REVIEW ARTICLE

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Topical Fenticonazole in Dermatology and Gynaecology

Current Role in Therapy

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Abstract

Fenticonazole is an imidazole derivative with a broad spectrum of antimycotic activity against dermatophytes and yeasts in *in vitro* and clinical studies. Fenticonazole exerts its unique antimycotic mechanism of action in the following three ways: (i) inhibition of the secretion of protease acid by *Candida albicans*; (ii) damage to the cytoplasmic membrane; and (iii) by blocking cytochrome oxidases and peroxidises. Fenticonazole has also been shown to exhibit antibacterial action, with a spectrum of activity that includes bacteria commonly associated with superinfected fungal skin and vaginal infections, and antiparasitic action against the protozoan *Trichomonas vaginalis*. Therefore, fenticonazole may be an ideal topical alternative to multi-agent treatment of mixed infections involving mycotic, bacterial, dermatophyte and/or *Trichomonas* spp.

Open-label clinical studies show that fenticonazole, in different pharmaceutical preparations administered once or twice daily, is effective in the treatment of superficial mycoses of the skin. In particular, fenticonazole is very effective (often with 100% of patients achieving a negative mycological assay) in pityriasis versicolor and candidiasis. For example, a large (n = 760) study showed fenticonazole 2% cream, spray or powder to be associated with a mycological response in 100% of patients with pityriasis versicolor, 96.3% of those with tinea infections and 95.2% of patients with *Candida* infections. Comparative clinical

studies show fenticonazole once or twice daily to be at least as effective as six different topical antimycotics (miconazole, clotrimazole, econazole, bifonazole, naftifine and cyclopyroxolamine) in the treatment of superficial mycoses of the skin. Intravaginal administration of fenticonazole is associated with a high rate of microbiological efficacy in patients with vaginal candidiasis, trichomoniasis, mixed infection and bacterial vaginosis. Intravaginal fenticonazole is at least as effective as clotrimazole and shows similar efficacy to miconazole in patients with vaginal candidiasis. Fenticonazole has a rapid onset of action and clinical efficacy is generally observed within days of commencing treatment.

Topical fenticonazole is very well tolerated; adverse events are generally mild to moderate in severity and transient. The most frequent adverse events are burning sensation/cutaneous irritation and itch when applied to the skin. In a large, open-label study in superficial mycoses of the skin, the incidence of adverse events was <5% and these were rarely responsible for treatment discontinuation. Burning sensation is the most common adverse event seen with fenticonazole when administered intravaginally. However, this symptom of vaginal fungal infection was often present in patients prior to drug administration.

Given the rising incidence of superficial fungal, and possibly mixed, infections, topical fenticonazole represents an important part of the topical antimycotic armamentarium.

The incidence of fungal infections is rising as a result of increasing numbers of immunocompromised individuals, such as the elderly and patients receiving immunosuppressants for co-morbid conditions, and patients with hyperglycaemia/uncontrolled diabetes mellitus;[1] this may also be true for mixed mycotic/bacterial infections of the skin and vulvovaginal tissues. Mixed infections can be controlled with a combination of antifungal, antibacterial and corticosteroid therapy. This approach is effective, but can induce resistance and is associated with a high rate of systemic and local adverse events.

Imidazole derivatives control fungal infections by damaging the fungal cell membrane via inhibition of the fungal P450 isozyme, which is required to convert lanosterol to ergosterol, an essential component of fungal cell membrane synthesis.[2]

Fenticonazole is an effective and well tolerated broad spectrum imidazole antifungal agent that is used in the topical treatment of fungal infections of the skin and vulvovaginal tissues. It has long been known from *in vitro*[3] and clinical[4] studies that fenticonazole, as with other imidazole derivatives, has high *in vitro* activity against a wide range of fungal pathogens, as well as Gram-positive bacteria. Morphological studies suggest that fenticonazole blocks yeast enzymatic activity (cytochrome oxidase and peroxidase)[5,6] and inhibits the synthesis, rather than the activity, of secretory aspartate acid proteinase, which is a virulence enzyme of *Candida albicans* that has been correlated with adherence of the yeast to epithelial cells.[7-9] This property has also been observed with fluorocytosine, but not with fluconazole, ketoconazole or miconazole.[7]

In vitro studies suggest that fenticonazole may have a role in the treatment of mixed mycotic and bacterial infections, such as fungal skin infections superinfected with *Staphylococcus aureus*, coryneforms and streptococci.[10] Fenticonazole has also demonstrated *in vitro* activity against bacteria that are commonly associated with vaginosis, such as *Bacteroides* isolates of the *Bacteroides melaninogenicus-B. oralis* group, *Gardnerella vaginalis*, *Mobiluncus* spp. and anaerobic, Gram-positive cocci.[10]

