

Fenticonazole Nitrate - A Symptomatic Approach to Vulvovaginal Infection

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Abstract

Abnormal vaginal discharge is a characteristic feature of vulvovaginal infections (VVI). It affects women of reproductive age group worldwide. The most common documented causes of symptomatic vaginal discharge include bacterial vaginosis, followed by vulvovaginal candidiasis and trichomoniasis. The relapse and recurrence rates are increasing due to the use of complex regimens with long treatment duration. Fenticonazole nitrate is an imidazole derivative with a broad spectrum of antimycotic activity against dermatophytes and yeasts *in vitro* and clinical studies. Fenticonazole has also shown to exhibit antibacterial action against bacteria commonly associated with superficial fungal and vaginal infections and anti-parasitic action against the protozoan *Trichomonas vaginalis* with high cure rates and good safety and tolerability with low relapse rates. Fenticonazole shows unique multimodal action against *Candida* species by Inhibiting of secretory aspartate protease thereby preventing the growth, adherence, and penetration of *Candida* sp. including N-acetylcysteine leading to clinically significant reduction in the relapse rate. Similarly, fenticonazole inhibits the growth of bacterial (*Gardenella vaginalis*) and Protozoan (*Trichomonas* sp.) by inhibition of pyruvate oxido reductase enzyme responsible for cell division or replication. Clinical evidences have shown that fenticonazole does not have any teratogenic effects and has been suggested to be used in high-risk cases from second trimester onward. Fenticonazole is a differentiated imidazole derivative that offers simplistic solution for syndromic approach to VVI infections.

Key words: Fenticonazole nitrate, *Gardenella vaginalis*, *Trichomonas*, Vulvovaginal candidiasis, Vulvovaginal infections

INTRODUCTION

Abnormal vaginal discharge is a frequent complaint for women of childbearing age that is often accompanied with inflammatory symptoms. The situation is compounded or complicated by the concomitant risk factors and current lifestyles adopted by population at large including tight clothing, poor menstrual hygiene, douching, smoking, antibiotic use, oral contraceptive pills (OCP's), and Type 2 diabetes. In most of these cases, the diagnostic challenges for empirical therapy are well highlighted by the overlapping symptoms representing either candidiasis, bacterial or *Trichomonas* infections. Similarly, the increasing incidence of relapse or recurrence in these cases has often necessitated the use of complex regimens with long treatment duration

notwithstanding the wide availability of conventional therapies including topical azoles.¹

Fenticonazole is a differentiated imidazole derivative that has been made available in India recently for the management of symptomatic vulvovaginal infections (VVI) including vulvovaginal candidiasis (VVC). The unique dechlorinated imidazole structure has been documented to have fungicidal yet broad spectrum activity against dermatophytes, yeasts, *Protozoa*, and *Bacterial* sp.^{2,3}

PHARMACODYNAMICS

Fenticonazole shows unique multimodal action against *Candida* species involving:

1. Inhibition of secretory aspartate protease (SAP) thereby preventing the growth, adherence, and penetration of *Candida* sp. including N-acetylcysteine leading to clinically significant reduction in the relapse rate (Figure 1).
2. Inhibits fungal cytochrome P450 3A enzyme, lanosine 14 α -demethylase responsible for conversion of lanosterol to ergosterol, the main sterol attributed to fungal cell membrane integrity and cell survival.

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3. Inhibits complimentary oxidase and peroxidase enzymes that lead to structural and functional changes in fungal cell due to its antioxidant action.

Similarly, fenticonazole inhibits the growth of bacterial (*Gardenella vaginalis*) and Protozoan (*Trichomonas* sp.) by inhibition of pyruvate oxido reductase enzymes responsible for cell division or replication.²

PHARMACOKINETICS

The systemic absorption with topical fenticonazole is nominal while the preclinical studies suggest excellent retention or “intrareservoir” effect in the local tissues for up to 72 h following topical application.^{4,5}

CLINICAL DATA

Clinical efficacy of topical fenticonazole has been evaluated in 17 randomized controlled clinical trials for various clinical states involving *Candida* sp., *Gardenella*, and *Trichomonas* in approximately over thousand patients.

