures. Efficacy scores and the overall clinical response were analysed using the Wilcoxon rank sum test.[15]

RESULTS

Patient population

The trial comprised a total of 75 women (mean age 30 years, range 16 – 56 years) with vaginitis that had been present for an

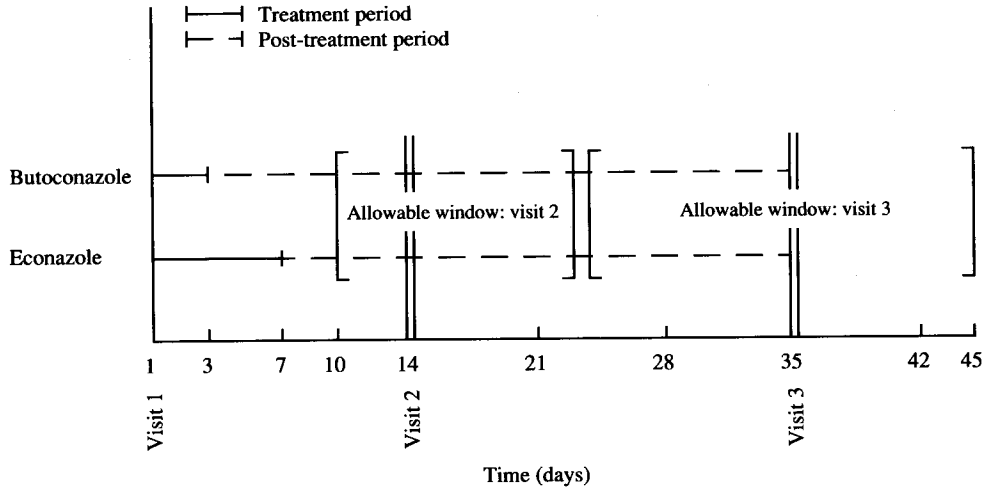

Fig. 1. Treatment and assessment schedule for patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days or 1% econazole nitrate cream for 7 days.

average of 12 days; for 57% of the patients this was the first episode of the disease. At admission to the study, patients in the two treatment groups were similar in age, disease duration and history, obstetric history and contraceptive use (Table 1).

Of these 75 women, four patients with negative culture results at baseline and five who did not return to follow-up were excluded from both efficacy and safety analyses; thus 66 patients (30 treated with butoconazole and 36 with econazole) were evaluated. A further two patients using econazole who had violated the protocol and one who had received butoconazole (despite a negative fungal culture at baseline) were excluded from the efficacy analyses; therefore, the results from 63 patients (29 treated with butoconazole and 34 treated with econazole), all of whom had provided cultures that yielded *C. albicans*, were analysed for efficacy.

Clinical variables

At visit 1, the only efficacy variable that was significantly different ($P = 0.0459$) for the two treatment groups was vulval oedema. Vulval erythema, oedema, excoriation and ulceration, and vaginal discharge, itching, burning, erythema, oedema, excoriation and ulceration responded to both butoconazole and econazole (Fig. 2). All mean severity scores recorded at visit 2 were significantly lower than those recorded at visit 1, except for vulval oedema in both treatment groups and vaginal oedema in econazole-treated patients; vaginal and vulval ulceration and excoriation were not analysed statistically because sample sizes were inadequate. There were no statistically significant differences between the two treatment groups at visit 2, with both drugs

Table 1
Characteristics of patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days or 1% econazole nitrate cream for 7 days

Variable	Butoconazole ($n = 35$)	Econazole ($n = 40$)	Total ($n = 75$)	*P*-value
Age (years)				
Mean ± SD	31.17 ± 9.80	29.28 ± 9.08	30.16 ± 9.41	0.3873[a]
Range	18 – 56	16 – 49	16 – 56	
Duration of current vaginitis (days)				
Mean ± SD	11.60 ± 14.80	12.25 ± 11.56	11.95 ± 13.08	0.8317[a]
Range	0 – 84	0 – 70	0 – 84	
First episode of vaginitis	19 (54.3%)	24 (60.0%)	43 (57.3%)	0.6177[b]
Nulliparous	11 (31.4%)	24 (47.5%)	30 (40.0%)	0.1564[b]

[a]Student's *t*-test.
[b]χ^2-test.

