Miconazole Mucoadhesive Tablets: A Novel Delivery System

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Oropharyngeal candidiasis (OPC) is among the most common opportunistic infections observed in persons infected with human immunodeficiency virus. A once-daily miconazole 50 mg mucoadhesive buccal tablet (MBT) is a novel delivery system with potent in vitro activity against many Candida species, including some that may be resistant to other azoles. MBT, although more expensive, offers an effective, safe, and well-tolerated topical treatment option for OPC that is administered as a convenient once-daily dose.

Oropharyngeal candidiasis (OPC) is an oral infection caused by Candida species yeasts. Although Candida is a commensal fungus of normal mouth flora in approximately 45% of healthy individuals, under certain circumstances, it can overgrow and cause symptomatic infection [1]. Immunocompromised patients, including individuals who have been infected with human immunodeficiency virus (HIV), undergone chemotherapy, or received organ transplants, are highly susceptible to the development of OPC [2, 3]. Although antiretroviral agents have been shown to decrease both the prevalence of OPC and the number of OPC relapses over the course of a year, candidiasis remains one of the most common opportunistic infections in HIV-positive patients, with an annual incidence of approximately 20% [4–6].

Until recently, clotrimazole troches (CT) and nystatin suspension have been the only topical antifungal agents available, and both have been recommended as a first-line treatment of uncomplicated OPC in the Infectious Diseases Society of America (IDSA) candidiasis clinical practice guidelines [7]. The Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and HIV Medicine Association (HIVMA) also recommend that initial episodes of OPC should be managed by these topical agents in HIV-positive adults [8]. Traditional oral topical antifungal therapies have limitations, including short contact time with the oral mucosa and the need for multiple doses each day. Compliance issues are a significant concern and a common problem. Nevertheless, due to their low systemic drug concentrations, fewer adverse events (AEs) and a low potential for drug–drug interactions, these modalities have frequently been preferred over systemic antifungal agents with associated systemic effects [7–9].

Miconazole is a synthetic imidazole antifungal agent that has been used since the early 1970s to effectively and safely treat superficial fungal infections [10, 11]. Miconazole has a broad spectrum of activity against Candida albicans and non-albicans species and is considered by some the only fungicidal azole, a property likely enhanced by its induction of reactive oxygen species [12–14].

Miconazole buccal tablets (MBT), which are unique because of adherence to buccal mucosa, allowing once-daily administration, are currently available and have been approved by the US Food and Drug Administration for the treatment of oropharyngeal candidiasis in adults [15].
DESCRIPTION

Miconazole buccal tablets contain 50 mg of miconazole base with the inactive ingredients of hypromellose, milk protein concentrate, corn starch, lactose monohydrate, and talc [15].

MECHANISM OF ACTION

Miconazole, like other azole antifungals, inhibits lanosterol 14-α demethylase (CYP51), which is an enzyme that catalyzes the final step in the synthesis of ergosterol, an important component of the fungal cell membrane [10, 11, 14]. Miconazole also has a direct effect on the fatty acids of cell membranes, causing leakage of proteins and amino acids and interference with the uptake of essential nutrients; it may also inhibit catalase systems, alter fungal adherence, and inhibit the formation of germ tubes and mycelia [11, 14]. Additionally, miconazole may also have fungicidal activity as a result of the induction of reactive oxygen species, which leads to oxidative damage and cell death [14, 16]. Reactive oxygen species levels are likely increased due to the inhibition of enzymes involved in the breakdown of free radicals [14, 16].

IN VITRO SPECTRUM OF ACTIVITY

Miconazole has potent broad-spectrum activity against many Candida species, including C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. dubliniensis, and C. famata [13, 17]. In addition, miconazole is also effective against species of Candida that are resistant to azoles (C. krusei, some C. glabrata) or amphotericin B (C. lusitaniae) [Table 1] [18].

