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CLINICAL STUDY

An evaluation of butoconazole nitrate 2% Site Release® vaginal cream (Gynazole-1®) compared to fluconazole 150 mg tablets (Diflucan®) in the time to relief of symptoms in patients with vulvovaginal candidiasis

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Abstract

Background. It is estimated that as many as 13 million cases of vulvovaginal infection occur in the United States annually, the majority of which are the result of *Candida albicans* infection. The symptoms of vulvovaginal infections are often painful and distressing to the patient. The objective of this study was to compare the time to symptomatic relief of vulvovaginal candidiasis (VVC) with butoconazole nitrate 2% Site Release® vaginal cream (Gynazole-1®) and oral fluconazole 150 mg tablets (Diflucan®).

Methods. This randomized, open-label, parallel study evaluated 181 female patients with moderate to severe symptoms of VVC. Patients were randomized to single-dose therapy with either butoconazole nitrate 2% Site Release® vaginal cream or fluconazole. The primary outcome measure was the time to onset of first relief of symptoms. Secondary measures included the time to overall relief of symptoms and the reinfection rate over the first 30 days following treatment. The overall safety of both products was investigated through the collection of adverse event reports.

Results. The median time to first relief of symptoms occurred at 17.5 h for butoconazole patients as compared to 22.9 h for fluconazole patients ($p < 0.001$). The time at which 75% of patients experienced first relief of symptoms was 24.5 h versus 46.3 h for butoconazole and fluconazole, respectively ($p < 0.001$). By 12- and 24-h post-treatment, 44.4% and 72.8% of patients in the butoconazole treatment group reported first relief of symptoms versus 29.1% and 55.7% of patients in the fluconazole group ($p = 0.044$ and $p = 0.024$ respectively). In patients experiencing first relief of symptoms within 48 h of dosing, the median time to first relief of symptoms in the butoconazole treatment group was significantly shorter at 12.9 h compared to 20.7 h for the fluconazole treatment group ($p = 0.048$). There were no significant differences between the two groups with respect to time to total relief of symptoms or reoccurrence of infection within 30 days of treatment. Butoconazole therapy was shown to have fewer reported adverse events, including drug-related adverse events, than fluconazole therapy. Vulvovaginal pruritis and vulvovaginal burning were the most common drug-related adverse events attributed to butoconazole. Headache, diarrhea, nausea, upset stomach and skin sensitivity were the most common drug-related adverse events attributable to fluconazole.

Conclusions. Single-dose butoconazole nitrate 2% Site Release® vaginal cream provides statistically significant improvement in time to first relief of symptoms in the treatment of VVC compared to fluconazole. There is no difference between these two treatments with respect to total relief of symptoms or reinfection rate. Although there was no significant difference in the incidence of adverse events judged by the investigator to be treatment-related, butoconazole treatment did result in fewer patients experiencing adverse events than fluconazole.

Keywords: *Butoconazole, fluconazole, vulvovaginal condidiasis, bioadhesive, vaginal drug delivery, vaginitis*

Introduction

Vulvovaginal infections are one of the most frequently diagnosed vaginal infections in the United States with approximately 13 million cases occurring per year [1]. Nearly all vulvovaginal infections are caused by the yeast *Candida* spp., with over 80% of all infections due to *Candida albicans* [2]. It has been estimated that 75% of all females will experience at least one episode of vulvovaginal candidiasis (VVC) with approximately 40% to 50% reporting a reoccurrence during their lifetime [3]. Although 25% to 40%

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of all infections are asymptomatic, in those patients who do develop symptoms these are often painful and uncomfortable and can include intense itching, irritation, vaginal discharge and dysuria [1–3].

The most commonly prescribed treatment for VVC infection in recent years has been the imidazole antifungals. These come in a number of different formulations including single, three and seven day cream applications, vaginal suppositories and oral tablets. These imidazole antifungals are available either by prescription or over-the-counter. While all of these products are effective when taken according to the approved dosage regimen, poor compliance, ease of use and side effect profile can prevent successful therapy in as many as 50% of women treating VVC infection [4]. In order to improve patient compliance, significant research and development has focused on developing single-dose imidazole formulations that are easy to use, effective and bring early relief for the signs and symptoms of VVC to the patient [5].

