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Fenticonazole: an effective topical treatment for superficial mycoses as the first-step of antifungal stewardship program

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Abstract. – The resistance of microorganisms to antimicrobial drugs is a major issue for public health, with important consequences in terms of morbidity, mortality and resource use. The phenomenon is so serious that in some areas of the world resistant strains to all available drugs have been selected.

Many conditions may result in the development of resistance: they include the indiscriminate or inappropriate (e.g., for viral infection or colonization) use of antibiotics, the excessive duration of the prescribed treatment regimens, as well as inadequate dosing or administration routes.

Resistance is well-known, but less studied, also for infections caused by fungi.

In the last decade, an impressive outbreak of *candidiasis* due to *non-albicans* strains (with variable patterns of resistance to azoles) was observed. This outbreak was likely associated with inappropriate use of oral azoles for the treatment of non-complicated candidiasis, such as vulvovaginal candidiasis or *Candida* dermatitis.

In this setting, fenticonazole may represent an effective topical drug for the treatment of mycotic infections of skin and mucosa. Topical treatment of superficial mycoses still holds a major importance as it helps reduce the exposure to oral systemic azoles – mainly fluconazole and itraconazole – of intestinal microbiota, which represents the main human reservoir of yeasts.

This strategy can contribute to reduce the selection of resistant strains of *Candida*, within the context of a really-effective antifungal stewardship program.

Key Words:
Antimicrobial stewardship, Fenticonazole, Antimicrobial drugs, Mycotic infections, Intestinal microbiota.

Introduction

Superficial fungal infections or mycoses are common, treatable conditions. Superficial fungal infections are defined as infections in which the pathogen is confined to the superficial layer, with minimal or no histological signs[1].

The dermatophyte or ringworm infections, superficial candidosis of the mouth, skin or genital tract and infections due to *Malassezia*, such as *Pityriasis versicolor*, are the main conditions. Tinea affects external areas of the body. Candidiasis is caused most often by the yeast *Candida albicans*, although in recent years, cases due to non-albicans strains are increasing significantly. Candidiasis often affects the genitals or inside of the mouth.

All these infections are usually diagnosed clinically. However, microbiological diagnosis is also crucial, and it becomes mandatory when infection by non-albicans strains of Candida species is suspected. Treatment largely depends on the use of azole (imidazole/triazole) or allylamine antifungals, applied in short courses topically or for longer periods orally, depending on the site and severity of the infection.

In particular, topical antifungal treatment with imidazole derivatives results in a relevant benefit for the treatment of superficial mycoses[2]. Among different therapies, fenticonazole applied once- or twice daily appears at least as effective as other topical antifungals (ciclopyroxolamine, naftifine, and many imidazole derivatives) in the treatment of superficial skin mycoses and vulvovaginal candidiasis[3,4]. This review presents and discusses current evidence on fenticonazole and the role of this molecule in clinical practice.

Pharmacology

Fenticonazole [alpha-(2,4-dichlorophenyl)-beta, N-imidazolylethyl 4-phenylthiobenzyl ether nitrate] is an imidazole derivative that was developed for the topical treatment of fungal infec-

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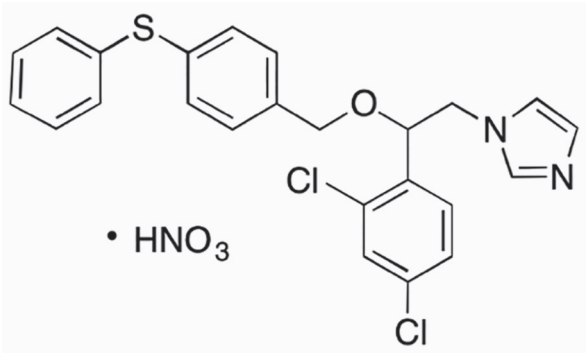

Figure 1. Chemical structure of fenticonazole.

tions. This molecule presents a wide spectrum of activity against dermatophytes and yeasts (Figure 1)[5,6].

Fenticonazole exerts antifungal activity by three different mechanisms: (1) inhibition of the release of protease acid by *Candida albicans*[9,10]; (2) alteration of the cytoplasmic membrane, via inhibition of the fungal P450 isozyme, which is necessary to convert lanosterol to ergosterol, an essential component of fungal cell membrane synthesis[11]; and (3) blockade of cytochrome oxidases and peroxidases[7-12].