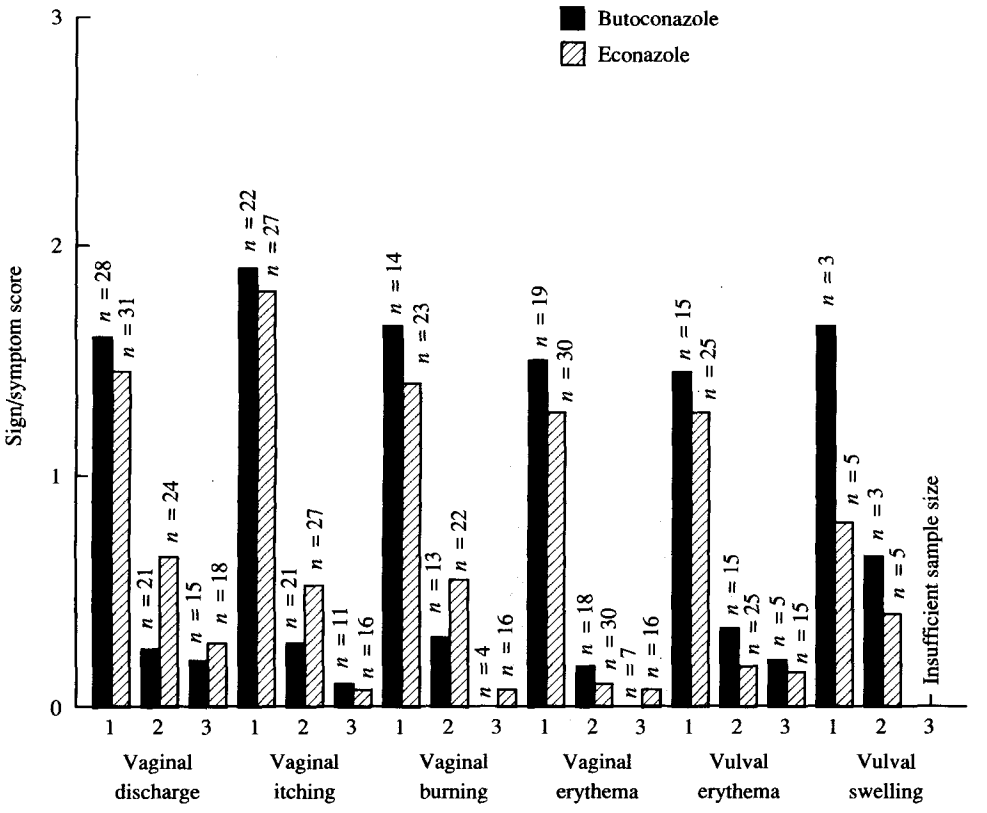

Fig. 2. Vaginal and vulval signs and symptoms measured on visit 1 (day 1), visit 2 (days 10 – 23) and visit 3 (days 24 – 45) on a scale of 0 – 3 (0, none; 3, severe) in patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days or 1% econazole nitrate cream for 7 days.

being equally effective in diminishing the signs and symptoms of vulvovaginal candidiasis. At visit 3, the mean scores for the efficacy variables were lower than those at visit 2, indicating that clinical improvement continued until the end of the study.

The overall clinical response rating was based on the reduction and amelioration of the signs and symptoms (Table 2), with 21 patients in each group having either a 'very good' or a 'good' response (93.1% of butoconazole users, 84.3% of econazole users), two in each group having a 'fair' response (6.9% and 6.3%, respectively) and three (9.4%) in the econazole group having no clinical response; the difference between the treatment groups was not statistically significant.

Laboratory variables

All patients admitted to the study had positive potassium hydroxide smears at visit 1. At visit 2, the potassium hydroxide smears of 24/27 (89%) patients treated with butoconazole demonstrated no *C. albicans* infection (Fig. 3); by comparison, 28/33 (85%)

Table 2
Overall clinical response for patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream or 3 days or 1% econazole nitrate cream for 7 days

	No. of patients	
Response	**Butoconazole**	**Econazole**
Very good	26 (89.7%)	24 (75.0%)
Good	1 (3.4%)	3 (9.4%)
Fair	2 (6.9%)	2 (6.3%)
No clinical response	0	3 (9.4%)
Total	29	32

$P = 0.1296$ compared with econazole (Student's t-test on ranks).

patients treated with econazole had no *Candida* present. At visit 3, 15/16 (94%) butoconazole-treated patients who had shown a negative potassium hydroxide smear at visit 2 remained free of infection and of those treated with econazole 17/20 (85%) remained free. None of the treatment differences at visit 2 or 3 was statistically different.

Cultures of samples obtained from all patients admitted to the study contained the fungus at visit 1. Of the butoconazole-treated patients, 24/27 (89%) were free of *C. albicans* at visit 2 (Fig. 4) and, of those treated with econazole, 24/30 (80%) were free of the organism. At visit 3, 15/16 (94%) butoconazole users and 17/20 (85%) econazole users remained free of infection, as indicated by culture results, with none of the treatment differences being statistically significant.

Cure rates

There were no statistically significant differences between the two treatment groups in terms of microbiological cure rates, clinical cure rates or therapeutic cure rates at either visit 2 or 3; however, both at visits 2 and 3, the percentages of patients cured were consistently higher among those treated with butoconazole.