Currently four single-dose therapies are available in the United States. These include an over-the-counter vaginal ointment and cream containing 6.5% tioconazole (multiple manufacturers), an over-the-counter vaginal ovule containing 1200 mg of miconazole nitrate (Monistat-1®, McNeil-PPC, NJ), a prescription-only butoconazole nitrate 2% single application vaginal cream (Gynazole-1®, Ther-Rx Corporation, St Louis) and prescription-only fluconazole 150 mg oral tablets (Diflucan®, Pfizer Inc, NY).

Gynazole-1® was developed with vagisite, a patented Site Release® technology. It is a single-dose, bioadhesive, butoconazole nitrate 2% Site Release® vaginal cream that is available in a prefilled, single-use applicator. The objective of developing this product was to provide patients with a single-dose topical formulation that was simple to use and would improve treatment compliance. Clinical studies demonstrated that this single-use formulation has a median vaginal retention time of 4.2 days compared with 2.57 days for the standard 2% cream [6]. Gynazole-1® was approved for marketing by the Food and Drug Administration (FDA) of the United States in 1999.

Fluconazole (Diflucan®) is the only orally available imidazole with approved labeling specific for the treatment of VVC. The recommended dosing regimen is a single 150 mg oral tablet. Several clinical studies have compared a single fluconazole 150 mg oral tablet with a number of different antifungal vaginal topical and vaginal suppository preparations. Review of these studies suggests that the overall cure rate with fluconazole 150 mg tablets is similar to that seen with other preparations [7–15].

As the symptoms of VVC are often painful and uncomfortable to the patient, time to first relief and time to total relief of symptoms should be an important factor for both the patient and caregiver to consider when deciding on a suitable therapy for a particular patient. The objective of this study was to compare the time to relief of symptoms due to moderate to severe VVC, using either butoconazole nitrate 2% Site Release® vaginal cream single-dose or fluconazole single-dose 150 mg oral tablets.

Materials and methods

Study design

This clinical trial was an open-label, randomized, parallel design study conducted at thirteen research facilities across the United States. Prior to initiation of the study, the protocol and informed consent were reviewed and approved by an independent Institutional Review Board. The study was conducted from May to November 2003.

Study population

To be eligible for participation, study patients had to meet the following inclusion criteria: female, aged 18 years or older, not pregnant as determined by urine pregnancy test and, if of child-bearing potential, willing to use a reliable method of contraception during the duration of the study. Patients verified understanding of the requirements of the study and willingness to participate by signing the informed consent form.

Confirmation of current vulvovaginal candidiasis (VVC) infection was made by use of KOH wet mount preparation, pelvic examination and patient's reporting of signs and symptoms. As the primary study endpoint was time to first relief of symptoms and not therapeutic efficacy, yeast cultures to confirm the KOH wet mount were not performed. Each patient was required to indicate the overall severity of major symptoms (itching, burning, irritation, etc.) on a scale from 0 (no symptoms) to 10 (severe symptoms). A total severity score of $\geqslant 4$ was required for inclusion in the study. Other than VVC infection, patients had to be in general good health, free of any other concurrent vaginal infection, and, in the opinion of the investigators, therapy with either butoconazole or fluconazole was warranted. Patients who had a history of recurrent VVC, as defined as more than four episodes in the previous 12 months, or were suspected of having a concurrent vaginal infection such as bacterial vaginosis, trichomoniasis or herpetic lesions were not eligible for participation. Patients who were menstruating, or anticipated they would start menstruating within two days of study drug dosing, were also excluded from the study. Any patient who had used any intravaginal or systemic antifungal medication within the previous

seven days, or had used any intravaginal product such as a spermicide, medicated douche or feminine spray within two days was also excluded. Current treatment for any medical condition that included systemic antimycotics, corticosteroids or immunosuppressive drugs also resulted in exclusion. In addition, a patient was not eligible if she had a medical history of hypersensitivity to any of the active or inactive ingredients of either of the study drugs or similar products, was taking any concurrent medication that was contraindicated with either of the test products, or in the investigator's opinion was not suitable for inclusion in the study. None of the patients enrolled could have participated in a previous research study within the last 30 days and were only eligible to participate on one occasion.

A total of 181 patients were enrolled into the study.