A scanning electron microscopic study of the effect of fenticonazole on cells of *C. albicans* revealed the induction of cytoskeletal changes and alterations in the structure of plasma membrane, more evident with increasing concentrations of the molecule[7]. Moreover, at concentrations close to the Minimal Inhibitory Concentration (MIC), the inhibition of the formation of pseudohyphae of *C. albicans* is observed[8]. Table I reports the MIC of fenticonazole for different *Candida* strains, with other azoles as comparison[13].

Fenticonazole exerts also an interesting antibacterial activity, with a spectrum that comprises Gram-positive bacteria (such as *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus spp.*), which often super-infect the skin and vaginal infections[14] and an antiparasitic action against *Trichomonas vaginalis*[15,16].

As a drug belonging to the class of imidazoles, where metronidazole is the prototype most commonly used today, fenticonazole is also active against parasites such as *Trichomonas vaginalis* or some bacterial species such as *Gardnerella vaginalis*. The anti-*Trichomonas* action seems to be based on the cyto-lethal activity of a radical anion distinguished by a short half-life, produced under anaerobic conditions, while the antibacterial activity would be linked to the effect of a selective cytotoxic oxidative metabolite[17].

The acute toxicity after oral and topical sub-chronic toxicity intake were studied in animal models[18]. The acute oral LD_{50} in dogs, mice and rats ranged between 1,000 mg/kg and 3,000 mg/kg. Topical sub-chronic toxicity was studied in rats and dogs, showing no histopathological abnormalities following the administration of fenticonazole.

Fenticonazole does not affect release and activity of histamine, adrenaline, noradrenaline and acetylcholine, and vital functions such as blood pressure, heart rate, and pulmonary ventilation[19].

Two other pharmacological characteristics of fenticonazole are worth mentioning. The drug is retained in the stratum corneum of the skin for a long time[20], and it has peculiar pharmacokinetic properties that allow its accumulation in the mucosal tissue as active drug up to 72 hours, this allowing the formation of a reservoir of fenticonazole and delaying consecutive administrations[21]. Furthermore, the determination of plasma levels of fenticonazole has confirmed that the drug is poorly absorbed at a systemic level[22].

Table I. Susceptibilities of 260 VVC isolates and quality control strains (EUCAST broth microdilution method).

Isolate	Fenticonazole		Itraconazole		Fluconazole		Ketoconazole	
	MIC_{50} range (µg/ml)	GM (µg/ml)	MIC_{50} range (µg/ml)	GM (µg/ml)	MIC_{50} range (µg/ml)	GM (µg/ml)	MIC_{50} range (µg/ml)	GM (µg/ml)
C. albicans	0.03-0.25	0.10	0.03-0.5	0.6	0.12-32	1.84	0.12-4.0	0.54
C. glabrata	0.03-0.5	0.28	0.03-0.5	0.10	2.0-≥64	7.51	2.0-8.0	2.13
C. parapsilosis	0.03-0.25	0.13	0.06-012	0.09	0.5-4	2.14	0.12-0.5	0.21
C. krusei	0.06-1	0.20	0.03-0.12	0.08	32-64	45.25	0.12-1	0.26

GM: geometric mean

Clinical Studies in Dermatology

A number of open, controlled trials on fenticonazole are available in the dermatology setting. Overall, clinical evidence shows that the different formulations of fenticonazole are effective in the treatment of cutaneous fungal infection, and that the side effects are rare and of mild severity.

A study conducted in 1987[23] on 30 patients with candidiasis, tinea versicolor and epidermomycoses treated with fenticonazole once daily has documented a clinical and microbiological response in all patients after 28 days of therapy (in the case of candidiasis and pityriasis), and after 32 days in 8 out of 10 patients with epidermomycoses.

One large clinical trial, conducted in 1988[24], was a multi-center, open-label trial in which fenticonazole cream, spray or powder were applied once or twice daily in 760 patients with superficial mycoses. The mycological negativity was achieved by the fifth week of treatment, with a marked clinical response in patients with tinea versicolor (100%) and candidiasis (95%). Twenty-nine patients reported adverse events, but only 8 subjects were required to stop treatment.

Controlled clinical trials on the use of fenticonazole led to similar results.

In a study by Clerico et al[25], 40 patients with tinea versicolor, candidiasis or dermatophytosis were treated with 2% fenticonazole or miconazole cream. Clinical response was observed in 16 out of 20 patients (80%) in the group treated with fenticonazole, versus 14/20 patients (70%) in the group treated with miconazole.

