Butoconazole Nitrate

Author(s): Demetris M. Tatum and Mark Eggleston

Source: *Infection Control and Hospital Epidemiology*, Vol. 9, No. 3 (Mar., 1988), pp. 122-124
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/30144167

Butoconazole Nitrate

Demetris M. Tatum, PharmD; Mark Eggleston, PharmD

INTRODUCTION

Imidazoles and their derivatives have been proven very effective in the treatment of fungal infections.[1] Butoconazole nitrate is an important addition to this class of antifungal agents. It was introduced to the market in 1985 for the short-term management of vaginal infections caused by *Candida* species. It has high activity against *Candida albicans* in vitro and is very effective clinically.[2]

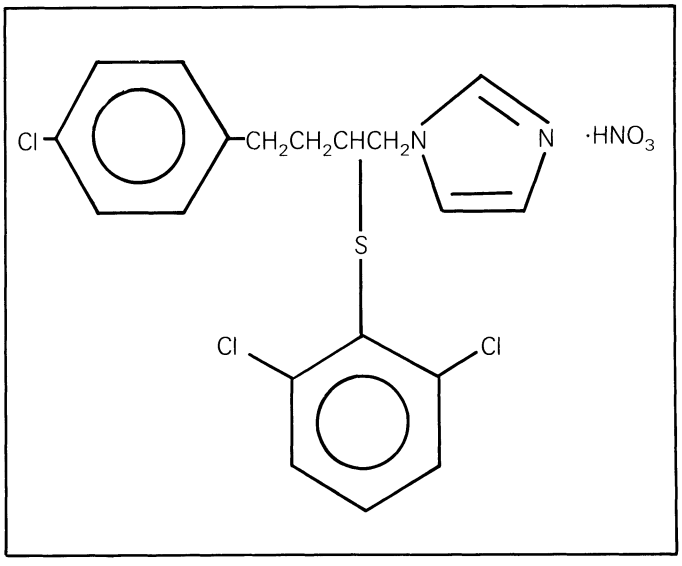
CHEMISTRY AND MODE OF ACTION

Butoconazole nitrate is an imidazole derivative with potent antifungal activity in vivo and in vitro[3,4] (Figure). When synthesized, it exists as a racemic mixture in which both components are optical isomers and equally active.

The exact mechanism of butoconazole activity is unknown. However, it is thought to alter the permeability of the cell by attacking the cell membrane, thus causing a decrease in osmotic resistance. More recently, it has been found to interfere with the biosynthesis of lipids and ergosterol, the main sterol in fungal cell membranes.[5,6] This disrupts replication and inhibits growth of the cell.[3,7,8] Butoconazole is fungistatic at low therapeutic concentrations, but by virtue of its activity on the cellular membrane, cell death may eventually occur. In addition, supression of fungal growth may facilitate the body's host defense mechanisms in clearing the infection.[9]

PHARMACOLOGY

Following a single intravaginal dose of butoconazole nitrate, an average of 5.5% of the drug is absorbed. Absorption from the vaginal mucosa is slow and estimated peak serum concentrations of the drug occurred between two and eight hours after dosing. The plasma half-life is approximately 21 to 24 hours. The plasma levels after a given dose averaged from 19 to 44 ng/mL. The sites of metabolism of butoconazole are not well established, but



Chemical composition of butoconazole

are thought to be similar to ketoconazole and clotrimazole, two orally administered antifungal derivatives that undergo extensive liver metabolism.[10-13]

Butoconazole nitrate and its metabolites are eliminated 50% through the kidney and 50% through the gastrointestinal tract.[2] Its elimination has not been studied in patients with reduced renal or hepatic function and thus it is not known to what extent renal or hepatic function alter the drug's elimination. Droegemueller et al found that the accuracy of absorption and elimination data was not compromised by excessive leakage of drug from the vaginal cavity after insertion of the dose.[14]

Butoconazole is formulated in a vehicle that causes minimal leakage from the vagina, thus allowing recovery of 86% to 97% of the administered dose. Data from absorption and elimination studies performed on similar imidazole-type antifungal agents are not as impressive. Such a vehicle may also improve patient adherence and acceptance of vaginal administration of medication.

From Howard University, College of Pharmacy and Pharmacal Sciences, Washington, DC.

Address reprint requests to Mark Eggleston, PharmD, PO Box 115, Woodbridge, VA 22191.