In vitro assays demonstrate miconazole minimum inhibitory concentration values for which 90% of isolates are susceptible (MIC90) for C. albicans, C. parapsilosis, C. tropicalis, C. lusitaniae, and C. dubliniensis of 0.03–0.5 μg/mL, whereas MIC90 values for C. krusei and C. glabrata range from 0.12 μg/mL to 0.25 μg/mL [Table 1] [18]. In the same study, the miconazole MIC90 values for fluconazole-susceptible strains were 0.12 μg/mL and a MIC90 value of 0.5 μg/mL was obtained against fluconazole-resistant strains of Candida [18]. However, some in vitro studies have demonstrated that some Candida strains exhibiting reduced susceptibility to one azole antifungal may also exhibit reduced susceptibility to other azoles, including miconazole, suggesting some degree of cross-resistance [18]. In vitro breakpoints for miconazole have not been established.

PHARMACOKINETICS

Salivary Absorption and Distribution

A single-dose MBT containing 50 mg of miconazole administered to the buccal mucosa in 18 healthy volunteers provided a mean salivary concentration of 15 μg/mL at 7 hours after the application of the tablet [17, 19]. This provided an average salivary exposure to miconazole estimated from the area under the curve (0–24 hours) of 55.23 μg/hour/mL. In healthy volunteers, the duration of buccal adhesion was an average of 15 hours. The half-life of a 50-mg MBT was 7 hours (2.0–24.1 hours).

Plasma

In the same study, the plasma concentration of miconazole was below the limits of detection (<0.4 μg/mL) in 97% of the samples taken from healthy volunteers following a single-dose application of a 50-mg MBT [17]. The few measurable plasma concentrations ranged from 0.5 μg/mL to 0.83 μg/mL.

Metabolism and Excretion

The majority of the absorbed miconazole is metabolized by the liver with <1% of the administered dose detected unchanged in the urine [11]. Miconazole is a known inhibitor of CYP2C9 and CYP3A4. Although uncommon, the use of miconazole oral gel and coumadin have been associated with easy bruising and bleeding [20]. In a more recent study, miconazole also inhibited CYP2D6, which was associated with increased exposure to oxycodone, although the actual clinical relevance to this interaction is modest [21].

HEALTHY VOLUNTEERS

Based on Cardot et al [17].

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<tr>
<th>Table 1. In Vitro Susceptibility of Candida Species Against Miconazole and Other Antifungals</th>
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Abbreviation: MIC<sub>90</sub>, minimum inhibitory concentration for which 90% of isolates are susceptible.

* Based on Cardot et al [17].
24 hours following systemic administration [17]. In addition, there are no active metabolites of miconazole [11].

**Special Population Pharmacokinetics**

There are no well-controlled studies evaluating MBT in pregnant women. MBT, as a category C drug, should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus [15].

In animal studies, miconazole administered orally at a dose of 80 mg/kg/day or higher to pregnant rats and rabbits crossed the placenta and resulted in embryotoxicity and fetotoxicity, including increased incidence of fetal resorptions. In addition, these doses also produced prolonged gestation and dystocia in rats [15]. Toxicity was not observed in intravenous studies using miconazole at doses of 40 mg/kg/day in rats and 20 mg/kg/day in rabbits. This dose is approximately 8 times higher than a dose a patient would receive if he or she swallowed a 50-mg MBT. Although it is not known if MBT is excreted in human milk, many azoles are normally excreted in breast milk, and therefore, caution should be used when MBT is administered to nursing women.

Studies in populations <16 years of age have not yet been performed. Use in younger children is not currently recommended because of the potential risk of choking. Insufficient numbers of patients >65 years of age have been studied in clinical trials thus far.

**Use in Hepatic and Renal Insufficiency**

It is important to note that miconazole is metabolized by the liver [11]. Although miconazole absorption and thus exposure are minimal following the application of an MBT, the use of MBT should be used with caution in patients with hepatic insufficiency. Because <1% of miconazole is excreted in the urine as unmetabolized drug, dosage adjustment is not required in patients with renal insufficiency.

**CLINICAL TRIALS**

Three clinical trials have been conducted to date. The initial study was an open-label, noncomparative multicenter study in 25 HIV-positive patients with OPC conducted by Dupon and Attali [19]. MBT 50 mg was administered daily for 14 days. The primary endpoint was clinical success at day 15. The results demonstrated an 84% efficacy in the intent-to-treat (ITT) group and an efficacy of 94.7% in the per-protocol (PP) group. Only 6 AEs were reported in the 25 patients. These included diarrhea, dysguesia, nausea, fever, gingival disorder, and headache.

