Miconazole revisited: new evidence of antifungal efficacy from laboratory and clinical trials

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In the past 40 years imidazoles have been used extensively in medicine for their antifungal properties. All members of the azole antifungal family inhibit ergosterol biosynthesis. However, the discovery of an additional fungicidal mode of action for miconazole has drawn renewed attention to this compound. In this article we review recent evidence of mechanistic efficacy, as well as clinical trial results of miconazole in new topical formulations.

Keywords: candidiasis, drug resistance, immunosuppression, miconazole

Fungal disease is ubiquitous in the world and antifungal medications account for sales of more than US$1 billion annually. Most fungal disorders are relatively benign but can become life-threatening in immunocompromised or malnourished populations. A wide variety of antifungal drugs are currently on the market. Nevertheless, new compounds are constantly developed and tested as pathogenic organisms acquire resistance. Patients with incompetent immune systems have a large contribution to both the increased use of antifungals and the evolution of resistant organisms. In this setting, older topical drugs with new, more efficient formulations are an attractive alternative to systemic treatment of fungal diseases. One such medication is miconazole.

The use of miconazole in medicine dates back to the early 1970s when a number of azole compounds were introduced to the market, mostly in topical form, for treatment of superficial fungal infections. Miconazole is a synthetic imidazole derivative that built a reputation for fast fungicidal action when used topically against a wide variety of yeasts and dermatophytes [1]. Systemic (intravenous) use of this drug for invasive fungal diseases had initial positive results [2] but was discontinued due to toxicity of the vehicle and reports of hepatic and cardiovascular side effects [3–5].

Thus, miconazole remains primarily a topical antifungal agent and millions of patients have been treated with this compound in various formulations. Common indications for topical miconazole include vaginal and oral candidiasis (thrush) and skin and nail infections due to *Trichophyton*, *Epidermophyton* and *Pityrosporon* species. In the USA, several products contain miconazole, typically as a 2–4% cream that is approved for over-the-counter sale. These facts are testament to the safety of topical miconazole.

It is interesting to note that, despite the wide availability and use of miconazole, fungal resistance to this drug remains relatively low [6]. Typical MIC has remained in the 1–10 ug/ml concentration range for most tested pathogens, including *Candida albicans* [7,8]. This fact becomes extremely important in light of constantly recurring opportunistic fungal disease in a growing HIV-infected, immune compromised population. In the following section we will review recent evidence on the efficacy of miconazole, with particular emphasis on its effect on *Candida* infections.

Review of the literature

Mechanism

Azoles, the most common antimycotics in the pharmacopeia, damage fungal organisms by interfering with ergosterol biosynthesis, which results in toxic methylated sterol levels [9]. Recently, Kobayashi *et al.* described an additional antifungal mechanism for miconazole: accumulation of drug-induced reactive oxygen species (ROS) within the fungal organism results in oxidative damage and cell death [10]. This mechanism was confirmed in another publication by Thevissen *et al.* [11]. These latter authors studied the effects of miconazole in *Saccharomyces cerevisiae* and *C. albicans* and demonstrated that the antifungal damages actin cables, which in turn interferes with the organization of the actin cytoskeleton; since the actin cytoskeleton regulates mitochondrial activity and endogenous levels of ROS, this putative effect of miconazole can act as a trigger for ROS induction followed by apoptosis. This report was the first to document an actin clumping effect leading to ROS accumulation and cell death induced by an azole medication.

Clinical studies

These new insights into miconazole's mechanisms of action correspond with results from clinical studies that confirmed the drug's efficacy

against various fungal organisms. A recent article by Bii *et al.* reported that 80 clinical isolates of *Cryptococcus neoformans* showed greater *in vitro* susceptibility to miconazole than to fluconazole or flucytocin [12]. A similar study that compared topical miconazole with econazole and nystatin for efficacy against vaginal candidiasis also showed the former two drugs to be effective and superior to the nystatin [13]. Using a different *in vitro* testing method, Uchida *et al.* demonstrated that itraconazole and miconazole performed equally well but significantly better than fluconazole in killing both *albicans* and non-*albicans Candida* species [14].

Less encouraging results were also published. Paniagua *et al.* tested 80 *C. albicans* strains from clinical sources and described 45% resistance to miconazole but 100% susceptibility to amphothericin B [15]. In a comparative study of *Candida* isolates from the UK and Italy, Manfredi *et al.* found significant differences in antifungal susceptibility between isolates from the two geographic locations [16]. Susceptibility to all tested azole compounds (including miconazole) was much lower in strains collected from the UK than the strains from Italy.