A multi-center, double-blind study[2] was conducted on 100 patients with cutaneous fungal infections, in order to compare the efficacy and tolerability of spray formulations of fenticonazole 2% and naftifine 1%. The patients were treated once a day for 2 to 4 weeks. *Candida albicans* was present in 33.3% of patients in fenticonazole group and 20.8% in naftifine group. At the end of treatment, only 3 (6.3%) and 5 (10.4%) patients – out of the 48 evaluated in each group – still had a positive mycological examination. The evaluation of the symptoms showed a marked improvement with respect to baseline: 90% of patients in each group were considered cured or greatly improved. Follow-up data showed that, among patients cured or greatly improved at the end of treatment, only 1 patient (3.2%) on fenticonazole and 2 patients (6.3%) on naftifine experienced mycological relapse.

Clinical Studies in Gynaecology

In the gynaecological setting, fenticonazole was studied in the treatment of *Candida* vulvovaginitis[26-36] and mixed infections[34,37-39].

In all studies, the diagnosis was based on clinical history and presentation, direct mycological examinations and cultures. However, no study to date evaluated recurring infections.

Most studies were open label[27,28,31,33-35,37-39] but four were double-blind, controlled or -single comparator trials[26,29,30,32,36]. Four studies compared fenticonazole with clotrimazole[26,29,30,32], and one fenticonazole with fluconazole[36].

Nine studies were conducted on ovule formulations[27,29,30,32-34,36-38]; two studies with the combination of cream with ovules[27,34]; and one study on the combination of ovules and vaginal lavage[39].

In more details, vaginal capsules (600 mg or 1 g as a single dose or 200 mg/day for three days), 2% cream for 3 or 7 days, or a combination of capsules with cream or vaginal lavage, were effective in the treatment of infections in 75-100% of patients and allowed the eradication of *Candida spp.* in 70-100% of patients[26-34,37]. Eradication was obtained within one week in most studies[27,29-33,37]. Fenticonazole 600 mg or 1 g as a single dose or 200 mg/day for three days has shown a similar efficacy profile[27].

In a study on 417 women with vaginal candidiasis, published in 2012[32], the efficacy and tolerability of treatment with a vaginal capsule of 600 mg of fenticonazole were evaluated. Patients were re-evaluated on day 1, 7 and 28 after treatment. After seven days, a significant reduction in symptoms (vaginal discharge and itching) was observed. Microbiological control with vaginal smear documented a complete response in 385/417 women (92.3%). After one week of treatment, 84 women have repeated the therapy for persistent symptoms or positive smear. At day 28, complete recovery was reported in 392 patients (94%), and only one patient showed worsening of symptoms. Side effects were infrequently reported, and mainly consisted of moderate redness of the vulva and vagina, and a slight itching during the first days of therapy.

In a recent study[35] on reproductive-aged patients with acute vaginal candidiasis, 54 women received one 600-mg vaginal fenticonazole capsule. Seven of them had acute complicated vulvovaginal candidiasis and received a second 600-mg fenticonazole capsule on day 4 after treatment initiation. In a subsequent stage of investigation, 57 patients with acute vaginal candidiasis were given 2 intravaginal fenticonazole capsules (days 1 and

4). Overall, the response rates were 100% in the first stage of the study and 97% in the second.

In a prospective study[36], 80 patients with confirmed vulvovaginal candidiasis were randomly assigned to either intra-vaginal tablet fenticonazole (600 mg) or oral fluconazole (150 mg). Two sequential doses of azoles were given 3 days later (short-course treatment). At 30 days after treatment, 32/40 patients (80%) in fenticonazole group and 31/40 patients (77.5%) in the fluconazole group were cured. Vulvovaginal pruritus was reduced in a lower time in patients assigned to fenticonazole than in those receiving fluconazole (2.3 days *vs.* 4.5 days, p=0.047).

In a multicenter, prospective, open-label study[39], fenticonazole (1 g vaginal suppositories once daily on days 1 and 3), was used for the treatment of mixed vulvovaginal infections with *Candida albicans*, *Trichomonas vaginalis*, and/or *Gardnerella vaginalis*. The rate of eradication of *Candida albicans* at day 8 was 90% (26/29); 28 days later, no recurrence was reported, while the success rate was 73% for *G. vaginalis*, and 77% for mixed infection. In addition, a significant improvement in signs and symptoms were observed at day 8, as compared with baseline (p<0.05). Overall similar results were reported in other studies on patients with vulvovaginal candidiasis[29,31,32], with fenticonazole resulting in an improvement of the signs (erythema, edema) and symptoms (itching, burning) within a couple of days since the first administration and complete resolution of some or all of symptoms in 52-100% of patients within one week.