The pivotal Study of Miconazole Lauriad Efficacy and Safety (SMiLES) was designed to evaluate the efficacy and safety of MBT (n = 290) vs CT (n = 287) for the treatment of OPC in HIV-positive patients in a noninferior, randomized, double-blind, double-dummy, parallel-group trial [22]. The study randomized a total of 578 patients and was conducted at 30 centers in the United States, Canada, and South Africa. Eligible patients were randomized to receive either once-daily MBT or CT 5 times per day for 14 days.

Clinical cure rate in the MBT group was statistically non-inferior to the CT group in both the ITT and PP populations at the test-of-cure (TOC) visit (days 17–22). In the ITT population, 61% of patients treated with MBT experienced clinical cure compared with 65% treated with CT (95% confidence interval [CI], −0.124 to .034). Results were similar in the PP population, with a clinical cure rate of 68% vs 74% resulting in a treatment difference of −0.059 (95% CI, −.140 to .022) at the TOC visit. Furthermore, at the TOC visit, mycological cure was numerically higher in the MBT group compared with the CT group in both patient populations, although not statistically significant.

Of the 172 MBT patients in the ITT population who experienced clinical cure at the TOC visit, 48 (27.9%) experienced a relapse by day 35, as compared with 52 of 185 (28.1%) patients in the CT group (P = .79; 95% CI, −9.5 to 9.1). The mean time to relapse was 16.2 days for MBT and 15.9 days for the CT group (P = .7).

The mean duration of adhesion was comparable between the MBT group (12 hours, 37 minutes) and the CT group that received placebo buccal tablets (13 hours, 10 minutes). The total number of tablets that detached within the first 6 hours after placement was only 6.3% of the MBT and 5.7% of the placebo buccal tablets. All miconazole plasma levels evaluated on day 7 were below the limit of assay quantification (0.1 μg/mL), indicating that systemic exposure to miconazole from the MBT was low.

Adverse events were comparable between treatment groups with respect to the incidence and severity of AEs reported, including treatment-emergent adverse events (TEAEs). The most frequently reported TEAEs were diarrhea, headache, nausea, and vomiting. The majority of patients (81%) in both treatment arms had no evidence of gingival inflammation at the application site after cessation of treatment.

The efficacy of MBT in this study is consistent with results reported for other topical agents currently used to treat OPC [23–26]. As in prior reports, mycological cure rates in this study were lower than clinical cure rates [23–26]. This is not unexpected, as Candida species are commensal organisms and difficult to completely eradicate from the oral cavity, which has large areas of protected niches.

A second clinical study evaluated MBT for OPC in irradiated head and neck cancer patients in an open-label, randomized, multicenter study comparing MBT 50 mg once daily to miconazole oral gel (MOG) 125 mg 4 times daily for 14 days [27]. Among the 306 patients randomized, 294 were in the ITT population and 282 in the modified ITT population.
(MBT = 141; MOG = 141). The primary endpoint of clinical success at day 14 in the MBT group was statistically non-inferior to the MOG group, with a 56% success rate for the MBT group compared with 49% for the MOG group (P < .0001). After adjustments for the extent of lesions and salivary secretions, a trend toward superiority was observed in favor of MBT, especially among patients with multiple lesions (success rates: MBT = 58.7% vs MOG 37.5%). Furthermore, in patients without impaired salivary secretion at the time of the study, the success rate on day 14 was 100% compared with a success rate of only 40% in the MOG group. On day 7, a very low clinical success rate of 14% was reported for the MBT group and 20% for the MOG group.

OPC recurrence rates were 19% vs 12.5% for the MBT and MOG groups, respectively, 14 days after therapy. Long-term recurrences 45 days after therapy were also low, with rates of 21.5% and 17% for the MBT and MOG groups, respectively, despite the refractory mucosal damage and persistent xerostomia. On average, the time to recurrence was 18.75 days for the MBT group and 20.6 days for the MOG group. Interestingly, despite significant xerostomia in both groups, tablet adherence rates were 92.2% at 6 hours and 62% at 12 hours for both groups.