Microbiological cure, defined as a combination of negative fungal cultures and negative potassium hydroxide smears, occurred in 85% of the butoconazole-treated patients at visit 2, with a relapse of 6% at visit 3, and there was a microbiological cure at visit 2 of 80% for econazole-treated patients and a relapse of 15% at visit 3.

The complete absence of signs and symptoms of vaginal candidiasis, excluding vaginal discharge, was considered a clinical cure. At visit 2 this occurred in 78% of butoconazole users compared with in 64% of econazole users and at visit 3 94% of butoconazole-treated women and 80% of econazole-treated women remained clinically cured.

At visit 2 the incidence of therapeutic cure, consisting of both clinical and microbiological cures, was 70% for those given butoconazole and 47% for those treated with

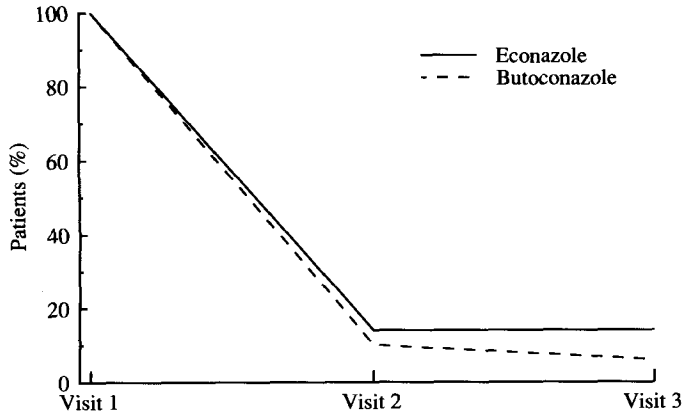

Fig. 3. Incidence of positive potassium hydroxide smears determined on visit 1 (day 1), visit 2 (days 10 – 23) and visit 3 (days 24 – 45) in patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days (n = 29) or 1% econazole nitrate cream (n = 34) for 7 days.

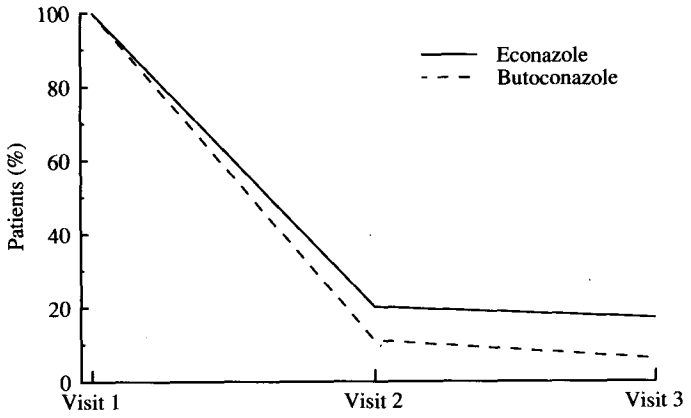

Fig. 4. Incidence of positive fungal cultures determined on visit 1 (day 1), visit 2 (days 10 – 23) and visit 3 (days 24 – 45) in patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days (n = 29) or 1% econazole nitrate cream for 7 days (n = 34).

econazole, and at visit 3 94% of the patients who had used butoconazole and 80% of those who had used econazole were therapeutically cured.

The investigators evaluated cures on the basis of patient results at their final follow-up visit, whether that visit was the second or the third, and they concluded that 83% of the patients who had received butoconazole and 59% of those who had received econazole were therapeutically cured (Fig. 5). This difference was clinically significant and approached statistical significance ($P = 0.055$).

Adverse events

No serious adverse events were either reported or observed, although one econazole-treated patient, who was considered microbiologically cured at visit 2, had vulval and vaginal erythema and swelling withdrew from the study at that time because of these symptoms. Overall, two patients using butoconazole had a total of five complaints – pruritus, headache, increased temperature, painful sutures and spotting – and three patients using econazole had a total of four complaints – spotting, vaginal odour, stinging and erythema.

DISCUSSION

In the present comparative study, the treatment time using 2% butoconazole nitrate cream was less than half that using 1% econazole nitrate cream but, in spite of this shorter treatment period of 3 days compared with 7 days, results were at least comparable and often superior. At both 2 and 3 weeks following the end of treatment, the percentages of patients considered cured according to microbiological,