Fenticonazole has also an antibacterial activity against Gram-positive bacteria and an antiparasitic action against *Trichomonas vaginalis*[15,16].

In three studies conducted in patients with vaginal trichomoniasis, fenticonazole vaginal capsules 600 mg or 1000 mg administered as a single dose, with[34] or without vaginal wash for 5 days, or daily for 2 days without vaginal wash eradicated all organisms in 28-65% of patients at 7 days; eradication of *Trichomonas vaginalis* and *Candida spp* was seen in 100% of patients at day 7. A single dose of fenticonazole 1000 mg was significantly more effective on *Trichomonas* than 600 mg single dose (p<0.01)[40,41].

In the case of mixed infections, two open-label studies (600 mg as a single dose, or 1000 mg on days 1 and 3) demonstrated the complete eradication in 45% of patients after 7-8 days[38,39]. At trial endpoint, 96% and 90% of patients eradicated *Candida albicans*, and 67% and 70% eradicated *Trichomonas vaginalis*, with fenticonazole 600 mg or 1000 mg, respectively.

With more specific reference to tolerability, fenticonazole – in any formulation – was very well tolerated for up to 4-6 weeks. The most common adverse event was burning, in most cases of short duration and mild-to-moderate, occurring in about 7% of patients[26,27,29-32,39]. However, this adverse event has been reported in <1% of patients in four studies[26,21,31,39], and was already present at baseline in most cases.

The Future of Topical Treatments of Superficial Mycoses: Antifungal Stewardship in Dermatology and Gynaecology

Antimicrobial resistance is a worldwide issue with large clinical and economic impact. The selection of resistant strains may eventually lead to the increased prevalence of non-albicans *Candida* strains, with variable sensitivity and even full resistance to azoles. This problem is rapidly emerging, mainly for two reasons. First, because oral antifungal medications are prescribed in most cases at low doses or inappropriately. A recent analysis[42] revealed that 12.6% of outpatient visits in the United States led to the prescription of an antibiotic, and 30% of these prescriptions can be considered inappropriate.

The direct-to-consumer sales might then further complicate the problem of inappropriate use: it has been shown that only one-third of patients with a self-diagnosed vulvovaginal candidiasis infection purchasing an over-the-counter (OTC) drug for treatment had a laboratory-confirmed diagnosis[43]. In the US, clotrimazole and miconazole were the first topical antifungal drug available as OTC, since 1991. A trend to a decrease in average annual rates of visits at physician office for symptoms of vaginitis and vulvovaginal candidiasis has been observed, clearly linked with the OTC availability. However, and not surprisingly, trends in antifungal prescriptions increased in favour of oral azoles, such as fluconazole. It means that women firstly self-treated infections with OTC drugs (and it was correct only in one third of cases), and then their gynaecologists prescribed preferentially oral azoles[44]. On the other hand, it must be acknowledged that in many countries it is impossible to guarantee a correct microbiological diagnosis for vulvovaginitis. Moreover, there is an increasing tendency to prescribe oral medications as a first-line therapy, although current guidelines indicate the equivalent topical therapy to

oral treatment in superficial infections[44]. Indeed, topical therapies are proven to be as effective as systemic treatments in uncomplicated fungal infections. In addition, oral formulations expose the intestinal microbiota to the active compound, thus promoting the selection of resistant strains. On these bases, it can be suggested that the use of topical anti-mycotic drugs with a broad spectrum of action, such as fenticonazole, either as an OTC or RX medication, can be considered a cost-effective solution, allowing woman with symptomatic vaginal discharge to successfully cure infections of different etiology minimizing the risk of selecting drug-resistant strains[45].

