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Miconazole mucoadhesive tablet for oropharyngeal candidiasis

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Abstract

Oropharyngeal candidiasis is a commonly encountered problem in daily clinical practice. Topical therapies for oropharyngeal candidiasis are considered preferable to systemic therapies in most patient populations. However, traditional topical therapies have limitations including short contact time with the oral mucosa and the need for multiple doses each day. Miconazole mucoadhesive tablet has recently been approved in Europe (Loramyc®) and the USA (Oravig™) for the treatment of oropharyngeal candidiasis. This tablet adheres to the oral mucosa and provides sustained local release of miconazole over a period of several hours with just one daily application. This article reviews the pharmacology, safety and efficacy of this novel agent.

Keywords

Loramyc®; miconazole mucoadhesive tablet; Oravig™; oropharyngeal candidiasis

Some fungal organisms, especially *Candida albicans*, are found as normal inhabitants of the oral cavity in a large proportion of individuals. Changes in the oral and/or systemic environment can result in an overgrowth of these fungal organisms, leading to clinical oral and pharyngeal fungal infection. Factors predisposing to oropharyngeal candidiasis (OPC) include hyposalivation/xerostomia (due to disease, medication or radiation therapy), local or systemic immunosuppression (such as in HIV or patients receiving chemotherapy), and changes in the oral flora (such as that caused by antibiotic therapy). A wide range of prevalence of OPC has been reported, depending on the severity of comorbidities present. For example, in a US population of HIV-infected adults, an incidence rate of 9.3 cases per 1000 person-months has been reported [1]. Among institutionalized South African pediatric HIV/AIDS patients, 13.8% of children had clinically detectable OPC [2]. Among patients receiving radiation therapy for head and neck cancer, 37.4% developed OPC during the course of radiation treatment [3]. A large study of over 2000 cancer patients treated with chemotherapy and/or radiotherapy reported an overall OPC prevalence of 9.6%, with the highest prevalence (22%) in patients treated with combined chemoradiotherapy [4].

Guidelines from the Infectious Diseases Society of America (IDSA), released in 2009, recommend the use of clotrimazole troches or nystatin suspension/pastilles as first-line

therapy for the management of mild OPC. For moderate-to-severe OPC, the IDSA guidelines recommend the use of fluconazole as the first-line systemic agent [5]. The guidelines do not define mild versus moderate-to-severe OPC.

Overview of the market

Currently available topical therapies for OPC include nystatin rinse/cream/ointment/pastilles, clotrimazole troches and miconazole oral gel (available in Europe). Limitations of these agents include:

- The need for dosing several times a day
- Short contact time of the active agent with the oral mucosa
- Sugar content of some of these formulations, which predisposes to dental caries and can promote yeast growth
- Unpleasant taste of some formulations, such as nystatin rinse
- Difficulty of using troches/pastilles in patients with a dry mouth or oral ulceration

Together, these limitations contribute to reduced compliance and efficacy of these topical agents, necessitating the use of systemic agents when topical agents fail.

Miconazole

Miconazole is an antifungal drug that has been on the US market since 1974. Miconazole mucoadhesive tablet (MMT) is a new controlled release formulation supplied as a tablet containing 50 mg of miconazole. The rounded side of the tablet is applied to the canine fossa, a depression in the upper gum, in the morning after brushing the teeth. The tablet is held in place for 30 s with slight pressure of the finger over the upper lip to make the tablet stick to the gum (Figure 1). As the tablet absorbs moisture from the mouth, it releases miconazole and slowly dissolves over time. Patients are instructed to re-apply the tablet if it does not adhere, or to apply a new tablet if a tablet is inadvertently swallowed within the first 6 h after placement (after 6 h in place, a dislodged tablet need not be replaced).

Chemistry

Miconazole is an imidazole antifungal agent and is described chemically as 1-[(2RS)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole with an empirical formula of $C_{18}H_{14}Cl_4N_2O$ and a molecular weight of 416.13. The structural formula is shown in Figure 2. Miconazole drug substance is a white to almost white powder.

