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Original Article

Fenticonazole in Vulvovaginal Infections: A Real-world Clinical Experience in India - Force India Study

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Abstract

Introduction: In recent decade, fungal infections have escalated due to mushrooming of immunocompromised patients like elderly and other patients receiving immunosuppressants for comaleficent diseases diabetes mellitus, etc. This holds true for infections of vulvovaginal tissues as well. Skin and vulvovaginal infections can be effectively treated by azole class of antifungals such as clotrimazole and miconazole. Fenticonazole belongs to same class of antifungals, which has been extensively studied against fungi and some Gram-positive bacterial cocci.

Aims and Objectives: We aimed to review etiological pattern of vulvovaginitis, drug use and/prescribing patterns using the World Health Organization - Drug Utilization indicators, and effects of fenticonazole (both beneficial and adverse).

Materials and Methods: A survey was conducted through pre-validated questionnaire, designed to assess the effectiveness and safety of fenticonazole 600 mg ovule in the treatment of vulvovaginitis.

Results: Among all variants of vaginitis, the most common variant was bacterial vaginosis (42.2%), followed by mixed vaginitis (33.2%), vulvovaginitis (14.9%), and trichomonas vaginitis (9.4%). Of 2037 prescriptions, 404 (19.8%) patients were prescribed single dose of fenticonazole, 1211 (59.4%) patients were given two doses, i.e., one ovule each, at day 1 and day 3 (D1/D3), and 419 (20.5%) patients were prescribed with two doses of fenticonazole on day 1 and day 7 (D1/D7). Prescribed daily dose of fenticonazole was more than defined daily dose. No serious adverse events were reported and it was well tolerated.

Conclusion: Most of the prescriptions in the real-world setting were in D1/D3 group implying that vulvovaginitis needs to be treated adequately with two-dose regime, in contrast to single dose recommendation of standard guidelines.

Key words: Drug utilization, Fenticonazole, Vulvovaginitis, World Health Organization

INTRODUCTION

In recent decade, fungal infections have escalated due to mushrooming of immunocompromised patients like elderly and other patients receiving immunosuppressants for comaleficent diseases diabetes mellitus, etc. This holds true for infections of vulvovaginal tissues as well.[1] Symptomatic inflammation of vagina, also involving vulval tissue instigated by candida, is conventionally defined as vulvovaginal candidiasis (VVC). Vaginal discharge (curdy white/cheesy discharge is peculiar) and itching are the prime manifestations of VVC.[2] Pregnancy, diabetes mellitus, use of systemic antibiotics, and poor intimate hygiene are some of its risk factors.[3,4]

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The pursuit of starting empirical therapy in vulvovaginitis is arduous due to diagnostic challenge owing to intersecting symptoms of VVC, bacterial, and mixed vaginal infections. This situation is more complicated by escalating emergence of resistant strains of pathogens which has compelled the use of intricate therapy regimes for longer duration.[5] Mixed infections are difficult to treat with monotherapy,

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and hence, they are treated with combination of antifungal, antibacterial, and corticosteroid.[6] Quandary of resistance and increased incidence of local and systemic adverse effects have overshadowed the success of this tactic.

Imidazole antifungals are commonly used to combat fungal infections which act by inhibition of ergosterol synthesis through blocking of P450 isozyme. Ergosterol is building block of fungal cell membrane.[6] Skin and vulvovaginal infections can be effectively treated with variety of azole antifungal drugs such as fluconazole, clotrimazole, and miconazole. Fenticonazole belongs to same class of antifungals, which is well endured and has extensive gamut of activity against fungi and some Gram-positive bacterial cocci.[7-9] Especially in VVC, it has been found to be more efficacious as compared to other orthodox therapies.[10,11] Findings of *in vitro* retrospective analysis prompt us to consider the active role of fenticonazole in treating mixed infections of vulvovaginal tissue with Gram-positive bacteria and fungi.[12] Moreover, it has shown high efficacy against three major sources of dermatophytosis-epidermophyton, trichophyton, and microsporum.[13] *In vitro* studies have also revealed that fenticonazole is active against most of the pathogens causing bacterial vaginosis such as mobiluncus, gardnerella, and bacteroides species.[12]

There are many ways by which pattern of drug use can be studied, like Drug Utilization (DU) retrospective analysis and prescription analysis. Whenever a DU retrospective analysis is planned, it is preferably done using anatomic and therapeutic classification (ATC)/defined daily dose (DDD) system laid down by the World Health Organization (WHO) since it is universally accepted and allows for better comparison of retrospective analysis findings. Each drug is classified in ATC in four levels with highest level being the organ system involved by the drug and subsequent levels being the drug identifiers. DDD is assumed average dose per day for that drug for the given indication in adult.[14] To the best of our knowledge, the present retrospective analysis is first of its kind to retrospective analysis prescriptions on fenticonazole in India and its analysis using the WHO - DU indicators; hence, it will have a value addition.