The objective of this review is to present the current clinical data on the use of fenticonazole, including the small amount of recent, interesting

data on its efficacy in mixed infections, and to discuss the ongoing clinical role of fenticonazole in dermatological and gynaecological indications. Relevant clinical studies for fenticonazole were identified and selected for inclusion in this review from systematic literature searches. Two separate literature searches were performed using the following criteria: 1980 to the present; all languages; human clinical study or review; on MEDLINE, EMBASE and AdisBase (a proprietary database of Wolters Kluwer Health | Adis), and deduplicated for (i) Fenticonazole AND Gynaecology; and (ii) Fenticonazole AND Dermatology.

1. Results

1.1 Dermatological Indications

Fenticonazole has been investigated for the treatment of dermatological infections in 24 clinical studies (table I). Fourteen studies were randomized, double-blind or comparator-controlled studies[11-24] and ten were open-label, noncomparative trials.[25-34] Fenticonazole was compared with miconazole,[15,16,23,24] econazole,[19,21,22] bifonazole,[14,18] naftifine,[12,20] clotrimazole,[17] cyclopyroxolamine[13] and placebo.[11] Fenticonazole 2% cream was administered in the majority of studies.[11,12,15-19,23-28,30-32] Other formulations included 2% solution, lotion or spray,[13,14,20,21,25,26,30-33] 2% foam,[22] 2% gel[34] or 2% powder.[11,30] Inclusion criteria in studies were tinea pedis,[11] cutaneous mycoses,[12,13,20,21] pityriasis versicolor,[14-16,22,25,26] dermatophytosis,[15,16,34] candidiasis,[16] dermatomycoses,[17-19,23-25,32] superficial mycoses,[27-32] or otomycoses.[33] Six studies are available as English abstracts only.[22,26,27,29,31,33]

1.1.1 Open-Label/Noncomparative Studies

The first study on the efficacy and tolerability of fenticonazole was published in 1984 by Lepine et al.[34] Twenty-eight patients with dermatophytosis were treated with fenticonazole 2% gel twice daily for 28 days. Clinical resolution was seen in all of the 25 patients who completed the study. A year later, Persi and Rebora[28] treated 46 patients with superficial mycoses with fenticonazole 2% cream for 13–28 days. Clinical and mycological remission was obtained in 35 patients (76.1%). In 1986, Clerico[31] used fenticonazole 2% lotion, spray or cream in 45 patients and observed good or excellent clinical results in all patients. Different formulations (fenticonazole 2% cream and fenticonazole 2% lotion, respectively) were used to treat 30 patients with dermatomycoses and 10 patients with pityriasis versicolor.[25] Fenticonazole was applied twice daily for 5 weeks. Twenty-six of 30 patients with dermatomycoses and all 10 patients with pityriasis versicolor were cured (36 of 40 patients [90%]).

In 1987, fenticonazole, used once daily for the first time, in 30 patients with candidiasis and pityriasis versicolor[27] demonstrated clinical and mycological healing in 100% of patients after 28 days of treatment, and in eight of ten patients with epidermomycosis after 32 days. The once-daily application of fenticonazole is based on the fact that the drug is retained on the skin for 72 hours after a single application in pretreated guinea pigs.[35] This property of fenticonazole was subsequently exploited in the treatment of recurrent dermatomycoses such as tinea pedis.[11] The most important open-label, multicentre clinical trial was published in 1988.[30] Fenticonazole cream, spray or powder was applied once or twice daily in 760 patients with superficial mycoses. A negative mycological assay was obtained within 28–35 days of treatment. The clinical and mycological response rate was very high in pityriasis versicolor (100%) and in candidiasis (95%). This study suggested that once-daily application of fenticonazole may induce a high patient compliance.

Clinical and mycological remission was obtained in 51 of 51 patients with superficial mycoses[29] and in 30 of 30 patients with pityriasis versicolor[26] in studies in which fenticonazole cream or lotion was applied twice daily for 2 weeks. In 27 of 27 patients treated twice daily with fenticonazole cream or spray, a clinical and mycological cure was achieved after 4 weeks.[32] In this study, determination of fenticonazole plasma concentrations confirmed that the drug is poorly absorbed.