1. In randomized comparative clinical trial with clotrimazole, fenticonazole was documented to have better clinical and mycological cure rates with significantly longer disease-free interval rates at 4 weeks following singly topical application of 600 mg ovule (Lawrence) (Figure 2).⁶
2. Fenticonazole (600 mg X 2 dose) offers “Quick Symptomatic anti-pruritic” effect compared to Fluconazole (150 mg X 2 dose) because of its complimentary anti-SAP action as highlighted by Murina *et al.*⁷ when administered in high-risk VVC patients on concomitant OCP.
3. Clinical efficacy of topical fenticonazole in VVI cases was documented by Bukovsky.^{8,9} Trichomoniasis (100%); *Candida* (48.7%); and other (34.8%) pathogens were identified at baseline visit and following single dose administration patient responder rates were documented at 87% at the end of 7 days (Figure 3).

The clinical utility and safety of combination strategy involving fenticonazole (600 mg ovule) and fluconazole (150 mg tablet) was documented by Kovachev¹⁰ in 118 relapsing or naive cases of VVC. At the end of 2 weeks, patient response rates were noted in 90.7% cases. The combination strategy showed better clinical and mycological cure rates with no incremental rise in treatment related adverse events (Figure 4).

In randomized, single-center comparative study between fenticonazole ovules (200, 600, and 1000 mg) was done to see the intravaginal reservoir effect. At 3 h., the 600 mg ovule

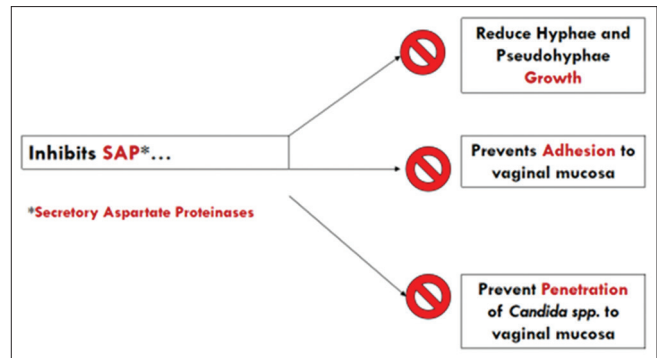


Figure 1: Fenticonazole offers differentiated anti-secretary aspartate proteinase activity against vulvovaginal candidiasis

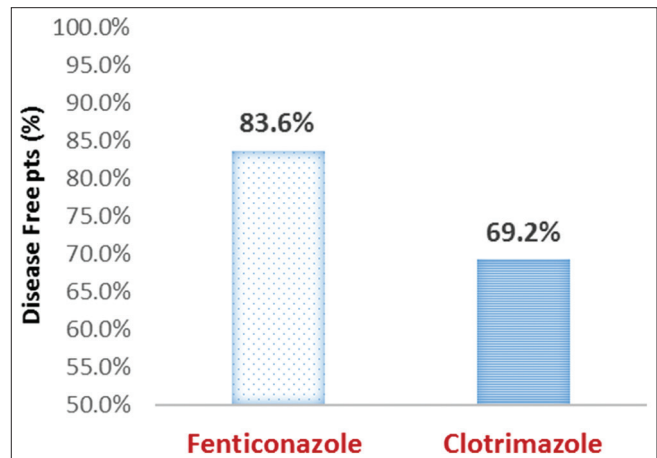


Figure 2: Disease-free patients (%) following fenticonazole and clotrimazole administration at 4th week