The results of this latter study are consistent with findings of increased microbial resistance patterns with increased use of antimicrobial compounds. Development of resistance is typically a multifactorial process that occurs after repeated exposure of the pathogen to a specific drug. However, resistant species can be transferred through person-to-person contagion. Fungal resistance can occur through a variety of mechanisms, including drug efflux (most common for azoles), alternative paths for sterol biosynthesis, alterations in drug targets and reduction of concentration of the target enzyme. Yeasts, particularly the non-*albicans Candida* species, are common offenders [17]. A number of factors are involved in the continually increasing development of microbial resistance, and their nature and significance are beyond the scope of this article. However, one factor in particular is pertinent to the current discussion, as the incidence and morbidity of fungal infections is of significance here: this factor is immune suppression and the increased longevity of patients in this population [17].

The immune suppression connection

The current medical era is partly defined by a relatively high prevalence of immunocompromised patients. Organ transplantation, cancer and autoimmune disease treatments include cytotoxic and immune-modulating agents that affect the hematopoietic system. However, the largest recent increase in the immune compromised population can be attributed to the appearance and rapid spread of HIV and the immune destruction this virus produces in infected individuals. Despite current therapeutic advances, HIV infection is not curable and continues to spread throughout the world. In this setting, opportunistic fungal infections are common and so is resistance to available remedies [18]. Oral candidiasis is one of the most common opportunistic infections in AIDS and its incidence increases with the viral load and decreased CD4 cell counts [18]. While highly active antiviral therapies have reduced its prevalence, candidiasis remains the most common opportunistic oral infection in HIV patients. This disease can have high morbidity in immunosuppressed patients; thus, its prevention and treatment in HIV groups is an important goal [19].

Oral candidiasis in HIV-infected patients

Oral candidiasis treatment in HIV-infected groups has been described in two systematic reviews of the literature [20,21]. Interestingly, neither of these articles mentioned miconazole. Nevertheless, the articles presented current data that suggest that systemic triazoles are superior to topical nystatin for both clinical cure and prevention of candidiasis. Similarly, both articles stated that increasing fungal resistance to triazoles in this patient population is worrisome. Both articles concluded that the evidence base is generally weak and more research is required. One article that did address the efficacy of miconazole in HIV-infected patients concluded that this drug was superior to nystatin suspension for controlling oral and esophageal candidiasis [22] No systemic treatments were tested in this study.

Another significant issue in the treatment of fungal diseases in the HIV-infected population is the potential for drug interactions. Systemic azoles affect the hepatic enzymes and, with them, the pharmacokinetics of other common HIV medications. Topical antifungals are not absorbed, and thus they do not interact with other medications [23]. However, due to the flushing effect of saliva in the oral cavity, the necessary drug concentration for therapeutic purposes is rarely achieved for adequate amounts of time at this site. Thus, an even greater problem and the main cause of treatment failure with

topical agents is patient noncompliance. Most topical antifungal agents require application to the oral mucosa several times per day (four times for miconazole and amphothericin B, five times for clotrimazole [24,25]) in order to achieve the necessary MIC for clinical cure. The taste of these topical preparations is another reason for noncompliance [24] Microbiological cure for oral candidiasis is rarely achieved regardless of the therapy [26].

Because of these problems, prescribers often forego topical treatment in favor of the more comfortable, less complicated use of systemic azoles. Unfortunately, results of this practice included significant drug interactions and development of resistance, particularly to fluconazole [24,27]. In 1998, resistant *Candida* species accounted for more than 5% of recurrences or oropharyngeal disease [24]. Thus, current treatment guidelines call for topical agents as the first line of drugs for oral and/or pharyngeal candidiasis in HIV patients [23–26].

New miconazole formulations

In an attempt to respond to the noncompliance problem, new topical antifungal formulations have been introduced and tested. Miconazole in a 50 and 100 mg mucoadhesive tablet (miconazole Lauriad®) formulated for extended release was initially tested in healthy volunteers [28]. Both concentrations were used once daily and had significantly longer duration and higher saliva concentration than a commercially available miconazole gel used three times per day. Importantly, the saliva concentration of miconazole after the administration of the Lauriad tablet exceeded the MIC for *Candida* species (1 ug/ml) for more than 7 h. Plasma drug concentrations were undetectable and no significant adverse events were reported. This study demonstrated that this new miconazole formulation is capable of maintaining adequate drug concentration for a prolonged period of time.