Emergence of resistant strains is a well-known issue in clinical microbiology, and it is raising dramatically also in fungal infections. As an example, most recently, the emergence of *Candida auris* was reported. This fungus can cause invasive infections, associated with high mortality and is often resistant to the three classes of antifungal drugs (azoles, echinocandins and polyenes). *C. auris* was first described in 2009 in Japan, and afterwards reports of infections, including systemic ones, have been published from Colombia, India, Israel, Kenya, Kuwait, Pakistan, South Africa, South Korea, Venezuela, and the United Kingdom[46]. Infections often occur as nosocomial outbreaks, affecting patients of any age. A large part of isolates is fluconazole resistant, and amphotericin B and echinocandin resistance rates are approximately 30%-40% and approximately 5%-10%, respectively. Not less than 50% of isolates are multidrug resistant (considering multidrug resistant those strains resistant to 2 or more antifungal classes). Pandrug resistant isolates were reported. Preferential treatment regimens are unknown. Mortality rates are high, up to 70% during candidemia[47].

Antimicrobial Stewardship Programs (ASPs) may represent a solution to minimize the development of resistance[48].

The Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) defined ASP as "*coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration"*.

In the field of ASPs for antifungal therapies, the international debate is mostly focused on the optimization of the prescription and use of systemic antifungal drugs of high cost. However, the high number of prescriptions of some systemic oral azoles (in particular fluconazole and itraconazole) is almost ignored by community medicine and hospitals. Noteworthy, hospitals may be the ideal setting to organize ASPs because they can be easily controlled and refer to a single pharmacy structure, which represents the fundamental support for their realization. However, ASPs are difficult to implement in hospitals and have a poor acceptance[49]. However, the use of antibiotics in hospitalized patients represents only 38.5% of the total market of antibiotics, while the largest part of the antibiotic market is administered to outpatients and is, therefore, more difficult to control[50].

An effective ASP must be designed and constructed with a comprehensive vision, *i.e.* by including all prescription contexts, from general practitioners to specialist offices and referral acute care hospitals.

To date, ASPs were mainly implemented in acute-care hospitals, but inappropriate antibiotic use and high prevalence of multi-resistant organisms are also common in long-term care facilities (LTCF) or community medicine. On the other hand, the ASP strategies used in the acute-care hospitals cannot be automatically extrapolated to LTCFs or general community medicine due to the differences in patients and available resources[51]. In fact, high-cost drugs (new azoles, echinocandins and lipid formulations of polyenes) are generally only used in hospitals. However, it is necessary to pay attention to all prescription contexts, and especially to the outpatient setting which is often the most relevant in terms of market share. In the case of superficial fungal infections, it should be taken into account that inexpensive drugs such as fenticonazole are available and represent suitable and effective options within an ASP. The availability of non-systemic drugs as fenticonazole, with proven efficacy in the treatment of uncomplicated infections, and without a significant impact on the microbiota should be highlighted with greater strength in the guidelines and reference documents issued by the national and international scientific societies. Fenticonazole is an antifungal drug for topical use which has shown a broad spectrum of action and a high efficacy for the treatment of mucocutaneous candidiasis and fungal infections of the skin. Given also the availability of different formulations, fenticonazole can certainly be considered a cornerstone in the effective treatment of non-severe

fungal infections, minimizing the risk of selecting drug-resistant strains.

To this end, current guidelines issued by the Infectious Diseases Society of America (IDSA) recommend a single 150-mg dose for fluconazole therapy[52]. However, this selection of dosage is based on studies published years ago[53,54], which may not immediately represent current Candida epidemiology. Dosing regimens producing prolonged sub-MIC effects appeared to contribute to the selection of resistant strains, as it was demonstrated with a murine model of systemic *Candida albicans* infection used to examine resistance emergence during exposure to the triazole antifungal fluconazole[55]. Moreover, a recent experience reported that patients with candidemia due to fluconazole-nonsusceptible *Candida* species were more likely to have received prior fluconazole therapy. Suboptimal initial dosing of prior fluconazole therapy was associated with candidemia with fluconazole-nonsusceptible *Candida* species[56].

Conclusions

Inappropriate treatment of uncomplicated infections can heavily affect the ecological characteristics of pathogenic fungi such as *Candida*, worsening the outcome of infections. In an effort to minimize this risk, ASPs need to be reformulated. It appears quite evident that until now it is only kept in mind the economic aspect, trying to contain the consumption of high-cost drugs, and ignoring the concept of appropriateness, which is the real aim of any ASP. In this setting, topical fenticonazole represents a safe and effective option which can help to reduce the exposure to oral systemic azoles – mainly fluconazole and itraconazole – of intestinal microbiota, which represents the main human reservoir of yeasts.

This strategy can contribute to reduce the selection of resistant strains of *Candida*, within the context of a really-effective antifungal stewardship program.

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Conflict of interest

The authors declare no conflicts of interest.

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