Miconazole mucoadhesive tablet contains 50 mg of miconazole base, USP and the following inactive ingredients: hypromellose USP, milk protein concentrate, corn starch NF, lactose monohydrate NF, sodium lauryl sulfate NF, magnesium stearate NF and talc USP.

Pharmacodynamics

Miconazole inhibits the enzyme cytochrome P450 14 α -demethylase, which leads to inhibition of ergosterol synthesis, an essential component of the fungal cell membrane. Miconazole also affects the synthesis of triglycerides and fatty acids and inhibits oxidative and peroxidative enzymes, increasing the amount of reactive oxygen species within the cell. Miconazole has shown *in vitro* activity against multiple *Candida* species including *C. albicans*, *C. krusei*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. dubliniensis* [6].

Pharmacokinetics & metabolism

In clinical trials of MMT in HIV patients and patients who had undergone head and neck radiation therapy, at least 90% of tablets were in place 6 h after application to the canine fossa. In healthy volunteers, the average duration of adhesion was 15 h following a single-dose application to the buccal mucosa.

For pharmacokinetic studies, a single dose of MMT 50 mg was applied to the buccal mucosa of 18 healthy volunteers. At 7 h after application, mean maximum salivary concentration ($C_{\max}$) of miconazole was 15.1 ± 16.2 µg/ml. This resulted in an average salivary exposure of 55.23 ± 35.1 µg/h/ml to miconazole, estimated from the $AUC_{0-24\text{ h}}$.

Plasma concentrations of miconazole were below the lower limit of quantification (0.4 µg/ml) in 157 out of 162 (97%) samples from healthy volunteers following single-dose application of MMT 50 mg. Measurable plasma concentrations ranged from 0.5 to 0.83 µg/ml. Plasma concentrations of miconazole evaluated after 7 days of treatment in a separate study of 40 HIV-positive patients were all below the limit of quantification (0.1 µg/ml).

Most of the absorbed miconazole is metabolized by the liver with less than 1% of the administered dose found unchanged in urine. In healthy volunteers, the terminal half-life is 24 h following systemic administration. There are no active metabolites of miconazole. A formal food effect study was not conducted; however, in clinical studies patients were allowed to eat and drink while taking MMT.

Clinical efficacy

Efficacy for OPC in HIV-infected patients

Owing to their immunosuppressed state, HIV-infected patients are at considerably higher risk for OPC (and many other infections) than the general population. A randomized, double-blind, double-dummy, multicenter trial was conducted to study the efficacy and safety of MMT in the treatment of OPC in HIV-infected patients in the USA, Canada and South Africa. This noninferiority trial compared MMT 50 mg once daily ($n = 290$) with clotrimazole troches 10 mg five times per day ($n = 287$), both used for 14 consecutive days. Patients were required to have signs (lesions) and microbiological documentation of OPC for study entry. Most of the infections were caused by *C. albicans* (85%), followed by *C. tropicalis* (9%) and *C. parapsilosis* (3%), with mixed infections present in some cases. In total, 75% of subjects were not receiving highly active antiretroviral treatment. The mean viral load was 117,000 copies/ml.

In the intent-to-treat population, a clinical cure (defined as a complete resolution of both signs and symptoms of OPC at the test of cure visit [days 17–22]) was seen in 61% of subjects receiving MMT and 65% of subjects receiving clotrimazole troches, which was well within the confidence intervals for the margin of noninferiority. A clinical relapse by days 35–38 (21–24 days after end of therapy) occurred in 27.3% of subjects clinically cured by MMT and 27.8% of subjects clinically cured by clotrimazole troches. A mycological cure (defined as eradication of *Candida* isolates at the test of cure visit [days 17–22]) was seen in 27.2% of all subjects treated with MMT, as compared with 24.7% of all subjects treated with clotrimazole troches [7].