Table I. Summary of clinical trials of fenticonazole (FEN) in the treatment of dermatological infections

Study (year)	Design (timepoint of efficacy evaluation)	Diagnosis	Treatment (no. of pts)	Primary outcomes	
				microbiological efficacy	tolerability
Albanese et al.[11] (1992)	R, DB (4 mo)	Tinea pedis	FEN 2% CR + 2% PDR[a] (15) PL[a] (15)	Relapse seen in 17% of FEN and 50% of PL recipients	Tolerability scores were excellent or good in all cases with FEN and PL
Altmeyer et al.[13] (1990)	R, DB (2–3 wk post treatment)	Cutaneous mycoses	FEN 2% SOL 2–4 wk (50) CYC 1% SOL 2–4 wk (50)	Positive microscopic findings were seen in 6.5% of FEN and 10.6% of CYC recipients following drug-free period	Treatment was terminated early in 1 FEN pt due to slight itching
Altmeyer et al.[12] (1990)	R, DB, MC (2–3 wk post treatment)	Cutaneous mycoses	FEN 2% CR 2–4 wk (49) NAF 2% CR 2–4 wk (48)	Positive microscopic findings were seen in 15.38% of FEN and 11.36% of NAF recipients following drug-free period	No adverse events were reported
Fioroni et al.[32] (1990)	OL (4 wk)	Dermatomycoses	FEN 2% CR + SPR ≤4 wk (27)	Mycological results were negative in 100% of pts after 4 wk	No adverse events were reported
Fusetti et al.[33][b] (1990)	OL (NR)	Otomycoses	FEN 2% SOL (50)	Complete mycological remission was achieved in 100% of pts	NR
Odeh et al.[21] (1990)	R, DB, MC (2–3 wk post treatment)	Cutaneous mycoses	FEN 2% LOT 2–4 wk (92) ECO 1% LOT 2–4 wk (93)	At endpoint, 8% of FEN and 13.4% of ECO recipients were positive for fungi by microscopy and 0% and 5.06% positive by culture	1 FEN recipient reported severe redness and itching and 1 reported mild local burning on application
Di Silverio et al.[26][b] (1989)	OL (NR)	Pityriasis versicolor	FEN 2% CR or LOT (30)	Disappearance of yeast was obtained on average after 2 wk	NR
Leiste et al.[20] (1989)	R, DB, MC (2–3 wk post treatment)	Cutaneous mycoses	FEN 2% SOL 2–4 wk (50) NAF 1% SOL 2–4 wk (50)	At endpoint, 8.3% of FEN and 11.1% of NAF recipients were positive for fungi by microscopy and 5.7% and 14.7% positive by culture	3 FEN and 4 NAF recipients reported burning sensation on application
Rabbiosi et al.[22][b] (1989)	R, DB (NR)	Pityriasis versicolor	FEN 2% foam (20) ECO 1% foam (20)	Mycological healing was seen in 100% of pts in both groups	1 pt receiving FEN discontinued treatment due to cutaneous irritation
Aste et al.[14] (1988)	R, DB (21 d)	Pityriasis versicolor	FEN 2% LOT 3 wk (23) BIF 1% LOT 3 wk (23)	22% of FEN and 30% of BIF recipients were cured at 21 d	2 pts receiving FEN reported transient desquamation
Jung et al.[18] (1988)	R, DB (28 d)	Dermatomycoses	FEN 2% CR ≤4 wk (21) BIF 1% CR ≤4 wk (20)	95% of FEN and 85% of BIF recipients were negative for fungi at endpoint	No adverse events were reported
Pizzino et al.[29][b] (1988)	OL (NR)	Superficial mycoses	FEN (51)[c]	FEN showed "marked clinical efficacy"	Local and systemic tolerance was good
Sartani et al.[30] (1988)	OL, MC (28–35 d)	Superficial mycoses	FEN 2% CR, SPR or PDR (760)	Mycological response was seen in 100% of pts with pityriasis versicolor, 96.3% with tinea and 95.2% with *Candida*	Adverse events were reported in 3.8% of pts; drug discontinuation occurred in ~1.0%