Treatments

Using a computer-generated randomization that was prepared prior to the study, patients who met the inclusion/exclusion criteria were allocated to one of two treatment groups. Patients in group A received a single application of approximately 5 g of butoconazole nitrate 2% Site Release® vaginal cream (Gynazole-1®, Ther-Rx Corporation). Patients randomized to group B received one fluconazole 150 mg tablet (Diflucan®, Pfizer). Patients were required to take the medication at the investigator's office and the time of dosing was recorded. Whenever possible, patients were dosed before noon, although some subjects received their doses in the early afternoon.

Following dosing, each patient was provided with a patient diary in which they were requested to record the date and time they first started to feel relief of symptoms, and the date and time they had complete relief of symptoms. Patient evaluated symptoms included vaginal itching, burning, and irritation. Patients were also requested to record any adverse events or concomitant medications.

Follow-up visits

Five to ten days following dosing, patients were required to return to the investigator's office for a follow-up visit. During this visit, the patient diary was checked for completion and the patient was questioned about any adverse events or concomitant medications.

Approximately 30 days after dosing, a telephone call was made to the patient to investigate whether she had required additional treatment for her yeast infection. If she had previously claimed that the initial VVC infection had been resolved, she was asked whether she had experienced a reinfection.

Statistical analysis

Baseline demographics (age, race, number of episodes of VVC in the previous 12 months and severity score) were tabulated and compared using descriptive statistics. Time to first relief of symptoms and time to total relief of symptoms for each individual patient were calculated using the dosing time and the time reported for each by the patient. Analysis of this data was performed using Kaplan–Meier estimates and 95% Confidence Interval analysis. Adverse event reports were coded into standardized MedDRA version 6.1 terminology and tabulated by treatment and event.

Statistical tests of superiority of butoconazole compared to fluconazole were two-sided and conducted at a 5% level of significance. p Values of less than 0.05 were considered statistically significant. All eligible patients who reported a date or time to first relief or total relief were included in the corresponding analysis. All patients who received study drug were included in the safety analysis.

Based upon exponential distributions of time to event, it was determined *a priori* that 150 patients (approximately 75 per treatment group) would provide 80% power to detect at least a 20% difference in superiority of butoconazole compared to fluconazole for time to first relief of symptoms.

Results

A total of 181 women were randomized to the study, with 93 assigned to butoconazole treatment and 88 assigned to fluconazole treatment. A total of 160 patients (81 in the butoconazole treatment group and 79 in the fluconazole treatment group) were eligible for inclusion in the analysis of time to first relief. A total of 136 patients (67 for butoconazole and 69 for fluconazole) were eligible for analysis of time to total relief, and all 181 patients were included in the safety analysis. Twenty-one patients (12 butoconazole patients and nine fluconazole patients) were excluded from the time to first relief analysis, 18 of which were due to missing data. Forty-five subjects were excluded from the time to total relief analysis (26 butoconazole-treated patients and 19 fluconazole-treated patients), 41 of which were due to missing data.

Baseline demographics were similar between the two groups. The mean age $\pm$ standard deviation (SD) was 38.8 ± 13.8 years for the butoconazole group and 37.0 ± 12.2 years for the fluconazole treatment group. The mean number of vaginal yeast infections in the previous year was 0.8 and 0.9 for butoconazole and fluconazole groups respectively. The mean baseline severity score $\pm$ SD for butoconazole was 6.9 ± 1.7 and 6.8 ± 1.9 for fluconazole.

As seen in Figure 1, during the course of all reported hours to first symptom relief, a higher percentage of patients treated with butoconazole experienced first relief of symptoms at all time points compared to fluconazole. Fifty percent of patients receiving butoconazole experienced first relief of symptoms within 17.5 h versus 22.9 h with fluconazole. The cumulative distribution of the time to first symptom relief was statistically significant between butoconazole and fluconazole ($p = 0.006$). Within 24.5 h, 75% of butoconazole-treated patients experienced first relief of symptoms. In contrast, only 55.7% of fluconazole patients had first relief of symptoms within 24 h and it took nearly two full days, 46.3 h, for 75% of fluconazole patients to exhibit first relief of symptoms, an approximate difference of 21.8 h (95% CI of the difference 21.7, 21.9, $p < 0.001$).

Over the first 48 h, the time to first relief of symptoms was consistently shorter with butoconazole therapy, reaching statistical significance between the two therapies as early as 2 h post-treatment (Table I). The percentage of patients exhibiting first relief of symptoms at 12 h was 44.4% for butoconazole and 29.1% for fluconazole ($p = 0.044$). Within the first 48 h post-treatment, 91.4% of butoconazole-treated patients experienced first relief of symptoms compared to 81% for patients treated with fluconazole.

