Fenticonazole for the treatment of *Candida albicans* infections

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Summary

**Background/Purpose.** This review discusses the treatment of cutaneous and vulvovaginal candidosis with topical fenticonazole, an imidazole derivative with a wide spectrum of activity against dermatophytes and yeasts.

**Data sources and study selection.** Review of published studies.

**Data synthesis.** The main mechanism of action of fenticonazole is based on the inhibition of the synthesis of aspartate acid proteinase, a virulence enzyme of *Candida albicans* correlated with the adherence of the yeast to epithelial cells. This activity is quite peculiar as it was not observed with fluconazole, ketoconazole and miconazole.

Topical treatment (1 application/day for 4 weeks) is recommended, while in widespread or everlasting mycotic infections, fenticonazole must be associated with an oral antimycotic. Fenticonazole in monotherapy is also effective in treating vulvovaginal candidosis (ovules, cream or douche; 1 application/day for 7 days).

In addition, all pharmaceutical formulations of fenticonazole are well tolerated.

**Limitations.** Although fenticonazole is one of the earliest imidazoles developed in Europe, no experimental and clinical data on development of *C. albicans* resistance have been published.

**Conclusions.** Literature data demonstrated that fenticonazole is effective in *Candida albicans* infections of the skin and female genitalia.

**KEY WORDS:** Candida albicans; Candida *sp.*; cutaneous candidosis; fenticonazole, vulvovaginal candidosis.

Introduction

Fenticonazole [(α-(2,4-dichlorophenyl)-β, N-imidazolylethyl 4-phenylthiobenzyl ether nitrate] is a topical imidazole derivative which demonstrated a wide spectrum of activity against dermatophytes and yeasts both *in vitro* and clinical studies. We present a review of literature data on the treatment of cutaneous and vulvovaginal candidosis with topical fenticonazole.

Toxicological studies

The toxicity profile of fenticonazole was studied in mice, rats, guinea pigs and beagles. The acute oral LD50 was 3 g/kg in mice and rats and 1 g/kg in dogs. The subchronic (6 weeks) topical toxicity was studied in guinea pigs and dogs: no histopathologic abnormalities were found. Fenticonazole does not affect physiological functions (blood pressure, heart rate, pulmonary ventilation); furthermore, it does not interfere with histamine, adrenaline, noradrenaline and acetylcholine release and activity. Fenticonazole does not show anti-inflammatory or analgesic activity. In mice, a mild depressant activity on the central nervous system has been observed, although it was lower than that reported with miconazole (1).

Fenticonazole was tested for mutagenicity by the *Salmonella* reversion assay: it was found to be negative in TA 98, TA 100, TA 1535, TA 1537 and TA 1538 strains, with and without microsomal activation (2). Furthermore, it showed no mutagenic activity by means of a mutational assay on *Schizosaccharomyces pombe* and the mitotic gene conversion test on *Saccharomyces cerevisiae* (3).

Several tests were conducted in order to evaluate the irritating, allergic and toxic potential of fenticonazole. When instilled into the conjunctival sac of rabbits, fenticonazole caused a mild erythema in only one animal. This erythema appeared one hour after the application of the drug and disappeared within 24 hours (4). Guinea pigs were treated with 2% fenticonazole...
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cream or gel for twenty days; they developed a mild erythema which appeared five days after the beginning of the treatment and disappeared when the treatment was stopped (4). However, treatment with 2% fenticonazole either in cream or gel did not induce allergic reactions (4); in addition, it was neither photoallergic nor photo toxic (4).

A double-blind, randomized trial was performed on twelve healthy volunteers to evaluate the irritating and allergic potential of 2% fenticonazole cream and spray versus 2% miconazole cream and 1% econazole spray. There was no evidence of irritation after treatment with fenticonazole cream, its excipients, miconazole cream and fenticonazole spray and its excipients (5, 6). Neither fenticonazole cream nor spray showed evidence of sensitization (6). Local tolerability of two fenticonazole foams (one containing 4 g and one 20 g of sodium lauryl ether sulphate) was studied in 46 healthy volunteers. A standard amount of foam was applied in the evening to an area of 20 cm² on the forearm or on the trunk of each subject for a period of two weeks. No reactions were observed in the group of 20 subjects who were treated with the foam containing 4 g of sodium lauryl ether sulphate. On the other hand 2 out of 26 subjects who received the foam containing 20 g of sodium lauryl ether sulphate developed a mild, transient local reaction (7).