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Table I. Contd

Study (year)	Design (timepoint of efficacy evaluation)	Diagnosis	Treatment (no. of pts)	Primary outcomes	
				microbiological efficacy	tolerability
Vannini et al.[24] (1988)	R, DB (35 d)	Dermatomycoses	FEN 2% CR od 3 wk (20) FEN 2% CR bid 3 wk (20) MIC 2% CR bid 3 wk (20)	80% FEN od, 90% FEN bid and 90% MIC recipients were negative for fungi on microscopic examination at endpoint	1 FEN od, 2 FEN bid and 1 MIC recipient reported mild itching and increased erythema
Aste et al.[25] (1987)	OL (5 wk)	Dermatomycoses or pityriasis versicolor	FEN 2% CR or LOT 5 wk (40 pts with dermatomycoses + 10 pts with pityriasis versicolor)	Mycological cure was seen in 100% of pts with pityriasis versicolor and 86.6% with dermatomycoses	Mild, self-limiting desquamation was reported in 7 pts
Clerico and Ribuffo[16] (1987)	R (30 d)	Pityriasis versicolor, candidiasis, or dermatophytosis	FEN 2% CR 30 d (20) MIC 2% CR 30 d (20)	Microscopic and cultural analysis remained positive in 5% of FEN and 10% of MIC recipients	No adverse events were reported
Fioroni et al.[27][b] (1987)	OL (NR)	Superficial mycoses	FEN 2% CR (30)	100% of pts with candidiasis or pityriasis versicolor and 80% with tinea pedis "healed"	Irritative contact dermatitis reported in 2 pts
Athow-Frost et al.[15] (1986)	R, DB, MC (2–3 wk post treatment)	Dermatophytosis or pityriasis versicolor	FEN 2% CR ≤4 wk (28) MIC 2% CR ≤4 wk (25)	92% of FEN and 79% of MIC recipients had negative mycology at endpoint	1 pt receiving MIC reported dry skin on the foot; no other adverse events
Clerico[31][b] (1986)	OL (NR)	Superficial mycoses	FEN 2% LOT, SPR or CR (45)	"Efficacy was good"	"Tolerability was good"
Finzi et al.[17] (1986)	R, DB (4 wk)	Dermatomycoses	FEN 2% CR ≤4 wk (21) CLO 1% CR ≤4 wk (21)	"Definite cure" was obtained in 86% of FEN and 62% of CLO recipients	No adverse events were reported
Kokoschka et al.[19] (1986)	R, DB (4 wk)	Dermatomycoses	FEN 2% CR ≤4 wk (28) ECO 1% CR ≤4 wk (24)	Clinical and mycological healing was seen in 15/28 (54%) of FEN recipients and in 10/24 (42%) of ECO recipients	No adverse events were reported
Persi and Rebora[28] (1985)	OL (28 d)	Superficial mycoses	FEN 2% CR ≤4 wk (46)	"Clinical cure" was experienced by 76.1% of pts	No adverse events were reported
Lepine et al.[34] (1984)	OL (28 d)	Dermatophytosis	FEN 2% gel 28 d (28)	Clinical resolution was seen in 100% of pts ending the study	Treatment was interrupted in 3 pts due to erythema or oedema at site of application
Stetter[23] (1984)	R, DB (4–8 wk post treatment)	Dermatomycoses	FEN 2% CR ≤4 wk (NR[d]) MIC 2% CR ≤4 wk (NR[d])	NR	No adverse events were reported

a Pts were treated with FEN 2% CR and 2% PDR for a month or until cured and subsequently randomized to FEN or PL.

b Available as English abstract only.

c Formulation NR in abstract.

d Total population for FEN plus MIC groups = 30 pts.

bid = twice daily; **BIF** = bifonazole; **CLO** = clotrimazole; **CR** = cream; **CYC** = cyclopyroxolamine; **DB** = double-blind; **ECO** = econazole; **LOT** = lotion; **MC** = multicentre; **MIC** = miconazole; **NAF** = naftifine; **NR** = not reported; **od** = once daily; **OL** = open-label; **PDR** = powder; **PL** = placebo; **pts** = patient; **R** = randomized; **SOL** = solution; **SPR** = spray.

Finally, complete clinical and mycological remission was observed in all patients (n = 50) affected by otomycoses and treated with fenticonazole for 2 weeks.[33]

1.1.2 Randomized Controlled Trials

Comparison with Miconazole

The first double-blind study of fenticonazole versus miconazole was published in 1984 by Stetter.[23] Thirty patients with symmetrical lesions caused by dermatophytes were treated. Both antimycotics were used as a 2% cream, twice daily, until healing occurred (maximum duration of the treatment was 28 days). More rapid healing of the lesions and faster disappearance of symptoms was recorded in patients receiving fenticonazole. Fenticonazole was compared with miconazole in a randomized, double-blind, multicentre study in 53 patients with dermatophytosis and pityriasis versicolor.[15] Both drugs were applied twice daily for 4 weeks. No statistically significant differences between the two drugs were recorded. However, negative mycological examination was obtained in 23 of 25 patients (92%) treated with fenticonazole and in 19 of 24 patients (79%) treated with miconazole.

Superimposable results were obtained in 40 patients with pityriasis versicolor, candidiasis or dermatophytosis who were treated with fenticonazole or miconazole cream. Clinical healing was observed in 16 patients (plus improvement in four patients) in the group treated with fenticonazole compared with 14 patients (plus improvement in five patients) in the group treated with miconazole.[16] In the most recent double-blind trial using miconazole as the comparator, fenticonazole (once or twice daily) was compared with miconazole applied twice daily in 60 patients with dermatomycoses. No differences were observed between the three groups of patients. However, the authors underlined the improvement in patient compliance with once daily application.[24]

Comparison with Clotrimazole

Only one double-blind study comparing fenticonazole 2% cream versus clotrimazole 1% cream has been published; both agents were administered twice daily for 4 weeks.[17] Eighteen lesions of 21 treated with fenticonazole and 13 lesions of 21 treated with clotrimazole were cured.

