Once-daily Fluocinonide-Bifonazole combination for the treatment of vulvar itching and vulvovaginal candidiasis

Preliminary study

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Summary: Vulvovaginitis presents a therapeutic challenge. Treatment of vulvovaginal candidiasis with topical imidazole preparations is well accepted. In our work we tested a new cream combining antifungal Bifonazole with a corticosteroid agent (Fluocinonide). The results suggest that most of the patients with vulvovaginitis can benefit from treatment with this new combination cream.

Key words: Vulvovaginitis; Bifonazole; Fluocinolone; Combination cream.

INTRODUCTION

Vulvovaginitis from candidal infection is the most frequent complaint of patients attending gynecologic clinics ([1]). Since no identifiable risk factors can be found in the majority of these patients, chronic or recurrent vulvovaginal candidiasis continues to present a therapeutic challenge. Conventional treatment consists primarily of repeated short courses of topical (vaginal and vulvar) preparations prescribed at the first appearance of symptoms.

The early imidazole preparations (miconazole and clotrimazole) introduced in 1969 ([2, 3]), have become the first-choice drugs in the treatment of many mycotic diseases. The azole derivatives differ from the other antimycotics in their broad spectrum of activity (against dermatophytes, multiphasic fungi and yeasts, and also some bacteria and protozoa) ([4]). Vulvovaginal candidiasis treated with topical azole agents has seen an overall cure (defined as eradication of symptoms and negative cultures) in the order of 80 to 90% ([5]). The addition of a corticosteroid to the topical antifungal agent may be beneficial in reducing inflammation more quickly ([6]).

We evaluated the efficacy and safety of the recently introduced combination

Received October 29, 1995 from the

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Revised manuscript accepted for publication Decembre 28, 1995.

corticosteroid-antifungal cream (Fluocinonide 0.05% and Bifonazole 1%) for the treatment of vulvar itching and vulvovaginitis. Bifonazole is known to be effective and well tolerated in patients with superficial fungal infections, and compared with other topical antifungal drugs it offers the convenience of once-daily administration, which may improve patient compliance ([7]).

The combination cream was prescribed by nine independent gynecologists to non-randomized patients who presented with external vulvitis, vulvar itching, and vulvar candidiasis in an open, postmarketing study. The physicians recorded the severity of the patients condition at the onset of treatment and evaluated the efficacy of the cream at the end of a period they deemed sufficient to have produced clinically meaningful improvement (efficacy period). Since each specific efficacy period depended on the patient's initial condition as well as on the underlying cause, they tended to vary even among patients under the care of the same physician. The statistical analysis detailed below apparently offers strong evidence in support of the claim that cream is effective against vulvovaginal candidiasis.

The tables cited in the text appear in appendix.

MATERIALS AND METHODS

Sample description: A total of 303 women were examined by nine independent gynecologists on a non-randomized, first-come-first-served basis. The sample size was not pre-determined by methodological clinical considerations.

It was however large enough to produce statistically significant results with a reasonable power. Patient ages ranged from 16 to about 80 years. The average age of the patients was 31.21 years with a standard deviation of 9.22 years; the median age was 29 years. The upper quartile age was 36 and the lower quartile age, 25. Because of some recording errors the number of assessable patients was less than 303 for some variables, but it never went below 300.

Variables: The following variables were considered in the assessment of the efficacy of the drug.

A) Patient's initial symptoms, divided into three categories:

1) severe (swelling, erythema, itching, fractures, and secondary infection);
2) moderate (erythema, itching);
3) mild (itching only).

B) Physician's assessment of efficacy, divided into four categories:

0) worsening;
1) no change;
2) detectable improvement;
3) significant improvement, or total cure.

C) Adverse event divided into two categories:

1) yes;
2) no.

D) Efficacy Period defined as the number of treatment days believed to be sufficient for a detectable improvement.

RESULTS

Table 1 shows the overall efficacy of the drug. Diagnosis at onset of the study revealed that of the original cohort, the condition was severe in 23.4%, moderate in 51.8% and mild in 24.8%. Of the 302 patients completing the study, 19 (6.3%) showed no improvement, 108 (35.8%) showed a detectable improvement, and 175 (57.9%) significant improvement or total cure. Thus the overall estimated odds of at least some improvement against no change were 14.87:1; that is on the average, for each patient showing no improvement there were about 15 patients showing at least a detectable improvement.

Altogether, 93.7% of the patients were at least mildly cured, with a p value of 10-11. Analysis of total cure produced a p value of only 10-4.

In Table 2 the association between the initial condition of the patients and the assessed efficacy of the drug is analyzed using the two tailed Fisher's exact test. The p value of 8.11×10^{-13} is strong evidence against a conjecture of "no association" between these variables.