TABLE 1
IN VITRO SPECTRUM OF ACTIVITY FOR BUTOCONAZOLE NITRATE AGAINST SELECTED BACTERIA, FUNGI, AND *TRICHOMONAS FOETUS*[15]

Organism	MIC* (mcg/mL)
Staphylococcus aureus	6.25
Streptococcus faecalis	3.12
Streptococcus pyogenes	0.0016
Escherichia coli	>200.00
Klebsiella pneumoniae	6.25
Serratia marcescens	>200.00
Trichophyton mentagrophytes	1.0
Trichophyton rubrum	0.05
Trichophyton tonsurans	0.5
Trichophyton concentricum	0.05
Microsporum canis	0.5
Microsporum gypseum	5.0
Epidermophyton floccosum	5.0
Candida albicans	≤10.00
Candida glabrata	≤0.3
Candida tropicalis	≤10.00
Cryptococcus neoformans	<1.00
Trichomonas foetus	100 MLC† (mcg/mL)

* *Minimum inhibitory concentrations (MICs) were determined using the agar dilution procedure.*
† *Minimum lethal concentrations (MLCs) were determined using a microdilution broth procedure.*

SPECTRUM OF ACTIVITY AND INDICATIONS

Butoconazole nitrate has fungicidal activity in vitro against *Candida, Trichophyton, Microsporum,* and *Epidermophyton.*[14] It has also shown some activity against gram-positive organisms. Clinically it has effectively treated vaginal infections caused by *Candida albicans, Candida tropicalis,* and similar fungal organisms (Table 1).[15]

Several studies have proven the clinical efficacy of butoconazole nitrate as a new treatment modality for vulvovaginal candidiasis.[4,14,16] Droegemueller et al, in a multicenter trial of 274 patients, found a three-day regimen of butoconazole nitrate cream to be as effective as a three-day regimen of clotrimazole vaginal tablets in relieving signs and symptoms of vulvovaginal candidiasis and clearing vaginal secretions of *Candida albicans.*[14] Efficacy was established on the basis of both clinical cure (absence of clinical signs and symptoms) and microbiological cure (absence of *Candida* in vaginal secretions). Cure rates 8 days and 30 days following treatment are compared in Table 2.

Bradbeer et al found a three-day course of butoconazole nitrate to be as efficacious as a seven-day course of miconazole in a single-blind study involving 69 patients.[4] Again, clinical and microbiological cure rates were assessed and there was no statistical difference in the efficacy of the two products. Jacobson first studied the clinical application of butoconazole nitrate cream.[17] This multicenter study compared 1% and 2% butoconazole and 2% miconazole, each administered for a six-day period. Patients were compared at two follow-up visits and

TABLE 2
CURE RATES 8 DAYS AND 30 DAYS POSTTREATMENT WITH 3-DAY REGIMENS OF BUTOCONAZOLE NITRATE AND CLOTRIMAZOLE

	Patients (No.)	MCR*	CCR†
I. 8 days following treatment			
3-days butoconazole nitrate cream 2%	122	95%	77%
3-days clotrimazole vaginal tabs 200 mg	124	91%	79%
II. 30 days following treatment			
3-days butoconazole nitrate cream 2%	117	79%	66%
3-days clotrimazole vaginal tabs 200 mg	122	73%	58%

* *MCR—Microbiological cure rate.*
† *CCR—Clinical cure rate.*

examined for decreases in discharge. There were no differences in cure rates among the three treatment groups, although a substantial decrease in discharge was noted in all three treatment groups.

Van Dyck compared a three- and six-day regimen of 1% and 2% butoconazole, a six-day regimen of miconazole, and placebo.[16] Butoconazole nitrate cream in a concentration of 2% given for three days and six days was found to have higher microbiological and clinical cure rates than the 1% cream, miconazole, and placebo. These results, however, did not reach the level of statistical significance.

The effectiveness of butoconazole in specialized groups more prone to resistant *Candida* infections was also evaluated. In the previously mentioned studies, a large number of patients were using oral contraceptives. There were no statistical differences in clinical or microbiological cure rates observed in these patients versus those using other forms of birth control.[14] No reference was made to success rates in patients with diabetes mellitus, on immunosuppressive drugs, or having other concurrent disease states that might impair the body's host defense mechanisms.

Butoconazole nitrate is available as a 2% vaginal cream and is approved for use in the treatment of vulvovaginal mycotic infections caused by *Candida* spp confirmed by potassium hydroxide (KOH) smears or cultures. Butoconazole has also been approved for use in patients concurrently using oral contraceptives and other antibiotic regimens. In addition, butoconazole has been effective in the treatment of fungal vaginal infections in pregnant women. Treatment should be reserved for the second and third trimesters.

SIDE EFFECTS

Butoconazole nitrate was well tolerated by subjects in the previously discussed studies. Side effects are usually local and mild and generally do not require discontinuation of therapy.

Droegemueller et al found no evidence of systemic side effects related to butoconazole administration.[14] Local side effects included vulvar, vaginal, and urethral burning. Of the 272 patients studied, only 6 patients reported side effects and only 1 patient using clotrimazole had to discontinue treatment.