Comparison with Econazole

Three randomized, double-blind trials of fenticonazole 2% versus econazole 1% have been published.[19,21,22] In the first study, 52 patients with dermatomycoses were treated twice daily for 4 weeks.[19] Clinical and mycological healing was achieved in 15 of 28 patients treated with fenticonazole and in only 10 of 24 patients treated with econazole. Furthermore, the onset of action of fenticonazole was more rapid than that of econazole, an observation previously published by Stetter.[23] In the study by Rabbiosi et al.,[22] fenticonazole 2% foam was compared with econazole 1% foam in 40 patients with pityriasis versicolor. Both products were applied once daily for 2 weeks. Negative mycological examination was obtained in 100% of patients in both treatments. The third trial on fenticonazole versus econazole is based on the largest group of patients with cutaneous mycoses.[21] Both drugs were applied as lotions once daily for 2–4 weeks. At the end of the study, 72.7% of patients treated with fenticonazole were considered clinically and mycologically recovered compared with 71% of patients treated with econazole.

Comparison with Bifonazole

Fenticonazole was compared with bifonazole in two randomized, double-blind studies.[14,18] In 41 patients with dermatomycosis, fenticonazole 2% cream or bifonazole 1% cream was applied once daily for 4 weeks.[18] The authors observed, once again, a faster therapeutic activity of fenticonazole compared with bifonazole. In the second trial,[14] 46 patients with pityriasis versicolor were treated with fenticonazole 2% lotion or bifonazole 1% lotion, both applied once daily for 3 weeks. The authors stated that the efficacy of fenticonazole is comparable with that of bifonazole.

Comparison with Ketoconazole

A comparative study of *in vitro* activity and clinical efficacy in 51 patients with superficial skin mycoses showed that fenticonazole had similar or superior activity against the isolated pathogens

and was at least as effective as ketoconazole, miconazole and intraconazole.[29] In a clinical comparison of fenticonazole with ketoconazole and nystatin in 80 patients with erythematous chronic candidiasis, a significant reduction in oral lesions was seen in all groups ($p < 0.0001$) with no significant between group difference in efficacy.[36]

Comparison with Naftifine

Two studies compared the efficacy of fenticonazole with naftifine in patients with cutaneous mycoses. In a double-blind, multicentre trial, 100 patients were treated with fenticonazole 2% spray or naftifine 1% spray once daily for 2–4 weeks.[20] At the end of the study, about 90% of patients in both groups were cured or greatly improved, both mycologically and clinically. In another double-blind, multicentre study in 97 patients,[12] fenticonazole 2% cream was compared with naftifine 2% cream (once daily application for 2–4 weeks). Overall, 43 of 46 patients in the fenticonazole group and 43 of 48 in the naftifine group were judged to be clinically and mycologically healed.

Comparison with Cyclopyroxolamine

Altmeyer et al.[13] also studied the efficacy of fenticonazole spray versus cyclopyroxolamine 1% spray in a double-blind trial. Both antimycotics were applied once daily for 2–4 weeks in 100 patients. Clinical improvement was seen in 91.8% of patients in the fenticonazole group versus 89.8% of patients in the cyclopyroxolamine group.

1.2 Gynaecological Indications

Fenticonazole has been investigated in the treatment of vulvovaginitis caused by *Candida* spp., *Trichomonas* spp., mixed infections or bacterial infections in 17 studies (table II). Four studies were double-blind, placebo- or comparator-controlled,[4,37-39] two were single (investigator) blind,[40,41] and the remainder were open-label.[42-52] Fenticonazole was compared with placebo,[4,38,39] clotrimazole[37,40,41,45] or miconazole[46] in studies. Fenticonazole intravaginal capsules or ovules were used in all of the studies except five, which used 2% cream,[4,37] or fenticonazole ovules with or without cream[50,52] or vaginal wash;[51] fenticonazole vaginal capsules were compared with fenticonazole cream in one study.[47] Inclusion criteria in studies were vaginal candidiasis,[37,40-42,45,47-52] vaginal trichomoniasis,[38,39,51] mixed infections[43,44] and bacterial vaginosis.[4] Five studies are available as English abstracts only.[4,42,46,51,52]