Throughout the study, the time to complete relief of symptoms was similar between the two treatment regimens ($p = 0.182$), as seen in Figure 2. The median time for total relief was 64.0 h for butoconazole treatment and 73.5 h for fluconazole treatment. Within 72 h of study treatment, 97.5% of butoconazole-treated patients experienced some relief of symptoms and 58.2% achieved complete relief. Similarly, 93.7% of patients treated with fluconazole experienced some relief at 72 h and 47.8% achieved complete relief. Among patients evaluable for complete relief, a total of nine patients (13.4%) treated with butoconazole and 13 patients (18.8%) treated with fluconazole experienced a reoccurrence of VVC within 30 days of study treatment.

Overall, 66 adverse events occurred in the butoconazole treatment group and 99 adverse events in the fluconazole treatment group. Among these events, 16 and 32 were considered drug-related in the corresponding treatment groups. The most commonly reported adverse events are listed in Table II. Adverse events considered to be drug-related were reported by 11.8% of butoconazole-treated patients compared to 20.5% of patients treated with fluconazole ($p = 0.114$). The most common drug-related adverse events reported for both treatments are listed in Table III. For butoconazole-treated patients, the most common drug-related adverse events included vulvovaginal pruritis and vulvovaginal burning. The most common drug-related adverse events attributed to fluconazole therapy were headache, diarrhea, nausea, skin sensitivity and upset stomach.

Discussion

Both butoconazole and fluconazole offer clinicians an effective regimen for the treatment of VVC with the added benefit of being a single-dose regimen, designed to increase patient compliance over multiple-dose therapies [5,9–11]. The goal of single-dose therapy is to increase patient compliance without sacrificing time to onset of relief of the symptoms of VVC. This study has shown that topical therapy exhibits a more rapid onset to relief of symptoms of VVC versus systemic therapy.

For this study, the overall time to complete relief of symptoms when treated with an oral versus a topical therapy, are consistent with those reported in the literature [5,7–11,16]. Similarly, the time to first relief of symptoms for patients treated with fluconazole in this study is similar to the results reported in studies of similar design using fluconazole. In a study comparing oral fluconazole with terconazole vaginal cream, Seidman et al. [17] reported that the median time to initial relief with fluconazole was 21.3 h. This correlates well with the 22.9 h seen in this study.

In the current study, for patients experiencing first relief of symptoms within 48 h, the time to onset of symptom relief was shorter with butoconazole therapy when compared to fluconazole therapy (12.9 h versus 20.7 h, $p = 0.048$). Overall, within 12 h of dosing, approximating when the majority of study patients may be preparing for bedtime, almost half of the women treated with butoconazole experienced first relief of their symptoms. With fluconazole therapy, within this same 12 h period, approximately one third of the study patients had experienced first relief of symptoms. From a clinical perspective, 24 h is a reasonable period of time for purposes of gauging general effectiveness of therapy for VVC. For butoconazole-treated patients, 72.8% experienced first symptom relief at one day versus 55.7% for fluconazole ($p = 0.024$). Consequently, this data may serve to support a clinician who informs patients treated for VVC that symptom relief may take longer with oral fluconazole than with topical butoconazole vaginal cream. Interestingly, in a survey conducted on women in 1992 with VVC, 71% reported that 'fast relief' of symptoms was the most important aspect of treating a yeast infection [18]. Treating with topical therapy more directly addresses and impacts this overwhelming patient priority.