Aims and Objectives

Objectives of the present retrospective analysis were to describe DU patterns of fenticonazole using the WHO - DU indicators, to get an insight into etiologies of vaginitis. Furthermore, we aimed to review drug use and/prescribing patterns, effects of fenticonazole (both beneficial and adverse), promotion of appropriate drug use through patient counseling, and other interventions. Final and the most important objective of present retrospective analysis were to provide results for the clinicians, to aid them in selecting appropriate antifungal drug.

MATERIALS AND METHODS

A survey was conducted through pre-validated questionnaire. The questionnaire was designed to assess the efficacy and safety of fenticonazole 600 mg in the treatment of vulvovaginitis. 6-month survey was carried out from April 2017 to October 2017. "Scrip intelligence database" was used to recognize gynecologists engaged in the treatment of vulvovaginitis. Only those gynecologists were included for final analysis who maintained complete patient record and Sobel's score. Of 95 gynecologists, 60 were selected from four directional zones of country by simple random sampling. Care was taken to select gynecologists uniformly over these four geographies. Pregnant patients were excluded from the retrospective analysis. "Patients suffering from vulvovaginitis treated with fenticonazole were analyzed in 3 groups viz., patients treated on day 1/D1, patients treated on day 1 and 3 (D1/3) and patient treated on day 1 and 7 (D1/D7)". Relevant data were entered in Excel sheet in predesigned format.

We used mean Sobel's score to assess the efficacy of fenticonazole in vulvovaginitis, where each symptom was graded on a scale from 0 (absent) to maximum of 3 (severe). Higher the score more severe was the disease presentation.[15] Optimal improvement was defined by reduction in mean Sobel's score by 1.5–2.0 points. Safety evaluation was done by evaluating occurrence of adverse events. The methodology adopted for the present retrospective analysis is depicted in Figure 1.

RESULTS

Of 2567 prescriptions screened, 2037 were included for our analysis. Mean age of patients in this retrospective analysis was 31.95 years. Among all variants of vaginitis, the most common variant was bacterial vaginosis found in 860 patients (42.2%) followed by mixed vaginitis in 677 (33.2%), vulvovaginitis in 304 (14.9%) patients, and trichomonas vaginitis in 193 (9.4%) patients [Table 1]. Of 2037 prescriptions, 404 (19.8%) patients were prescribed single dose of fenticonazole, 1211 (59.4%) patients were given two doses, i.e., one ovule each, at day 1 and day 3 (D1/D3), and 419 (20.5%) patients were prescribed with two doses of fenticonazole on day 1 and day 7 (D1/D7) [Figure 2]. Prescribed daily dose (PDD) of fenticonazole was more than DDD [Table 2].

Figure 3 shows symptom-wise effect of fenticonazole on mean of Sobel's score in patients of D1 group. Mean improvement in Sobel's score was found to be 1.47 in all symptoms with highest improvement in erythema and least in excoriation. In D1/D3 group, overall improvement in mean Sobel score was by 1.76 with highest positive effect on vaginal discharge and least in case of excoriation [Figure 4].

In D1/D7 prescription group, overall reduction in mean Sobel's score was 1.45 with highest improvement in vaginal discharge and least in excoriation [Figure 5]. On scrutiny, it was found that the most common adverse effect was vaginal burning sensation followed by itching/irritation, erythema, and desquamation. Incidence of these adverse effects was most in D1/D3 group (mean 1.6%) followed by D1/D7 group (mean 1.2%) and least in D1 group [Table 3].