Bradbeer et al reported no serious side effects, however, there was an increase in side effects associated with both drugs compared with previous studies.[4] The most common complaints were stinging or irritation on application, unpleasant odor, staining of clothes, and leakage of cream. The percentage of patients complaining of leakage was greater in the miconazole group than in the butoconazole group and the difference was statistically significant. Jacobson reported side effects in 6 of the 130 patients he studied.[17] The most common were vaginal bleeding and burning, headache, and leakage of cream. In Van Dyck's study, 2% of the patients studied discontinued therapy due to side effects.[16] Such side effects included vulvar swelling, burning on urination, and urinary frequency. However, only 1% of these side effects were considered to be related to the study medications.

DOSAGE AND ADMINISTRATION

Butoconazole nitrate 2% vaginal cream is packaged with three disposable dose applicators. For nonpregnant patients, the recommended dose is one applicatorful of cream (approximately 5 g) intravaginally at bedtime for three days. Treatment can be extended for three additional days if indicated. The recommended dose for pregnant patients in the second and third trimester is one applicatorful of cream intravaginally at bedtime for six days. If sensitization is reported during use, the treatment should be discontinued. Patients should be cautioned against discontinuing dosage administration prematurely due to menstruation or relief of symptoms.

CONCLUSIONS

With the high incidence and recurrence of vaginitis, products that can treat such disease with the lowest possible dose, a low incidence of side effects, and a short duration of therapy are very desirable. Butoconazole nitrate may prove to be a very useful alternative in treating vaginal infections caused by various fungal organisms.

REFERENCES

1. Beggs WH: The effect of antifungal imidazoles on resting cells of *Candida parapsilosis*. *Int Res Commun Sys J Med Sci* 1983; 11:667-679.
2. Brown D: Therapeutic alternatives and new treatment modalities in vulvovaginal candidiasis. *J Reproduct Med* 1986; 31:653-654.
3. Borger M: Mechanism of action of antifungal drugs, with special reference to imidazole derivatives. *Rev Infect Dis* 1980; 2:520-534.
4. Bradbeer CS, Mayhew SR, Barlow D: Butoconazole and miconazole in treating vaginal candidiasis. *Genitourin Med* 1985; 61:270-272.
5. Henry MJ, Sisler HD: Effects of miconazole and dodecylimidazole on sterol biosynthesis in Ustilago maydis. *Antimicrob Agents Chemother* 1979; 15:603-607.
6. Walker KAM, Braemer AC, Hitt S, et al: 1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-n-butyl]-1H-imidazole nitrate, a new potent antifungal agent. *J Med Chem* 1978; 21:840-843.
7. Pye GW, Marriott MS: Inhibition of sterol C-14 demethylation by imidazole containing antifungals. *Sabouraudia* 1982; 20:325-329.
8. Sud IF, Feingold DS: Mechanism of action of the antimycotic imidazoles. *J Invest Dermatol* 1981; 76:438-441.
9. Gardner HL, Kaufman RH: *Benign Diseases of the Vulva and Vagina,* ed 2. Boston, GK Hall Medical Publishers, 1981.
10. Brass C, Galgiani JN, Blaschke TF, et al: Disposition of ketoconazole, an oral antifungal in humans. *Antimicrob Agents Chemother* 1982; 21:151-158.
11. Brett L: Femstat Vaginal Cream 2%. Product Summary, Syntex Laboratories, January 1986.
12. Haller I: Mode of action of clotrimazole: Implications for therapy. *Am J Obstet Gynecol* 1985; 152:939-944.
13. Henzl M: Metabolism of butoconazole. *J Reproduct Med* 1986; 31:658-659.
14. Droegemueller W, Adamson GD, Brown D, et al: Three day treatment with butoconazole nitrate for vulvovaginal candidiasis. *Obstet Gynecol* 1984; 64:530-534.
15. Hurley R, deLouvois J: *Candida* vaginitis. *Postgrad Med J* 1979; 55:645-647.
16. Van Dyck W: A comparative study of butoconazole, miconazole, and placebo. *J Reproduct Med* 1986; 32:662-663.
17. Jacobson JB, Hajman AJ, Wiese J, et al: First clinical experience with a new antifungal agent, butoconazole nitrate: A double blind comparison to miconazole nitrate. 10th World Congress of Gynecology and Obstetrics, October 17-22, 1982, San Francisco, California. New York, Academy Professional Information Services, 1982, p 368.
18. Matthews T: Butoconazole: Pharmacologic considerations, chemistry, and microbiology. *J Reproduct Med* 1986; 31:655-657.

ADDITIONAL SUGGESTED READINGS

Ritter W: Pharmacokinetic fundamentals of vaginal treatment with clotrimazole. *Am J Obstet Gynecol* 1985; 152:945-947.

Sobel JD: Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 1985; 152:924-935.