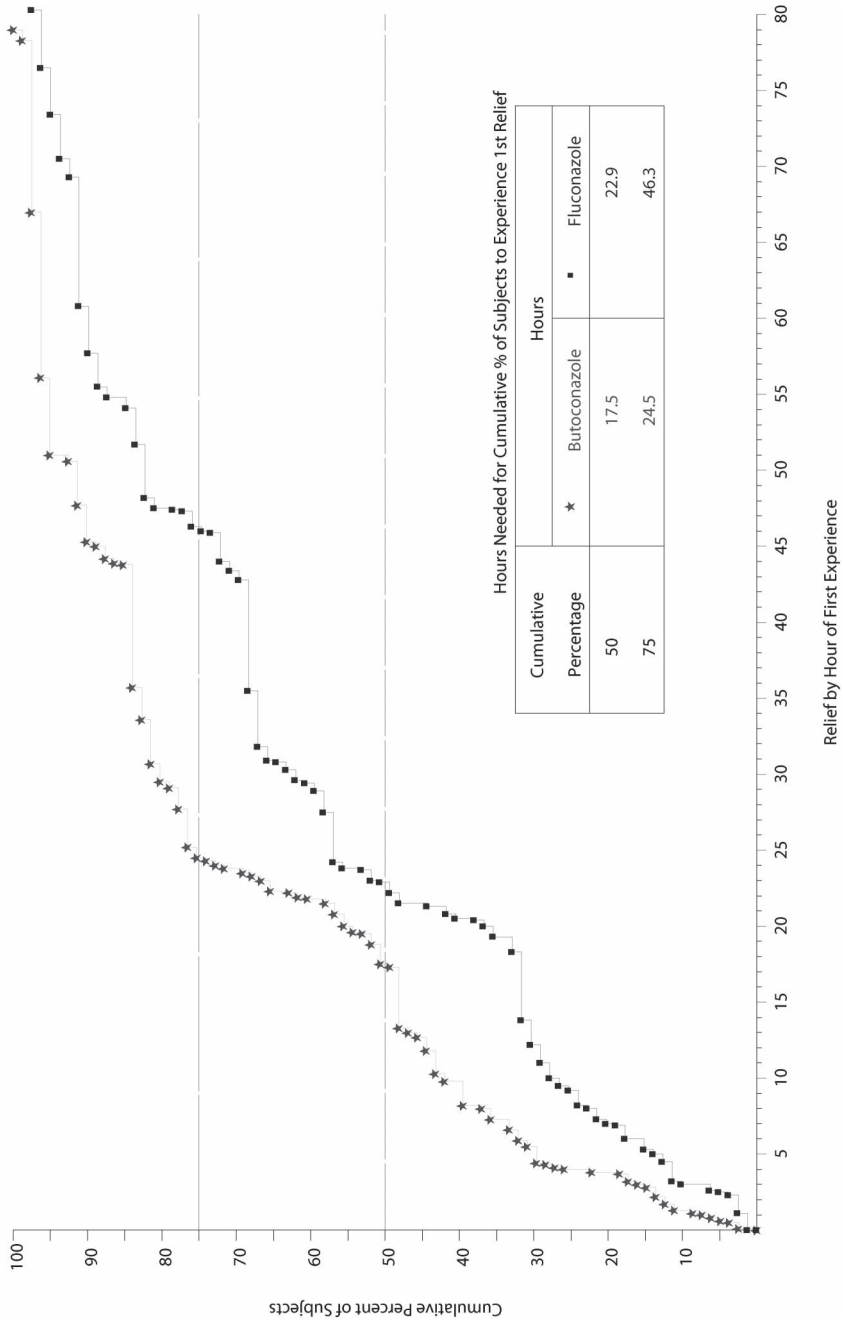

Figure 1. Time to first symptom relief (hours).

Table I. Cumulative percentage of patients with first relief of symptoms following dosing by treatment group.

Hours after dosing	Butoconazole group Cumulative % ($N = 81$)	Fluconazole group Cumulative % ($N = 79$)	p value (*statistically significant)
2	12.3	2.5	0.018*
4	25.9	11.4	0.019*
6	32.1	17.7	0.036*
8	37.0	22.8	0.049*
10	42.0	27.8	0.061
12	44.4	29.1	0.044*
14	48.1	31.6	0.033*
16	48.1	31.6	0.033*
18	50.6	31.6	0.015*
20	55.6	36.7	0.017*
22	61.7	48.1	0.083
24	72.8	55.7	0.024*
26	76.5	57.0	0.009*
28	77.8	58.2	0.008*
30	80.2	62.0	0.011*
32	81.5	67.1	0.037*
34	82.7	67.1	0.022*
36	84.0	68.4	0.020*
38	84.0	68.4	0.020*
40	84.0	68.4	0.020*
42	84.0	68.4	0.020*
44	86.4	72.2	0.026*
46	90.1	74.7	0.010*
48	91.4	81.0	0.057