DISCUSSION

The finding of mean age in the present study was slightly different from findings of other comparative studies of fenticonazole with other antifungal drugs which showed mean age of patients to be around 27 years.[16,17] Bacterial vaginosis was the most common cause of vaginitis in the present study followed by mixed vaginitis. This in corroboration with findings of other study.[18] However, some authors cited VVC as the 2nd most common cause of vaginitis.[19] Maximum prescriptions were in D1/D3 group, i.e., two doses were given on day 1 and day 3. Mean Sobel's score was highest in D1/D3 group followed by D1/D7 group and least in D1 group. In recent editorial research paper by Verma and Madhu, authors opine that drastically changed clinical pattern of fungal infections has enabled dermatologists to use antifungal drugs for a longer period than that specified in standard guidelines to obtain optimal benefit.[20] The same is reflected in PDD and DDD findings wherein PDD was greater than DDD. PDD reflects average of per diem dose of drug which is actually prescribed. When there is discrepancy in findings of PDD and DDD for anti-infective the diagnosis, optimal duration of therapy and national therapeutic guidelines should also be taken into account.[14]

As per our knowledge, the present retrospective analysis is first of its kind to analyze the prescription pattern of fenticonazole using DU indicators laid down by the WHO.

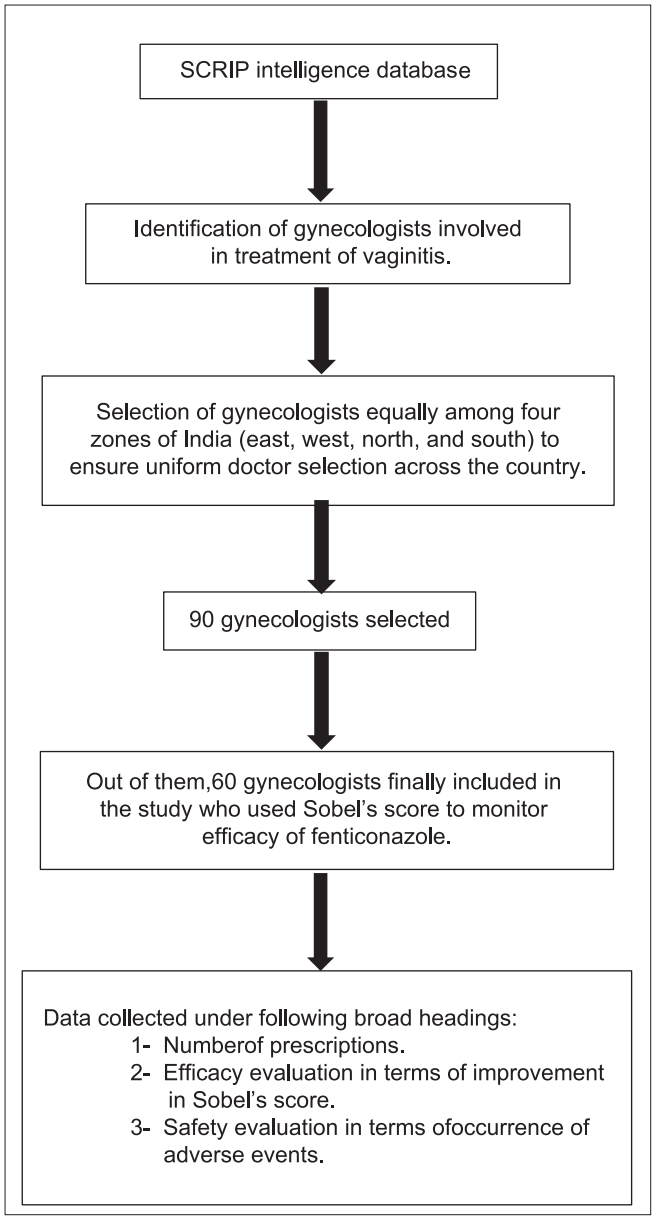

Figure 1: Methodology adopted for current retrospective analysis

Table 1: Prescription details and diagnosis in patients of present study

Item	Sub item	Number of patients
Total number of prescriptions screened		2567
Prescriptions included for analysis		2037
Mean age		31.95
Diagnosis	VVC	304
	Bacterial vaginosis	860
	Trichomonas vaginitis	193
	Mixed vaginitis	677