Efficacy for OPC in patients who have received head & neck radiation therapy

Radiation therapy for head and neck cancer often results in salivary hypofunction due to the effects of radiation on the salivary glands. The resulting dry mouth places this population at an increased risk of OPC. The efficacy and safety of MMT in treating OPC in this

population was evaluated in an open-label, randomized, multicenter, noninferiority trial comparing MMT 50 mg once daily (n = 154) to miconazole oral gel 125 mg four times daily (n = 152), both used for 14 consecutive days. Most of the infections were caused by *C. albicans* (71%) and *C. tropicalis* (8%), with mixed infections present in some cases. In total, 54% of subjects in the MMT group had mucositis at baseline; however, this did not impact on study medication use since the canine fossa region is rarely affected by mucositis.

In a modified intent-to-treat population (all randomized subjects who received at least one treatment dose and had at least one efficacy evaluation after randomization), a complete response (defined as complete disappearance of candidiasis lesions, based on a blinded assessment) was seen in 52.5% of subjects receiving MMT, as compared with 45.4% of subjects receiving miconazole oral gel ($p < 0.0001$) [8]. In patients who experienced a clinical cure (no signs or symptoms of OPC), a clinical relapse occurred in 14.3% of subjects receiving MMT and 9.3% of subjects receiving miconazole oral gel by day 30, and in 14.3% of subjects receiving MMT and 14% of subjects receiving miconazole oral gel by day 60. A mycological cure (defined as complete eradication of *Candida* or less than ten colonies per plate) was seen in 45.4% of subjects receiving MMT and 54.6% of subjects receiving miconazole oral gel [Attali P, Pers. Comm.].

Safety & tolerability

Miconazole mucoadhesive tablet is contraindicated in patients with known hypersensitivity to miconazole, milk protein concentrate or any other component of the product.

Miconazole can enhance the anticoagulant effect of warfarin. Although the systemic absorption of miconazole following MMT use is minimal, the potential exists for interaction with drugs metabolized through CYP2C9 and CYP3A4 such as oral hypoglycemics, phenytoin and ergot alkaloids. Animal data indicates that miconazole can cause fetal harm if used in pregnant women. It is not known if miconazole is excreted in human milk. The safety and effectiveness of MMT in patients below the age of 16 years has not been established.

The most common adverse reactions seen in patients receiving MMT in clinical trials were diarrhea, headache, nausea, dysgeusia (altered taste), upper abdominal pain and vomiting. Table 1 and Table 2 present the most common adverse reactions seen in the two major clinical trials of MMT.

Regulatory affairs

Miconazole mucoadhesive tablet is approved by the US FDA (Oravig™) for the local treatment of OPC in adults and adolescents 16 years of age and older. MMT is approved in the EU (Loramyc®) for the treatment of OPC in immune-compromised patients.

Conclusion

Miconazole mucoadhesive tablet is safe and effective for the treatment of OPC in adults.

Expert commentary

Miconazole mucoadhesive tablet has several advantages over previously available topical therapies. The once-daily dosing is user-friendly and should result in improved compliance as compared with treatments needing dosing several times a day. The increased contact time with the oral mucosa should result in improved efficacy. Other advantages include the lack of sugar in the formulation, and the ability to be used in patients with oral ulceration or dry

mouth (where troches/pastilles are difficult to dissolve). A potential challenge to its widespread adoption is its increased cost compared with other topical agents and systemic fluconazole, which are available as generics. Because of its placement in the canine fossa, it cannot be used in patients who wear upper dentures that include this region.

Five-year view

Miconazole mucoadhesive tablet is the first new topical formulation approved for OPC in many years. Although newer classes of systemic antifungal agents (such as the echinocandins) will be more widely used, these are rarely used for the management of OPC. Thus, the list of first-line treatment options for OPC is unlikely to change significantly in the next 5 years.