Patients enrolled in this study were encouraged to dose study drugs in the morning where possible to prevent first relief of symptoms occurring during sleeping hours. It was determined that no subjects in this study reported first relief of symptoms between the hours of 12:30 am to 5:30 am, therefore a sub-analysis was conducted to investigate the possible effect that time spent in sleep may have on reported relief of symptoms. Butoconazole-treated subjects dosed prior to 11:00 am experienced first relief of symptoms the same day (median 11.5 h). Whereas those butoconazole-treated subjects dosed after 11:00 am had a median time to first relief of symptoms of 19.6 h. For fluconazole-treated patients, the median time to first relief of symptoms was 29.6 h at or before 11:00 am and 21.5 h after 11:00 am. These results should not be interpreted that dosing in the afternoon delays time to onset of relief, rather patients who are asleep may not realize a decrease in symptoms until they awaken. The median time of dosing in this study was 11:50 am for butoconazole-treated patients and 11:30 am for fluconazole-treated patients. Therefore, the reported time to first relief of symptoms of 17.5 h for butoconazole-treated patients may reflect a delay for the time these subjects spent in slumber (Figure 3).

The overall objective of any therapy for the treatment of vaginal candidiasis is the eradication of the infecting organism and the absence of any signs and symptoms. A limitation in the current study is the absence of definitive data on the true rates of cure based upon follow-up mycological examination. This study, however, was designed to identify the time to first relief of the symptoms of VVC following therapy with either a single-dose oral or a single-dose vaginal regimen. As a result, the time to total relief of symptoms and apparent reinfection rate are used as general markers of the absence of the infecting organism. The rates of time to total relief and rates of reinfection were not statistically different between the two study medications.

In addition, the time to relief of symptoms and reinfection rates in this study support other published data that butoconazole is at least as efficacious in microbiological cure as other topically approved therapies [5,19,20]. The microbiological activity of butoconazole tested favorably against four other commonly used azole antifungals in an *in vitro* susceptibility study by Lynch and Sobel [19]. The authors reported consistently high levels of antifungal activity and comparatively lower MICs for