1.2.1 Microbiological Efficacy

Vaginal Candidiasis

Fenticonazole intravaginal capsules, at doses of 600 mg or 1000 mg as a single dose or 200 mg daily for 3 days, 2% cream applied daily for 3 or 7 days, or a combination of fenticonazole intravaginal capsules plus cream or vaginal wash were effective at eradicating *Candida* spp. in 75–100% of patients and all organisms in 70–100% of patients with vaginal candidiasis.[37,40-42,45-52] 'Mycologic cure' was obtained in 92% of patients in a further study where the dosage of fenticonazole intravaginal capsules was not stated.[42] These eradication rates were obtained within 7 days in the majority of studies[40-42,45,46,48,49,52] and sustained for between 4 to 6 weeks in two trials.[37,51] Fenticonazole 600 mg or 1000 mg as a single dose or 200 mg daily for 3 days[49] and fenticonazole intravaginal capsules 200 mg or fenticonazole 2% cream used daily for 3 days[47] showed similar efficacy in open-label studies.

No significant differences in the proportion of patients negative for all organisms,[45] *Candida* spp.[40] or *C. albicans*[41] were seen after treatment with single doses of fenticonazole 600 mg or clotrimazole 500 mg. Moreover, *Candida* spp. were eliminated from a similar proportion of patients receiving fenticonazole cream or clotrimazole cream in a double-blind study.[37] Similar microbiological efficacy was seen at 7–10 days when fenticonazole 200 mg and miconazole 400 mg daily for 3 days were compared (both 97.5%).[46]

Vaginal Trichomoniasis

In three studies in patients with vaginal trichomoniasis, fenticonazole vaginal capsules 600 mg or 1000 mg administered as a single dose, with[51] or

Table II. Summary of clinical trials of fenticonazole (FEN) in the treatment of gynaecological infections. FEN was administered as an intravaginal capsule or ovule unless stated otherwise

Study (year)	Design (timepoint of efficacy evaluation)	Diagnosis	Treatment (no. of pts)	Primary outcomes	
				microbiological efficacy	tolerability
Fernandez-Alba et al.[44] (2004)	OL, MC (8 d)	Mixed infections	FEN 1000 mg, d 1 + 3 (101)	90% of pts were negative for *Candida albicans*, 70% for *Trichomonas vaginalis*, 67% for *Gardnerella vaginalis* and 45% for mixed infection	No treatment-related adverse events reported
Naud et al.[4]a (2003)	R, DB (9 or 28 d)	Bacterial vaginosis	FEN 2% cream 5 g, d 1–7 (NR[b]) PL (NR[b])	The "cure rate" was significantly higher with FEN vs PL (85% vs 35%; p = 0.003)	Mild treatment-related adverse event was seen in 1 FEN recipient
Munoz Reyes et al.[46]a (2002)	R, OL (7–10 d)	Vaginal candidiasis	FEN 200 mg, d 1–3 (40) MIC 400 mg, d 1–3 (40)	Microbiological efficacy was considered satisfactory in 97.5% of pts in both groups	Minor adverse events were seen in 0 FEN and 2 MIC recipients
Belaisch[42]a (1996)	OL (7 d)	Vaginal candidiasis	FEN d 1 (116) FEN d 1 + 4 (58) [dose NR]	Mycological cure demonstrated by microscopic examination seen in 92% of pts	Treatment acceptance and tolerance rated as "good" or "excellent" by 92–98% of women
Scalambrino et al.[51]a (1996)	OL, MC (28–35 d post treatment)	Vaginal trichomoniasis ± candidiasis	FEN 1000 mg d 1 + vaginal wash × 5 (67)	Vaginal smears were negative for *T. vaginalis* and *Candida* spp. in 100% of pts	Tolerability was judged as "excellent"
Gorlero et al.[39] (1994)	R, DB, MC (7 d)	Vaginal trichomoniasis	FEN 600 mg, d 1 + 2 (21) FEN 1000 mg, d 1 + 2 (20) PL (20)	Significantly more pts receiving FEN 1000 mg (58.8%) or 600 mg (65.0%) were negative for *T. vaginalis* vs PL (15.0%) [p ≤ 0.005]	Mild or moderate burning sensation (2 pts) or burning sensation and discharge (1 pt) were reported with FEN 1000 mg
Gorlero et al.[38] (1992)	R, DB (4 d)	Vaginal trichomoniasis	FEN 600 mg, d 1 (32)[c] FEN 1000 mg d 1 (33)[c] PL (31)[c]	Significantly more pts receiving FEN 1000 mg (64%) were negative for all organisms vs FEN 600 mg (28%) and PL (16%) [p < 0.01]	Tolerance to all treatments was generally good
Bukovsky et al.[43] (1991)	OL (7 d)	Mixed infections	FEN 600 mg, d 1 [+ d 7 if symptoms persisted] (87)	45% of pts were negative for all organisms, 67% for *T. vaginalis* and 96% for *C. albicans*	No systemic or local adverse events reported
Lawrence et al.[45] (1990)	R, OL (7 d)	Vaginal candidiasis	FEN 600 mg, d 1 (75) CLO 500 mg, d 1 (78)	A similar proportion of FEN and CLO recipients were negative for all organisms (92.0% vs 88.5%)	Mild, local and short-lasting burning (2 pts), soreness (2 pts) or vaginal discharge (1 pt) were reported with FEN