Information resources

Once-daily Oravig™ miconazole buccal tablets 50 mg: www.oravig.com

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Financial & competing interests disclosure

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References

Papers of special note have been highlighted as: • of interest

1. Chattopadhyay A, Caplan DJ, Slade GD, Shugars DC, Tien HC, Patton LL. Incidence of oral candidiasis and oral hairy leukoplakia in HIV-infected adults in North Carolina. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 2005; 99(1):39–47. [PubMed: 15599347]
2. Blignaut E. Oral candidiasis and oral yeast carriage among institutionalised South African paediatric HIV/AIDS patients. *Mycopathologia.* 2007; 163(2):67–73. [PubMed: 17295100]
3. Lalla RV, Latortue MC, Hong CH, et al. Fungal Infections Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of oral fungal infections in patients receiving cancer Therapy. *Suppor. Care Cancer.* 2010; 18(8):985–992.
4. Gligorov J, Bastit L, Gervais H, et al. the Candidoscope Study Group. Prevalence and treatment management of oropharyngeal candidiasis in cancer patients: results of the french candidoscope study. *Int. J. Radiat. Oncol. Biol. Phys.* 2010 on behalf. DOI: 10.1016/j.ijrobp.2010.02.006. Epub ahead of print.
5. Pappas PG, Kauffman CA, Andes D, et al. Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2009; 48(5):503–535. [PubMed: 19191635]
6. Isham N, Ghannoum MA. Antifungal activity of miconazole against recent *Candida* strains. *Mycoses.* 2010; 53(5):434–437. [PubMed: 19531099]
7. Vazquez JA, Patton LL, Epstein JB, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad® Efficacy and Safety (SMiLES). *HIV Clinical Trials.* 2010; 11(4):186–196. [PubMed: 20974574] • Large clinical trial of miconazole mucoadhesive tablet for oropharyngeal candidiasis in HIV-infected patients.
8. Bensadoun RJ, Daoud J, El Gueddari B, et al. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomized, single-blind, multicenter, comparative, Phase III trial in

patients treated with radiotherapy for head and neck cancer. *Cancer*. 2008; 112(1):204–211. [PubMed: 18044772] • Large clinical trial of miconazole mucoadhesive tablet for oropharyngeal candidiasis in patients who had received head and neck radiation therapy.

Figure 1.
Application of miconazole mucoadhesive tablet.

Figure 2.
Miconazole.

Table 1Adverse events in HIV-infected patients[†]

Adverse event	No. of patients (%)	
	<i>MMT (n = 290)</i>	<i>Clotrimazole troches (n = 287)</i>
Diarrhea	26 (9)	23 (8)
Headache	22 (8)	19 (7)
Nausea	19 (7)	22 (8)
Vomiting	11 (4)	9 (3)
Anemia	8 (3)	5 (2)
Cough	8 (3)	5 (2)
Fatigue	8 (3)	6 (2)
Local adverse reactions [‡]	35 (12.1)	27 (9.4)

MMT: Miconazole mucoadhesive tablet.

Modified from [7].

[†]Treatment-emergent adverse events reported in $\geq 3\%$ of patients receiving MMT.[‡]Including oral discomfort, oral burning, oral pain, gingival pain, gingival swelling, gingival pruritis, tongue ulceration, mouth ulceration, glossodynia, dry mouth, application-site pain or discomfort, toothache, loss of taste and altered taste.

Table 2Adverse events in patients who had received head and neck radiation therapy[†]

Adverse event	No. of patients (%)	
	<i>MMT</i> (<i>n</i> = 147)	<i>Miconazole oral gel</i> (<i>n</i> = 147)
Abdominal pain	5 (3.4)	4 (2)
Local adverse reactions (including the following)	14 (9.5)	16 (10.9)
Dysgeusia (altered taste)	9 (6.1)	0 (0)
Oral discomfort	4 (2.7)	5 (3.4)
Glossodynia	0 (0)	3 (2)
Toothache	1 (0.7)	2 (1.4)

MMT: Miconazole mucoadhesive tablet.

Modified from [8].

[†] Adverse events reported in ≥3% of patients receiving MMT.