On the basis of the results of these studies, all pharmaceutical preparations of fenticonazole can be considered as barely and mildly irritating and very rarely sensitizing.

Preclinical studies

The in vitro activity of fenticonazole as antimycotic and antibacterial agent was assessed in 1981; the antibacterial activity was observed only in Gram-positive bacteria, whereas no activity was detected against Gram-negative bacteria (8, 9). However, no controlled clinical trials on the antibacterial activity of fenticonazole were published.

The in vitro antimycotic spectrum was very broad and included dermatophytes, yeasts and dimorphic fungi (10-12). The highest activity against yeasts was registered in vitro, at a pH ranging from 4 to 5 (10-12). Fenticonazole was active against Candida albicans, and its activity was demonstrated to be higher than that of miconazole (8); in addition, at low concentrations, fluconazole inhibited filamentation of this microorganism on HEp2 cell line (13). Activity against Microsporum canis and Candida sp. was demonstrated experimentally in guinea pigs (10, 12, 14): in two separate studies, treatment with 1-3% fenticonazole induced a complete healing in 100% of the animals (10, 14).

The study of morphological changes induced by fenticonazole on Candida albicans blastoconidia, by means of the scanning electron microscope, suggested that this agent acts by blocking the enzymatic activity of cytochrome oxidase and peroxidase (15, 16).

Furthermore, some Authors demonstrated that fenticonazole inhibits the synthesis, rather than the activity, of aspartate acid proteinase, a virulence enzyme of Candida albicans which is correlated with the adherence of the yeast to epithelial cells (17, 18). This activity was also observed with 5-fluorocytosine, but not with fluconazole, ketoconazole and miconazole (18).

Clinical studies on cutaneous candidosis

Open clinical studies

In 1987, a study was conducted on 30 patients who received fenticonazole treatment once a day. Clinical and mycological healing was recorded in 100% of patients with candidosis and pityriasis versicolor after 28 days of treatment, and in 8 out of 10 patients with epidermomyces after 32 days. The Authors observed two cases of irritant contact dermatitis, which improved spontaneously after stopping the therapy (19).

The once daily application of fenticonazole was based on the fact that skin retention time of the drug reaches 72 hours after a single application in guinea pigs (20).

The most important open, multicenter clinical trial was published in 1988. Fenticonazole cream, spray or powder was applied once or twice daily in 760 patients with superficial mycoses. Mycological negativization was obtained within 28-35 days of treatment. Clinical and mycological response rate was very high in patients with pityriasis versicolor (100%) and candidosis (95%). Twenty-nine patients reported adverse events, although only 8 subjects needed treatment discontinuation. This study demonstrated that once-daily application of fenticonazole induces a high patient’s compliance and a low cost/effectiveness ratio (21). Determination of fenticonazole plasma levels confirmed that the drug is poorly absorbed (22).

In summary, open clinical studies showed that fenticonazole, in different pharmaceutical preparations, administered once or twice daily, is effective in the treatment of superficial mycoses of the skin. Furthermore, these studies proved that local side effects caused by fenticonazole are rare and mild in severity.

Controlled clinical studies

Two controlled clinical studies were published on the use of fenticonazole reporting similar results in terms of efficacy and safety to those already discussed. Forty patients with pityriasis versicolor, candidosis or dermatophytosis were treated with 2% fenticonazole or miconazole cream. Clinical healing was observed in 16 patients out of 20 in the group treated with fenticonazole versus 14 patients out of 20 in the group treated with miconazole (23). Moreover, both drugs were well tolerated.

A multi-center, double-blind trial was carried out in 100 patients with cutaneous mycotic infections, to compare the efficacy and tolerability of spray formulations of 2% fenticonazole and 1% naftifine. Patients were treated once daily for 2 to 4 weeks. Candida albicans was present in 33.3% of patients in the fenticonazole...
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Fenticonazole was investigated in the treatment of vulvovaginal candidosis caused by Candida sp. (25-33) and mixed infections (32-35). All studies dealt with vulvar infections and not in a recurrent form. In all trials, diagnosis was based on medical history, clinical picture, direct mycological examinations and cultures. Most of the studies were open label (26, 27, 30, 32, 33, 35), while 4 were double-blind, comparator-controlled or single (investigator) blind (25, 28, 29, 31) trials. Fenticonazole was compared with clotrimazole in four studies (25, 28, 29, 31). A number of pharmaceutical forms and combinations were investigated: vaginal capsules or ointments were used in 6 studies (26, 28, 29, 31, 32, 35); ointments were combined with cream in two studies (27, 33) and with vaginal douche in one study (32). Cream alone was employed in one study (32).