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Table II. Contd

Study (year)	Design (timepoint of efficacy evaluation)	Diagnosis	Treatment (no. of pts)	Primary outcomes	
				microbiological efficacy	tolerability
Schneider et al.[48] (1990)	OL (7 d)	Vaginal candidiasis	FEN 600 mg, d 1 [+ d 8 if symptoms persisted] (72)	76% of pts were negative for all organisms and 92% negative for *C. albicans*	No local or systemic adverse events were reported
Studd et al.[40] (1989)	R, SB, MC (7 or 8 d)	Vaginal candidiasis	FEN 600 mg, d 1 (23) CLO 500 mg, d 1 (20)	A similar proportion of pts receiving FEN or CLO were negative for *Candida* spp. (78% vs 70%)	Short-lasting burning sensation was reported by 1 pt receiving FEN
Wiest et al.[41] (1989)	R, SB (7 d)	Vaginal candidiasis	FEN 600 mg, d 1 (40) CLO 500 mg, d 1 (40)	A similar proportion of pts receiving FEN or CLO were negative for *C. albicans* (87.5% vs 92.5%)	No local or systemic adverse events were reported
De Cecco et al.[50]a (1988)	OL, MC (NR)	Vaginal candidiasis	FEN cream, d 1–3 (31) FEN 200 mg d 1–3 (192) FEN 200 mg + cream, d 1–3 (46)	80.6% of pts treated with cream, 83.1% treated with ovules and 83.8% treated with cream + ovules showed negative microscopy	Local adverse events were reported in 4 pts and systemic adverse events in 2 pts
Sartani et al.[47] (1988)	OL, MC (≤15 d)	Vaginal candidiasis	FEN 200 mg, d 1–3 (334) FEN 2% cream, d 1–3 (50)	A similar proportion of suppository and cream recipients were negative for all organisms (82.6% vs 70.0%)	Adverse events were reported in 9 vaginal capsule and 3 cream recipients
Scienza et al.[52]a (1987)	OL (10 d)	Vaginal candidiasis	FEN 200 mg od or FEN cream 100 mg bid, d 1–3 (20)	Cultures were negative in 100% of pts 7 d after end of treatment	No local or systemic adverse events were reported
Wiest and Ruffman[49] (1987)	R, OL (7 d)	Vaginal candidiasis	FEN 200 mg, d 1–3 (20) FEN 600 mg, d 1 (20) FEN 1000 mg, d 1 (20)	A similar proportion of pts receiving FEN 200, 600 or 1000 mg were negative for *C. albicans* (80%, 75% and 85%)	Local burning sensation was reported by 1 pt receiving FEN 200 mg and 2 pts receiving FEN 1000 mg
Brewster et al.[37] (1986)	R, DB (4–6 wk)	Vaginal candidiasis	FEN 2% cream 5 g, d 1–7 (27) CLO 1% cream 5 g, d 1–7 (27)	Mycological swabs were negative in 96.0% of FEN pts and 96.1% of CLO pts	No local or systemic signs or symptoms of toxicity were reported

a Available as English abstract only.

b Total population for FEN plus PL groups = 47 pts.

c All women received an additional dose of fenticonazole 600 mg if still positive for *Trichomonas* at d 4 regardless of treatment allocation.

bid = twice daily; **CLO** = clotrimazole; **DB** = double-blind; **MC** = multicentre; **MIC** = miconazole; **NR** = not reported; **od** = once daily; **OL** = open-label; **PL** = placebo; **pts** = patients; **R** = randomized; **SB** = single-blind.

without[38] vaginal wash for 5 days, or daily for 2 days without vaginal wash[39] eradicated all organisms in 28–65% of patients at 7 days; eradication of *T. vaginalis* and *Candida* spp. was seen in 100% of patients at day 7. A single dose of fenticonazole 1000 mg was significantly more effective than fenticonazole 600 mg ($p < 0.01$),[38] but no significant between-group difference was seen with fenticonazole 1000 mg or 600 mg administered daily for 2 days.[39]

Mixed Infections

Fenticonazole 600 mg as a single dose or 1000 mg on days 1 and 3 eradicated all organisms in 45% of patients after 7–8 days in two open-label studies.[43,44] At trial endpoint, 96% and 90% of patients were negative for *C. albicans*, and 67% and 70% were negative for *T. vaginalis* following treatment with fenticonazole 600 mg or 1000 mg, respectively.