Table 1. — *Frequency of overall efficacy.*

0	1	2	3	Total
0	19	108	175	302

Table 2. — *Joint frequency distribution.*

	Assessment of efficacy			
Initial symptoms	1	2	3	Total
1	12	37	22	71
2	7	63	87	157
3	0	8	66	74
Total	19	108	175	302

Further inspection of the table reveals the following pattern. Of the patients whose initial condition was severe, 83.1% were either cured or showed a detectable improvement, and 16.9 % remained unchanged. Of those whose initial condition was moderate, 55.41%, were cured and 40.13% improved for a total of 95.54% with at least a detectable improvement; in 4.46% symptoms were not relieved.

All patients with a mild initial condition either improved or exhibited a complete cure. More specifically, 89.19% of the mildly affected patients significantly improved or were cured, and 10.81% showed a detectable improvement.

Adverse events were recorded in 10 patients (3.3%). This proportion is apparently significantly different from zero, suggesting perhaps a non-random cause(s).

Further inspection of the data indicated that the adverse events occurred in only three centers, 6 patients from one center, 3 from another, and one from the third. The center that recorded the majority of these events also had the second lowest rate of complete cure. When the analysis was made conditional on the centers, the statistical significance of the proportion of adverse events disappeared.

The efficacy results reported above were shared by most of the treating physicians. Differences between physicians fell approximately within the sampling error. No significant correlation was found between length of treatment and efficacy. Most of the patients (99.3%) were treated for four to nine days.

DISCUSSION

The present study examined the efficacy and safety of a new once-daily combination cream. Its antimycotic component, Bifonazole is a substituted imidazole, structurally related to other drugs in the azole group ([7]). Both non-comparative and comparative clinical trials have clearly demonstrated the efficacy and safety of various formulations of bifonazole 1% applied once daily in the treatment of superficial fungal infections of the skin ([8]).

It is well known that long-term glucocorticoid use may produce epidermal atrophy and, if the steroids are withdrawn, rebound will occur ([9]). The latter may be prevented by only a once-daily application of the preparation. It has also been previously shown that one daily application of fluocinonide 0.05% yields the same improvement rate as two applications of betamethasone ([9]). Moreover bifonazole might have some anti-inflammatory activity providing rapid relief from signs and symptoms of fungal infections ([10]). Its possible mechanism of action is inhibition of leukotriene biosynthesis ([11]) and calmodulin activity ([12]).

Thus, we assumed that the combination of bifonazole and fluocinonide would be beneficial in reducing inflammation more quickly. If the sample participating in this trial indeed represents the entire population, the results provide strong support for the efficacy of this cream for the specific indications.

In conclusion, it seems that an overwhelming majority of patients with vulvovaginal candidiasis can benefit from treatment with combination of fluocinonide-bifonazole cream, with only a minor risk of adverse reaction.

REFERENCES

1) Horowitz B. J., Giaquinta D., Ito S.: "Evolving pathogens in vulvovaginal candidiasis: implications for patient care". *J. Clin. Pharmacol.*, 1992, *32*, 248-255.
2) Godefroi E. G., Heeres J., Van Cutsem J. H., Janseen P. A. J.: "The preparation and antimycotic properties of derivatives of l-phenylethylimidazole". *J. Med. Chem.*, 1969, *12*, 784-791.
3) Plempel M., Bartmann K., Buchel K. H., Regel E.: "BAY b 5097, a new orally applicable antifungal substance with broad spectrum activity". *Antimicrob. Agents Chemother.*, 1969, *1969*, 271-274.
4) Borgers M., Van den Bossche H.: "The mode of action of antifungal drugs". In: Levine H. B. (ed.), 'Ketoconazole in the management of fungal disease'. 1st edition, Adis Press, Australia, 1982, pp. 125-47.
5) Sobel J. D.: "Controversial aspects in the management of vulvovaginal candidiasis". *J. Am. Acad. Dermatol.*, 1994, *31*, S10-S13.
6) Giannotti B.: "Current treatment guidelines for topical corticosteroids". *Drugs*, 1988, *36* (Suppl. 5), 9-14.
7) Lackner T. E., Clissold S. P.: "Bifonazole: A review of its antimicrobial activity and therapeutic use in superficial mycoses". *Drugs*, 1989, *38*, 204-225.
8) Plempel M., Regel E., Buchel K. H.: "Antimycotic efficacy of Bifonazole in vitro and in vivo". *Drug Res.*, 1983, *33*, 517-524.
9) Fritz K. A., Weston W. L.: "Topical glucocorticosteroids". *Ann. Allerg.*, 1983, *50*, 68-76.
10) Hegemann L., Stettendorf S.: "The use of antifungal azole derivatives in inflammatory skin disorders". *J. Geriat. Dermatol.*, 1993, *1*, 28-37.
11) Bremm K. D., Plempel M.: "Modulation of leukotriene metabolism from human polymorphonuclear granulocytes by bifonazole". *Mycoses*, 1991, *34*, 41-45.
12) Hegemann L., Toso S. M., Lahijani K. I., Webster G. F., Uitto J.: "Direct interaction of antifungal azole-derivatives with calmodulin: a possible mechanism for their therapeutic activity". *J. Invest. Dermatol.*, 1993, *100*, 343-346.

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