The incidence of AEs was similar in both groups, with 29.3% in the MBT group and 27.2% in the MOG group. The most common AEs were nausea, vomiting, and dysguesia.

The overall results of this study demonstrated that the MBT is an effective and safe alternative to systemic antifungals for the treatment of OPC in patients who received head and neck cancer after radiation therapy despite the presence of xerostomia.

**DOSAGE AND ADMINISTRATION**

The recommended dosing for MBT is to apply one 50-mg MBT to the upper gum region (canine fossa) once daily for 14 days, preferably in the morning, by holding it in place with slight pressure over the upper lip for 30 seconds to ensure adhesion. The tablet is round on one side for comfort against the gums, but either side of the tablet can be applied to the gum. Once applied, the MBT stays in position and gradually dissolves. The MBT should not be crushed, chewed, or swallowed. Food and drink can be taken normally when the MBT is in place. If the MBT does not adhere or falls off within the first 6 hours, the same tablet is to be repositioned immediately. If the tablet still does not adhere, a new tablet is placed. If the MBT falls off or is swallowed after it was in place for 6 hours or more, a new tablet is unnecessary. Patients should avoid situations that could interfere with the adhesion of the tablet.

**CONTRAINDICATIONS**

Miconazole buccal tablets are contraindicated in patients with known hypersensitivity (eg, anaphylaxis) to miconazole, milk protein concentrate, or any other component of the product [15].

**DISCUSSION**

The CDC, IDSA, NIH, and HIVMA endorse the use of topical antifungal agents for the treatment of mild cases of OPC [7, 8]. However, systemic agents are frequently used because of the limitations of currently available topical agents, including frequent daily dosing (4–5 times a day), transient drug delivery during the dosing period, and oral discomfort [26]. Additionally, many topical agents are highly sweetened with sugar, which may negatively affect dental health [28]. These drawbacks can result in poor treatment compliance and have contributed to the continued use of systemic agents [2, 26].

The SMiLES study was the largest clinical trial evaluating the topical treatment of OPC in HIV-positive patients and demonstrated that MBT is as effective and safe as clotrimazole for the treatment of OPC in HIV-positive patients [22]. Although both drugs are topical agents, the high and sustained levels of salivary miconazole concentrations with MBT combined with its unique mode of administration should increase its utility as a local therapeutic agent for mild OPC, as well as more severe disease. Compliance is typically higher in clinical trials than daily practice, however, and the convenience of once-daily dosing may translate into increased routine adherence to the treatment regimen.

Although national treatment guidelines emphasize that topical antifungal therapy should serve as first-line therapy for OPC, many clinicians continue to prescribe oral ingestable and systemic antifungals. In an era of fluconazole-resistant refractory OPC, education should be directed at encouraging clinicians to use topical antifungal agents in mild and moderate OPC. Clinical options are not, however, numerous. Oral nystatin has ceased to be widely available and topical amphotericin B is not available in the United States, leaving multidose regimens of clotrimazole as the only option. The recent availability of a single daily dose of miconazole offers a new alternative but does not represent a more potent or effective regimen. Clinical studies that were reported in this review indicate that the single daily dose regimens of mucosa-adherent miconazole tablets are as effective but not more so than multidose regimens and are equally safe and well tolerated [22, 29]. Nevertheless, although the MBT regimen is considerably more expensive than conventional therapy, it is more convenient and can be useful for the poorly compliant individual. For most clinicians, achieving successful treatment of OPC is not a challenge. For physicians dealing daily with oncologic patients, (especially those with head and neck cancer), patients with
xerostomia, and patients with HIV, oropharyngeal candidiasis is not a trivial entity and is much more of a challenge when fluconazole-resistant strains of *C. albicans* and *C. glabrata* emerge. For these physicians, the availability of another user-friendly effective antifungal regimen is extremely valuable.

Note

Potential conflicts of interest. All authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References