Bacterial Vaginosis

A significantly higher microbiological cure rate was seen in patients with bacterial vaginosis treated with fenticonazole 2% cream 5 g daily for 7 days compared with placebo in a randomized, double-blind study (85% vs 35%; $p = 0.003$) [timepoint not stated in abstract].[4] The recurrence rate was 11.8% in the fenticonazole group and 50% with placebo.

1.2.2 Clinical Efficacy

In the majority of studies in patients with vaginal candidiasis, fenticonazole produced an improvement in signs and symptoms (e.g. erythema, pruritis/irritation/burning, discharge, oedema) within days and complete resolution of some or all symptoms in 52–100% of patients within 1 week.[40,42,45-48] In a randomized comparative study, symptom relief was considered satisfactory in 100% of patients receiving fenticonazole and 97.5% of patients receiving miconazole.[46]

In vaginal trichomoniasis, significantly greater symptomatic improvement (discharge, pruritus, erythema, oedema and overall score) was seen with single-dose fenticonazole 1000 mg compared with fenticonazole 600 mg or placebo at day 4 and 8 (all $p < 0.05$), but no significant difference was seen between fenticonazole 600 mg and placebo.[38] However, in a later, larger study, fenticonazole 1000 mg and 600 mg daily for 2 days, but not placebo, significantly improved all individual and total symptom scores from baseline at day 7, although no significant difference between the active groups was seen.[39]

Fenticonazole produced significant improvements from baseline in signs and symptoms of vaginal infection in two studies of mixed infections at 7–8 days (all $p < 0.05$).[43,44]

1.3 Tolerability

Fenticonazole 2% cream, lotion/solution, foam and powder were well tolerated when administered for up to 4 weeks in patients with cutaneous mycoses, pityriasis versicolor, dermatomycoses or tinea pedis. The most common adverse events associated with topical application of fenticonazole were burning sensation/cutaneous irritation and itch on application, which occurred in 1.1–6.0%[20-22] and 1.1–10.0%[13,21,24] of patients, respectively. However, in a large number of studies, no adverse events were reported.[12,16-19,23,28,32] In a large (n = 760), open-label study, adverse events were reported in 3.8% of fenticonazole recipients and these precipitated drug discontinuation in approximately 1% of patients.[30] Other adverse events occurring in >1% of patients following topical application of fenticonazole included erythema[21,24] and desquamation.[14,25]

Fenticonazole vaginal capsules or ovules and cream were well tolerated in women with vaginal candidiasis, trichomoniasis, bacterial or mixed infections in studies of up to 4–6 weeks' duration. The most common treatment-related adverse event was burning sensation, often short-lasting and mild to moderate in severity, occurring in up to 7.3% of patients receiving fenticonazole;[37,39-41,43-49] however, this adverse event was reported in <1% of patients in six of these studies.[37,41,43,44,46,48] It is worth noting that burning sensation, a recognized symptom of vaginosis, was used as a parameter to symptom score eligible patients in several studies and was sometimes present at baseline. Other ad-

verse events reported in >1% of patients receiving fenticonazole vaginal capsules or cream were vaginal soreness (2.7%) and vaginal discharge (1.3%).[45]

2. Conclusions

Fenticonazole has broad spectrum activity against *Candida* spp. and other yeasts, dermatophytes, *Trichomonas* spp. and many of the bacteria commonly associated with skin and vaginal infections. Fenticonazole is the only imidazole antifungal agent to demonstrate single-dose and dose-dependent suppression of candidal proteinase secretion *in vitro*. Fenticonazole provides rapid control and is well tolerated in a variety of skin and vaginal infections. No systemic effects and no major local tolerability issues have been reported in over 20 years of clinical use. Recent *in vitro* studies have suggested that fenticonazole may be effective in the treatment of mixed infections involving mycotic, bacterial, dermatophyte and/or *Trichomonas* organisms, and this has been shown in several clinical studies. Although fenticonazole is one of the earlier imidazoles developed, recent studies have continued to demonstrate its clinical usefulness as a low-cost, first-line agent in the treatment of skin and vulvovaginal infections. In view of the increasing incidence of mixed aetiology infections due to population aging and increasing co-morbidity, the potential clinical utility of fenticonazole in this area warrants further investigation in large, randomized clinical trials.

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