VVC: Vulvovaginal candidiasis

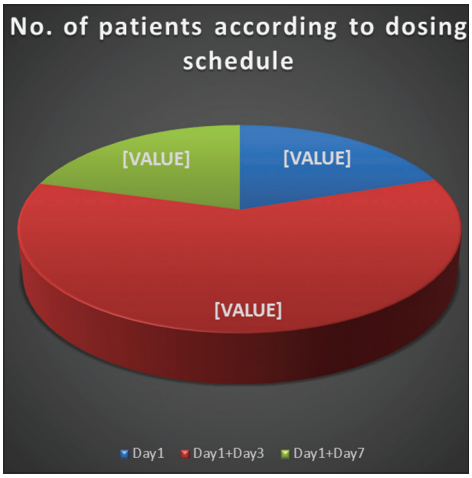

Figure 2: Number of prescriptions in day 1, day 1/3, and day 1/7 regimen

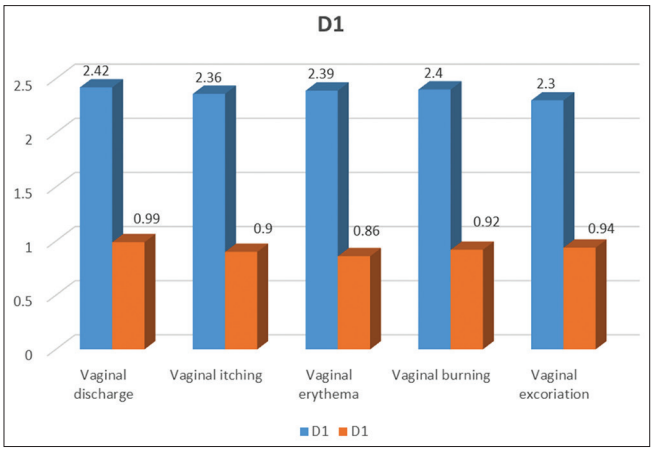

Figure 3: Effect of fenticonazole (day 1) on various symptoms of vulvovaginitis

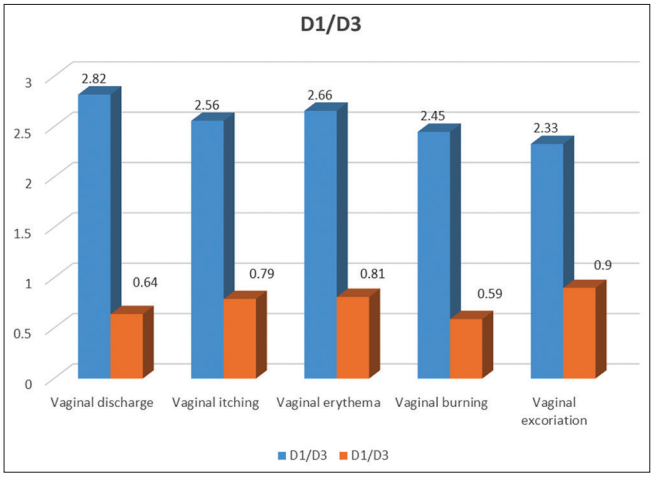

Figure 4: Effect of fenticonazole (given on day 1 and day 3) on various symptoms of vulvovaginitis

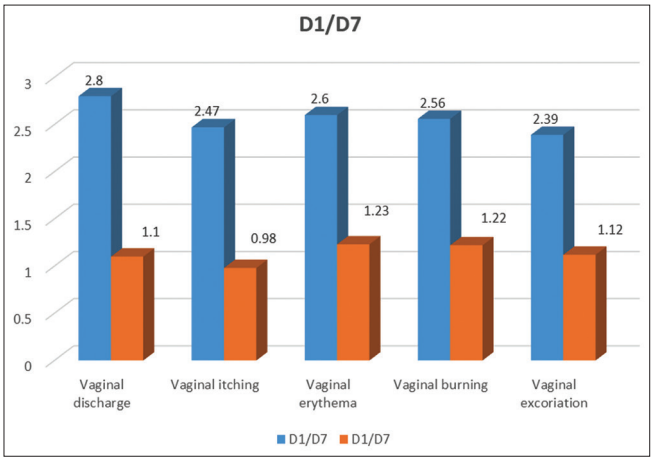

Figure 5: Effects of fenticonazole (given on day 1 and day 7) on various symptoms of vulvovaginitis