Vaginal capsules (600 mg or 1 g as a single dose or 200 mg/day for three days), 2% cream (one application/day for 3 or 7 days), or a combination of capsules with cream or vaginal douche were effective in treating infections in 75-100% of patients, and specifically for eradication of Candida sp. in 70-100% of patients (25-33). Candida sp. was eliminated from a similar proportion of patients receiving fenticonazole cream or clotrimazole cream in a double-blind study (25). Eradication rates were obtained within one week in the majority of studies (26, 28-31, 33). Fenticonazole 600 mg or 1 g as a single dose or 200 mg/day for three days showed similar efficacy (26).

In a multicenter, prospective, open-label study, fenticonazole, administered as 1 g vaginal ointment, once daily on days 1 and 3, was used for vulvovaginal mixed infections (35). Candida albicans eradication on day 8 was 90% (26 out of 29 patients, p<0.001); 28 days later, no relapse was recorded. Furthermore, significant improvement in signs and symptoms were observed from baseline within 8 days (p<0.05) (35). In the majority of the studies in patients with vulvovaginal candidosis, fenticonazole induced an improvement in signs (erythema, edema, discharge) and symptoms (pruritus, burning) within a few days and complete resolution of some or all symptoms in 52-100% of patients within one week (28, 30, 31).

Fenticonazole vaginal capsules or ointments were very well tolerated in studies of up to 4-6 weeks' time. The most common adverse event was burning sensation, often short-lasting and mild to moderate in severity, occurring in up to 7.3% of patients (25, 26, 28, 30, 31, 35). However, this adverse event was reported in <1% of patients in four of these studies (25, 29, 30, 35). It is worth noting that burning sensation, a well known symptom of vulvovaginitis, is sometimes present at baseline. Other adverse events occurring in >1% of patients were vaginal soreness (2.7%) and vaginal discharge (1.3%) (31).

Although fenticonazole is one of the earliest imidazoles developed in Europe, no experimental and clinical data on development of Candida albicans resistance have been published. No data are available about the in vitro and clinical activity of fenticonazole in non-Candida albicans vulvovaginitis.

**Conclusions**

Toxicological studies with fenticonazole showed that it does not affect physiological functions, it is not mutagenic, photoallergic or phototoxic. Furthermore, it is seldom and mildly irritating and very rarely sensitizing. In vitro fenticonazole has a broad spectrum of activity against dermatophytes, yeasts (in particular Candida albicans), some Gram-positive bacteria and Trichomonas vaginalis.

Fenticonazole acts by blocking the enzymatic activity of Candida albicans. Furthermore, it inhibits the synthesis of aspartate acid proteinase, a virulence enzyme responsible for the adherence of Candida albicans to epithelial cells.

Open clinical studies showed that fenticonazole, administered in different pharmaceutical preparations, once or twice daily, is effective in the treatment of superficial mycoses of the skin, including cutaneous candidosis. These studies also demonstrated that local side effects are rare and mild in severity. Two comparative controlled trials were published. They showed that fenticonazole, compared to miconazole and naftifine, is effective in the treatment of superficial mycoses of the skin, including candidosis. These studies again supported the evidence that local side effects are rare and mildly severe.

Several studies were published on the treatment of vulvovaginal candidosis. Fenticonazole was used as vaginal capsules or ointments, cream or douche. These studies demonstrated that this drug is mycologically and clinically effective. In addition, its activity is very rapid. Recent studies recommended fenticonazole as a cheap, first-line agent in the topical treatment of vulvovaginal candidosis (36).

As previously mentioned, the main mechanism of action of fenticonazole is the inhibition of the synthesis of aspartate acid proteinase, a virulence enzyme of...
Candida albicans which is correlated with the adherence of the yeast to epithelial cells. This activity is unique to fenticonazole as it was not observed with fluconazole, ketoconazole and miconazole (17, 18).

Fenticonazole in monotherapy, used as ointment and cream or douche (1 application/day for 7 days), is also effective in treating vulvovaginal candidosis, where it induces a rapid relief of pruritus.

All pharmaceutical formulations of fenticonazole are very well tolerated: we observed no cases of allergic contact dermatitis.

Although fenticonazole is one of the earliest imidazoles developed in Europe, no experimental and clinical data on development of Candida albicans resistance have been published.

Declaration of interest

The Authors state no conflict of interest and have received no payment for the preparation of this manuscript.

Authors contribution

All Authors contributed to literature collection, interpretation of data, and manuscript drafting.

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