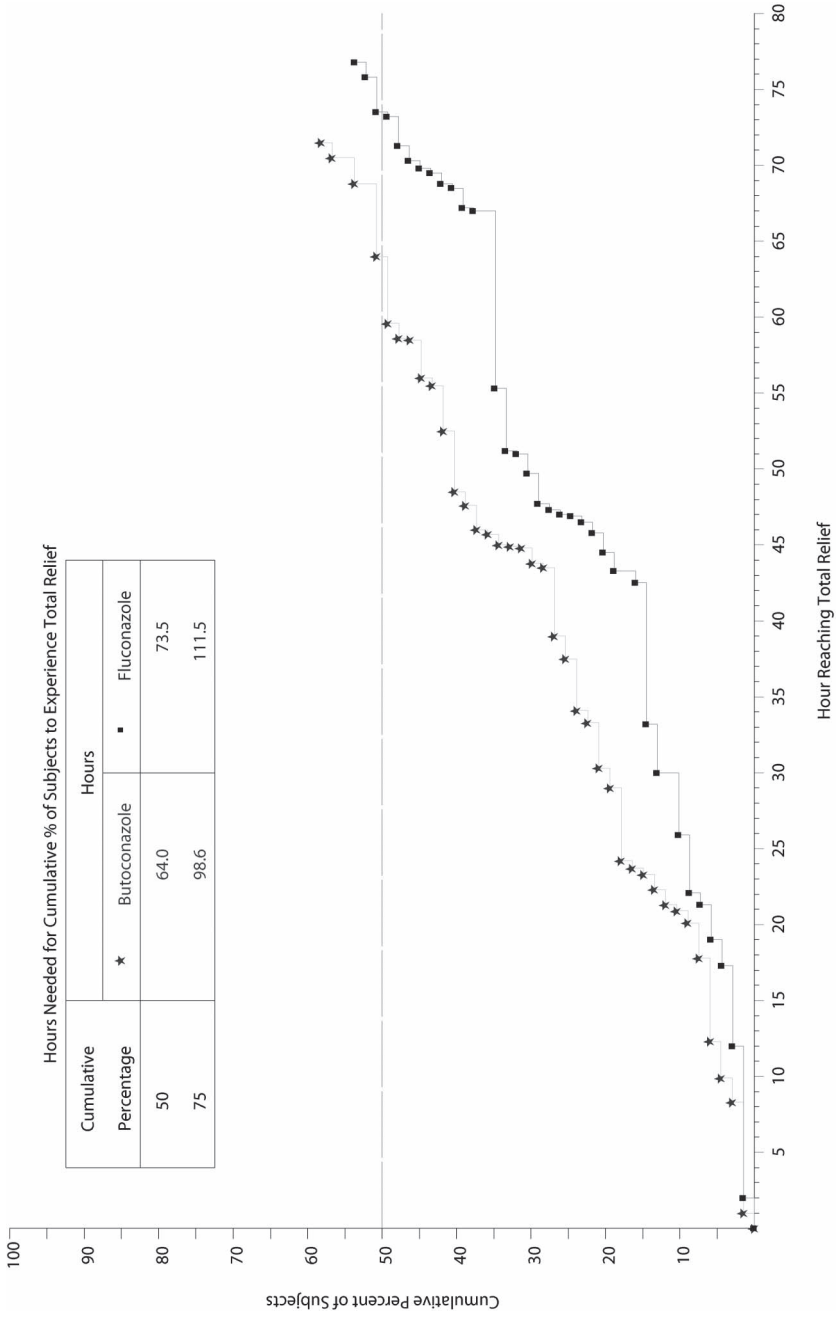

Figure 2. Time to total symptom relief (hours).