The above report was followed by a Phase III study, which tested the efficacy of the new miconazole formulation in 282 head and neck cancer patients treated with radiation therapy [29]. Patients with clinical oral candidiasis were assigned to either miconazole Lauriad 50 mg once daily or miconazole oral gel 500 mg four-times daily and examined for disease resolution after 7 and 14 days. The Lauriad preparation was slightly superior ($p = 0.13$) to the gel, particularly in patients with multiple lesions ($p = 0.013$). This noninferiority study showed again that miconazole Lauriad was well tolerated and as effective as the gel preparation used four times per day. No other antifungals were included in this study. A similar Phase III study in HIV-infected patients is currently ongoing.

Miconazole Lauriad has been approved for topical use in oral candidiasis in Europe (including the UK) and has a good chance of receiving FDA approval in the USA pending the results of the ongoing Phase III trial.

Another mucoadhesive miconazole-containing tablet has been developed and tested in an HIV-infected population [30]. This randomized trial compared a 10 mg once-daily miconazole tablet with 400 mg systemic ketoconazole also used once daily. Clinical and microbiologic responses were similar in the two groups but side effects were more common in ketoconazole patients. Although the noninferiority of the topical treatment was proven here, we note that the systemic treatment dosage was subtherapeutic, which may render these results invalid.

A formulation of miconazole in a 33% collagen base has been tested *in vitro* and shown to have stronger antifungal effect than miconazole gel on *Candida* species [31]. We are not aware on any further developments of this miconazole formulation. Last, a 0.25% miconazole nitrate/zinc oxide ointment for diaper dermatitis complicated by candidiasis has shown significant efficacy [32] and is currently the only prescription product for that purpose. This preparation has not been tested for other forms of fungal disease.

Conclusion

Fungal diseases continue to be highly prevalent and can have significant morbidity in immune compromised populations. Unfortunately, the growth of these populations is unlikely to abate soon, which will probably increase the need for antifungal medications, as well as the development of resistant organisms. In this setting, topical formulations that overcome the limitations of bad taste and multiple daily applications have an important role in early treatment and control of fungal overgrowth. Miconazole is a topical fungicidal medication that has multiple mechanisms of action. Despite its long presence on the market and common usage, relatively little fungal resistance to this medication has been reported. New formulations of miconazole, such as the Lauriad compound, may provide a vital alternative to systemic therapy in patients with limited disease.

Executive summary

- Significant increases in immune-incompetent patients and drug-resistant fungal organisms have created the need for new therapeutic options.
- A growing population of immunocompromised patients require convenient and effective control of oral and pharyngeal candidiasis. Current topical antifungal agents have limited use due to taste and need for frequent application.
- Miconazole is a fungicidal drug with multiple mechanisms of action that has been successfully used for about 40 years. New formulations of miconazole that allow once-daily application have shown promising results in Phase II/III studies. One of these, miconazole Lauriad® (Loramyc), has been approved in Europe; FDA approval in the USA is pending results of an ongoing Phase III trial.

Future perspective

With the epidemic growth in predisposing diseases (e.g., diabetes, HIV and cancer) there is a clear need for effective topical therapies for oral and pharyngeal candidiasis. Once they inhabit the oral cavity, *Candida* species can rarely be eliminated, and will almost certainly return after cessation of treatment as long as the conditions (i.e., immune deficiency) persist. Thus, we fully expect the market for antifungals to continue growing in the USA and abroad.

Current topical antifungals tend to be shunned in oropharyngeal candidiasis as their taste and need for frequent application lead to noncompliance. Instead, most physicians and dentists prescribe once-daily systemic therapy with one of the triazole compounds, usually fluconazole. This practice has led to frequent drug interactions and development of drug resistance in *Candida* species. In these conditions, new formulations of miconazole will be a welcome addition to the pharmacopeia. The main challenge to the company promoting the drug will be convincing the prescriber that their product is not inferior to the current standard of care which, as mentioned above, consists of systemic azoles, not another topical agent.

Information resources

For additional information on the new miconazole formulations, the reader may contact Bioalliance Pharma and Tibotec BVBA.

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