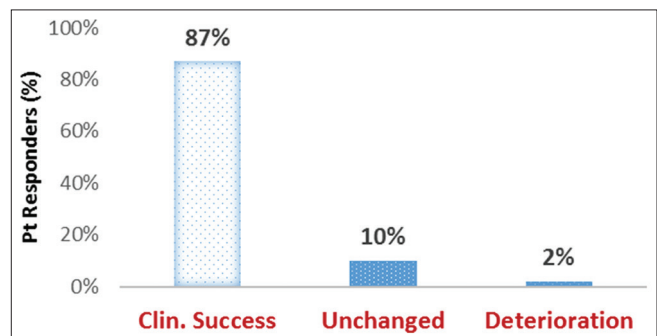


Figure 3: Clinical response rate on day 7 in symptomatic vulvovaginal infections cases

provided the highest concentrations compared to 1000mg. This study was documented by Gorlero (8) (Figure 5).

SAFETY

Risk of VVI including VVC remains higher during pregnancy. The real world challenges of clinical diagnosis in such persistent cases often warrants the use of

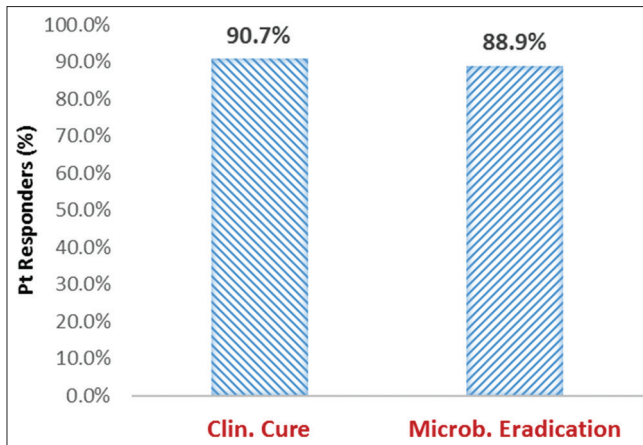


Figure 4: Clinical cure and microbiological eradication at 2 weeks following fenticonazole administration

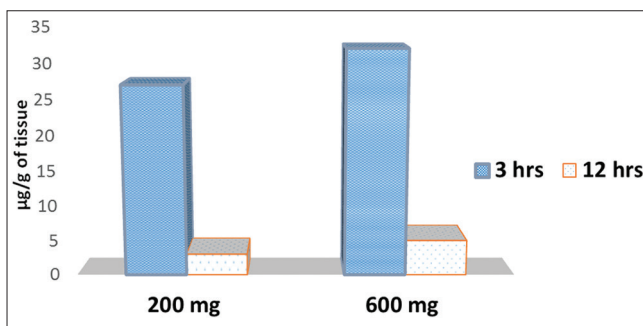


Figure 5: Fenticonazole vaginal tissue levels at 3 and 12 h after the application of a single 200, 600, mg ovule means \pm standard deviation

complex treatment regimens including those involving metronidazole or oral triazoles that may be best avoided during pregnancy. Women with VVC in pregnancy can be treated with topical imidazoles as per Faculty of Sexual and Reproductive Healthcare Clinical Guidelines by British Association for Sexual health and HIV. Pre-clinical studies have shown that fenticonazole does not have any teratogenic effects and has been suggested to be used in pregnancy from second trimester when the benefits outweigh the risk involved in such cases.¹¹

DOSAGE AND ADMINISTRATION

Fenticonazole 600 mg intravaginal ovule is usually administered by deep insertion once at bed time. The dosage may be repeated on the 3rd day if the symptoms persist.²

SUMMARY

VVI including symptomatic, relapsing, and uncomplicated VVC remains a clinical enigma with overlapping symptoms and diagnostic challenges. This often requires simplistic, holistic treatment regimens as empirical therapy that could be realistically applicable in real world outpatient settings of India. Fenticonazole is a novel imidazole with unique mechanism of action that covers a wide spectrum of organisms including *Candida* sp., *Gardnella vaginalis*, *Trichomonas vaginalis* and consequently clinically documented with high responder rates in patients with VVI. In most of these cases, fenticonazole offers short course therapy benefits that can be safely given to high-risk patients including pregnancy albeit from second trimester onward.

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