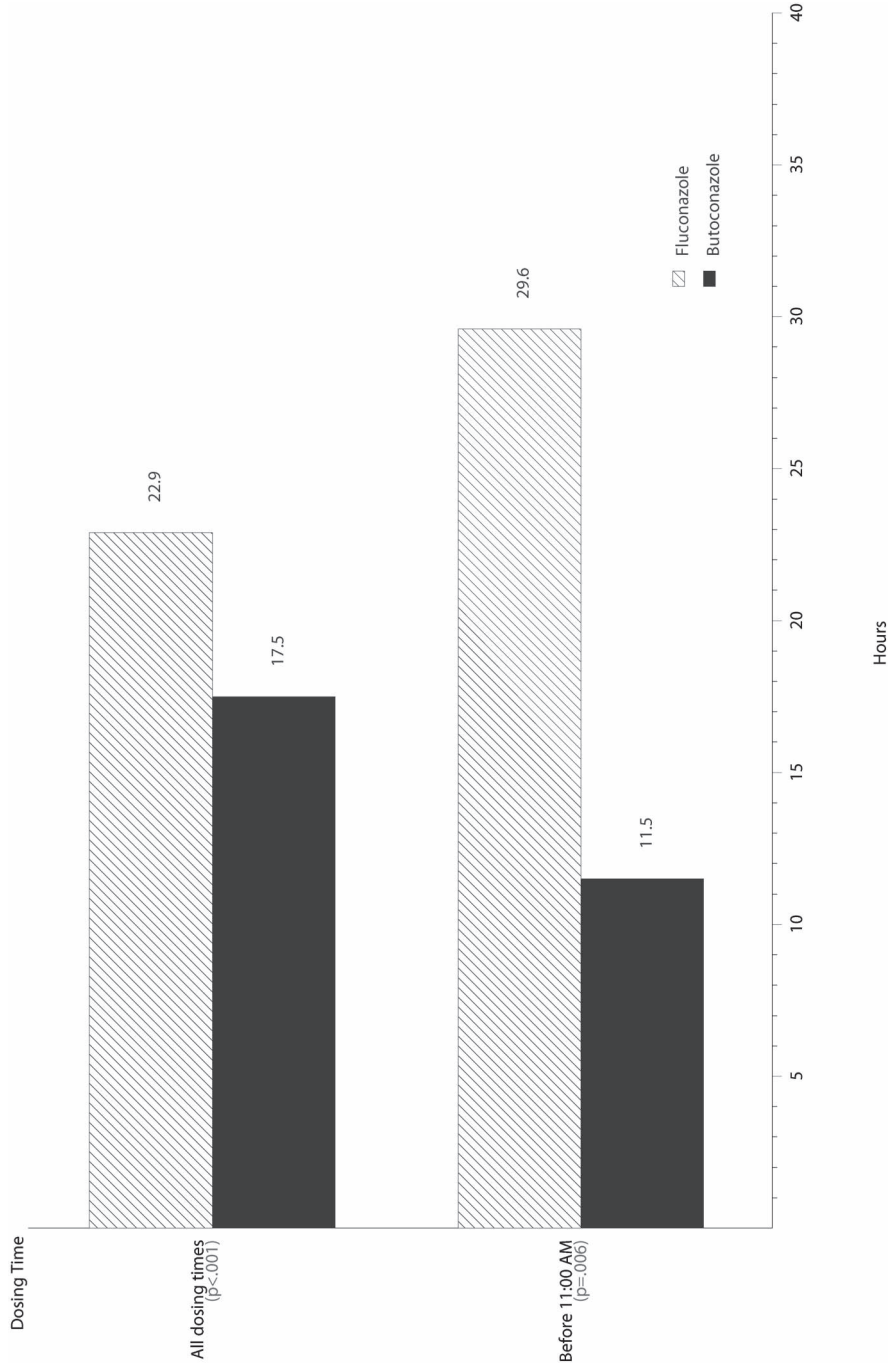

Figure 3. Median time to first symptom relief with sleep-effect isolated.

Table II. Most common patient-reported adverse events whether or not drug-related.

Adverse event	Butoconazole-treated group	Fluconazole-treated group
Headache	11	10
Vulvovaginal candidiasis	8	8
Vulvovaginal pruritis	3	3
Upper respiratory infection	3	2
Vulvovaginal burning	3	2
Abdominal cramps	3	1
Abdominal pain	1	3
Flatulence	0	4
Nasal congestion	2	2
Nausea	1	2

Table III. Most common patient-reported adverse events, drug-related.

Adverse Event	Butoconazole-treated group	Fluconazole-treated group
Headache	1	6
Vulvovaginal pruritis	3	1
Vulvovaginal burning	3	0
Diarrhea	0	2
Nausea	0	2
Skin sensitivity	0	2
Upset stomach	0	2
Vulvovaginal irritation	1	1
Abdominal pain	0	1
Burning after intercourse	0	1

butoconazole against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *S. cerevisiae*, *C. lusitaniae*, *C. krusei*, *C. kefyr*, and *C. stellatoidea*. In a separate portion of this same study, fluconazole similarly showed excellent activity against *C. albicans*, but appeared to be far less active against the other species listed above, particularly *C. glabrata* and *S. cerevisiae*. While *in vitro* susceptibility testing cannot always predict *in vivo* activity or clinical success, it does offer a valuable tool for the clinician in evaluating and understanding the spectrum of activity of both butoconazole and fluconazole against pathogens commonly encountered in clinical practice.

Although this study was not powered to compare the incidence of adverse events between treatment groups, fewer patients in the butoconazole-treated group reported drug-related adverse events than patients treated with fluconazole. However this difference did not reach statistical significance, as there was an insufficient number of reported drug-related adverse events to reach any conclusions about statistical significance. A larger trial, designed to evaluate drug-related adverse events, may be warranted to further investigate this finding. The reduced incidence of adverse events reported for butoconazole, whether or not drug-related, may be an indication of improved tolerability to a topical therapy for a topical infection such as VVC. In addition to an increased potential for adverse events, systemic therapy for a local infection poses an increased risk for drug interactions. According to the Diflucan® prescribing information, drug interactions have been reported with cimetidine, rifampin, warfarin, phenytoin, cyclosporine, zidovudine, theophylline, oral hypoglycemics, rifabutin, tacrolimus and cisapride [21]. The Gynazole-1® prescribing information indicates that there are no known drug interactions, however, issues related to product leakage and vaginal irritation upon administration may be encountered. The difference in patients reporting adverse events with butoconazole therapy versus fluconazole therapy, in addition to the increased potential for drug interactions with oral therapy, merits further investigation.

Conclusion

This study demonstrates that a single application of butoconazole 2% vaginal bioadhesive cream more rapidly achieves first relief of the signs and symptoms of vaginal candidiasis compared to fluconazole 150 mg oral tablets. Almost half, 44.4%, of patients using butoconazole nitrate 2% Site Release® vaginal cream obtained first relief of their symptoms within 12 h of application compared to 29% for fluconazole. Three quarters of patients treated with butoconazole experienced first relief of symptoms within 24.5 h versus 46.3 h for fluconazole-treated patients. Butoconazole nitrate 2% Site Release® vaginal cream addresses an important patient preference, speed of symptom relief, and should be considered as an important first line therapy in patients presenting with the signs and symptoms of vaginal candidiasis.

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