In all the three groups, there was clinically significant improvement in vaginal discharge as indicated by changes in mean Sobel's score. This finding is corroborated with

Table 2: ATC/DDD evaluation of DU of fenticonazole

Item	Value
ATC code	G01AF12
DDD	0.1 g
PDD	0.6 mg

ATC: Anatomic and therapeutic classification, DDD: Defined daily dose, PDD: Prescribed daily dose, DU: Drug utilization

Table 3: Adverse effects seen with fenticonazole

Adverse effect/s	Number of patients facing the AE *n* (%)			Total
	D1 (*n*=404)	D1/D3 (*n*=1211)	D1/D7 (*n*=419)	
Burning sensation	4 (0.9)	30 (2.4)	8 (1.9)	42
Vaginal itching	3 (0.7)	26 (2.1)	6 (1.4)	35
Erythema	4 (0.9)	24 (1.98)	5 (1.1)	33
Desquamation	2 (0.4)	7 (0.5)	3 (0.7)	12

findings of other such studies in western part of the world [16,21-23] Usually, if the symptoms persist, then patients are called up for the 2nd dose at 7th day.[24] However, in the present study, maximum patients were given the 2nd dose on day 3. This may be because fenticonazole forms its "vaginal reservoir" for 72 h during which drug is released slowly.[25] Hence, in light of this finding, 2nd dosing at day 3 is in complete corroboration. This is supported by findings of other studies wherein optimal improvement in Sobel's score was obtained by giving fenticonazole on day 1 and day 3.[24,26,27] Single dose efficacy was found to be less in some studies.[17,28] The efficacy of fenticonazole given on day 1 and day 7 was more or less same as on day 1 and day 3 in other studies.[17,21,29,30] The United Kingdom Guidelines recommend topical therapy of fenticonazole 600 mg stat or 200 mg for 3 days.[31] Furthermore, it has been found that systemic absorption of fenticonazole is very minimal; therefore, repeated dosing poses no significant threat of exposing other tissues to the drug.[32,33] It is well-known fact that successful treatment of mixed infections is a challenging issue, which may be endorsed to sundry comportment of pathogenic flora in vagina.

Currently, vulvovaginitis is treated with combination of antifungal, steroid, and antibiotics, which augments the prospect of exterminating the culprit pathogens and provides expeditious relief of symptoms. However, it has been found that adverse events and resistant strains are more with use of such approach.[34] One unique advantage of fenticonazole is that it is the only imidazole antifungal which inhibits Candida proteinase, which is responsible for its adherence to epithelial cells, even in single dose.[35] From findings of the present study, we recommend that fenticonazole be used as the first-line drug in the treatment

of VVC. This is in line with findings of other such study wherein authors concluded that fenticonazole is economically feasible, the first-line therapy for the treatment of VVC.[10,36] These efficacious effects of fenticonazole in VVC may be attributed to its multifaceted action such as inhibition of fungal secretory aspartate proteinase (SAP), blocking of cytochrome oxidase and peroxidase, and disruption of fungal cytoplasmic membrane by inhibiting fungal P450 isoenzyme which is usually required for fungal cell wall sterol synthesis.[35] Inhibition of SAP is unique to fenticonazole since it is the only imidazole antifungal to do so, even in single dose. Inhibition of SAP leads to following three effects:

1. Reduction in number of hyphae and pseudohyphae - prevents growth of fungus
2. Prevents adhesion to vaginal mucosa
3. Prevents penetration of candida into the vaginal mucosa.[35]

Moreover, efficacy of fenticonazole has been studied in various head-to-head trials with conventional antifungal therapies like clotrimazole where fenticonazole had shown a favorable response in VVC.[1,37] Emergence of resistant strains is the foremost quandary with conventional antifungal therapies. Currently, the concept of stewardship is globally inculcating into daily clinical practice to curb the menace of resistance.

The present analysis had certain limitations. Due to its analysis design, chances of selection bias cannot be ruled out. Treatment with other drugs was not considered for the present analysis, which would have impacted the final outcome. The findings of the present analysis should be compared with that of other such studies so that results can be generalized.

CONCLUSION

Most of the prescriptions in the real-world setting were in D1/D3 group implying that vulvovaginitis needs to be treated adequately with two-dose regime, in contrast to single dose recommendation of standard guidelines.

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