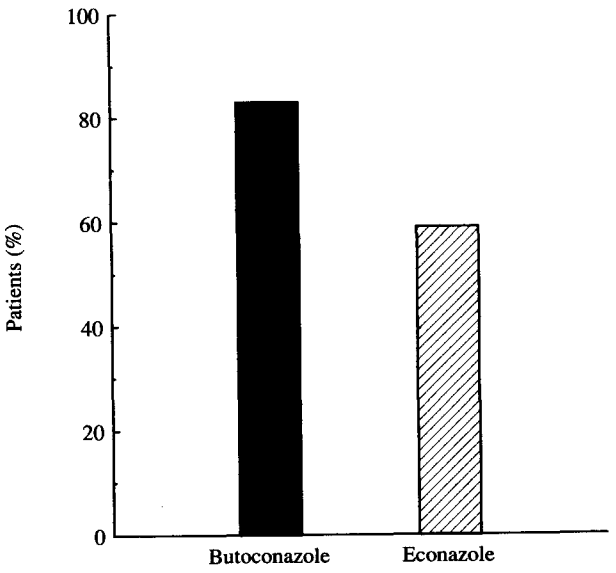

Fig. 5. Incidence of cure assessed by investigators at visit 3 (days 24 – 45) in patients with vulvovaginal candidiasis treated with 2% butoconazole nitrate cream for 3 days ($n = 29$) or 1% econazole nitrate cream for 7 days ($n = 34$).

clinical or therapeutic criteria were consistently higher among those treated with butoconazole, although the differences were not statistically different. According to the investigators' evaluations of the results at the final visits, the therapeutic cure rate was 83% for those who had been treated with butoconazole as compared with 59% for those who had been treated with econazole, a difference approaching statistical significance (P = 0.055).

Both treatments were safe and well tolerated, and only minor complaints were reported by two patients receiving butoconazole and by three receiving econazole.

Shorter periods of administration generally result in better patient compliance and improved patient compliance leads to higher success rates. Since the period of treatment with butoconazole in the present trial was considerably shorter than that with econazole and since results with butoconazole in some cases were equal to and in other cases superior to those with econazole, the efficacy of this short-duration butoconazole regimen was considered to be greater than that of the longer econazole regimen.

The present study demonstrates that a cream containing 2% butoconazole nitrate was a highly effective and safe antimycotic agent for the treatment of vulvovaginal candidiasis, a disease of increasing frequency, with symptoms that can be intolerable. It is concluded, therefore, that it is preferable to treat vulvovaginal candidiasis with a 2% butoconazole cream rather than a 1% econazole nitrate cream because of the former's shorter duration of treatment and its superior clinical and microbiological performance.

REFERENCES

1. Gardner HL: Candidiasis. In: *Benign Diseases of the Vulva and Vagina* (Gardner HL, Kaufman RH, eds). Boston: GK Hall, 1981; pp 217 – 242.
2. Beggs WH: Influence of growth phase on the susceptibility of *Candida albicans* to butoconazole, oxiconazole, and sulconazole. *J Antimicrob Chemother* 1985; **16:** 397 – 399.
3. Holt RJ: Topical pharmacology of imidazole antifungals. *J Cutan Pathol* 1976; **3:** 45 – 59.
4. Droegemueller W, Adamson DG, Brown D, *et al:* Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. *Obstet Gynecol* 1984; **64:** 530 – 534.
5. Sargent EC, Pasquale SA: Evaluation of monistat cream (miconazole nitrate 2%) in a reduced regimen for the treatment of vulvovaginal candidiasis. *J Reprod Med* 1977; **19:** 67 – 69.
6. 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.
7. Forssman L, Milsom I: Treatment of recurrent vaginal candidiasis. *Am J Obstet Gynecol* 1985; **152:** 959 – 961.
8. Heel RC, Brogden RN, Speight TM, *et al:* Econazole: review of its antifungal activity and therapeutic efficacy. *Drugs* 1978; **16:** 177 – 201.
9. Brown D, Binder GL, Gardner HL, *et al:* Comparison of econazole and clotrimazole in the treatment of vulvovaginal candidiasis. *Obstet Gynecol* 1980; **56:** 121 – 123.
10. Walker KAM, Braemer AC, Hitt S, *et al*: 1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-n-butyl]-1*H*-imidazole nitrate, a new potent antifungal agent. *J Med Chem* 1978; **21:** 840 – 843.
11. Matthews TR: Butoconazole. Pharmacologic considerations, chemistry and microbiology. *J Reprod Med* 1986: **31** (suppl 7): 655 – 657.
12. Jacobson JB, Hajman AJ, Wiese J, *et al:* A new vaginal antifungal agent – butoconazole nitrate. *Acta Obstet Gynecol Scand* 1985; 241 – 244.
13. Bradbeer CS, Mayhew SR, Barlow D: Butoconazole and miconazole in treating vaginal candidiasis. *Genitourin Med* 1985; **61:** 270 – 272.
14. Armitage P: *Statistical Methods and Medical Research*, 1st edn. Oxford: Blackwell Scientific, 1971.
15. Siegel S: *Nonparametric Statistics for the Behavioural Sciences*. New York: McGraw-Hill, 1956.