Research Article

New Generation Antifungal Agents and Their Role in Management of Oral Candidiasis

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Substantial progress has been done in treating fungal diseases with the development of new drugs and advanced diagnostic procedures. The ‘second generation’ triazoles display an encouraging pharmacokinetic and toxicity profile and hold high activity against resistant pathogens. Nonetheless, only Voriconazole and Posaconazole have been adequately studied in Phase III studies and approved for the management of invasive fungal infections, respectively in comparison to Rivaconazole, Isavuconazole and Albacazonazole. All these drugs are available in oral formulation and only Voriconazole, Rivaconazole and Isavuconazole are also available in the intra venous formulation. In sight of the well-known resistance pattern of some Candida species and the evolving phenomenon of Aspergillus fumigatus, triazole pan resistance seems to be of crucial importance in the near future. Moreover an inadequate exposure of the fungal pathogen to the treatment or excess drug concentrations with potential toxicity should be considered in clinical practice. As one of the latest agents in an enduring class of pharmaceuticals, it will take some time to get accustomed to these new agents. This review aims to incorporate the present knowledge on Luliconazole and Posaconazole pharmacokinetics, pharmacodynamics, toxicity, resistance, and the clinical trials, and need to formulate new therapeutic approaches in order to get a strong understanding of the clinical use of this drug.

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INTRODUCTION:
Oral candidiasis is most common fungal infection caused by candida albicans. Candidiasis is commonly present as creamy white lesion in oral cavity. The oral infection is more frequent in infants, immunosuppressed individuals, people with extreme ages and people suffering from underlying diseases. Failure to properly treat this disease can result into recurrence of the disease\(^1\). Many antifungal drugs are used in the management of oral candidiasis, but there are many limitations to these drugs. New generation antifungal agents have been developed to overcome the limitations of these first generation antifungal drugs. New generation antifungal agents have better bioavailability, less toxicity and there is improvement in the antifungal spectrum\(^2\). They possess increased activity against resistant and emerging pathogens\(^3\). New generation antifungal drugs include Albacnazole, Isavuconazole, Posaconazole, Ravuconazole, Voriconazole and Luliconazole\(^2\). Posaconazole and Luliconazole have shown effective results in treating oral candidiasis. Other new generation antifungal agents like Albacnazole, Isavuconazole and Ravuconazole are under development\(^2\).

PHARMACOKINETICS
Among the new generation antifungal drugs, Posaconazole, Luliconazole, Voriconazole and Albacnazole are available as potent drugs\(^3\). The chemical structure of Voriconazole, Ravuconazole, Isavuconazole and Albacnazole resembles to that of Fluconazole\(^3\). Posaconazole is structurally similar with Itraconazole\(^4\). Modifications include fluorine instead of chlorine and a furan ring instead of the dioxolane ring, which causes an extended spectrum of antifungal activity of Posaconazole. Posaconazole molecular formula is C\(_{37}\)H\(_{42}\)F\(_2\)N\(_8\)O\(_4\) with a molecular mass of 700.8g/mol\(^4\). Posaconazole is available in three formulations, with the two most recent formulations (i.e., delayed-release tablet and intravenous formulation) providing higher and more stable exposure than the oral suspension\(^5\). Luliconazole bears chemical resemblance to Lanoconazole with molecular formula of C\(_{14}\)H\(_9\)Cl\(_2\)N\(_3\)S\(_2\) and molecular weight of 354.267g/mol. Luliconazole is available as topical agent\(^5\). Posaconazole has shown effective in vitro results against a wide variety of fungal pathogens, including Candida species, Coccidioides immitis, Fonsecaea pedrosi and Aspergillus species\(^3\). In addition, some species of Fusarium, Rhizopus and Mucor are susceptible to Posaconazole\(^4\). Posaconazole is approved for management of oropharyngeal candidiasis, for the management of patients with invasive fungal diseases (IFD) who did not respond to first-line therapy and as salvage therapy for IFD caused by uncommon pathogens such as fusariosis, chromoblastomycosis, mycetoma, and coccidioidomycosis\(^5\). Luliconazole has shown effective in vitro results against Candida albicans, Malassezia species, and Aspergillus fumigatus\(^7\). Luliconazole has strong fungicidal activity against Trichophyton species, similar to that of terbinafine. Luliconazole 1% cream was approved for the treatment of tinea infections in Japan in 2005\(^7\). Luliconazole has recently been approved for the management of tinea pedis (athlete’s foot), tinea cruris (affecting tissue surrounding and/or including the groin), and tinea corporis (ringworm) by US Food and Drug Administration\(^7\).

Mechanism of Action:
Similar to other azole derivatives, Posaconazole and Luliconazole inhibits the enzyme lanosterol 14\(^\alpha\)-demethylase and consequently inhibits the biosynthesis of ergosterol, which is an essential component of fungal cell membrane\(^5,8\). This result in an aggregation of methylated sterol precursors and levels of ergosterol within the cell membrane decreases, thereby weakening the structure and function of the fungal cell membrane\(^5,8\).

Absorption and Distribution:
Posaconazole is well absorbed but dissolves slowly (high permeability/low solubility)\(^4\). Absorption is influenced by the frequency of doses and meals\(^9\). After oral administration of Posaconazole, absolute bioavailability has been estimated to range from 8% to 47%\(^9\). The relative bioavailability of Posaconazole has been observed to be significantly increased by
administration in divided doses. The apparent volume of distribution of Posaconazole ranges from 5 to 25 l/kg, indicating extensive distribution and tissue penetration. Posaconazole is highly protein bound (>98%), predominantly to albumin in a concentration-dependent fashion. Absorption and distribution of Luliconazole is yet to be discovered.

**Metabolism and Elimination:**
After administration of the Posaconazole suspension, 77% of the dose is excreted in feces, of which > 66% is unchanged, while 13% of the dose is eliminated in urine, of which < 0.2% is unchanged. Posaconazole is not metabolized by fungal cytochrome P450 (CYP) pathway, unlike Itraconazole and Voriconazole. Minor inhibition of CYP3A4 has been demonstrated. The limited metabolism of Posaconazole is mediated predominantly through phase II biotransformation via uridine diphosphate (UDP)-glucuronosyltransferase (UGT) enzyme pathways. Rise in Posaconazole clearance by P-glycoprotein inducers, like phenytoin and rifabutin, indicates that P-glycoprotein is involved in Posaconazole excretion. The half-life of Posaconazole is long (range 20–66 h). Metabolism and elimination of Luliconazole is yet to be discovered.

**Dose and Administration:**
Posaconazole can be administered in three formulations i.e. oral suspension, delayed-release oral tablet and intravenous formulation. The Posaconazole oral suspension solution has certain limitations so its use has been replaced by newer formulations. Oral suspension formulation is limited by saturable absorption. A delayed-release oral tablet of Posaconazole has been approved by FDA in November 2013. This tablet was largely aimed to overcome the absorption limitations related with the oral suspension. The current delayed-release tablet of Posaconazole is aimed to decrease the active drug release at low gastric pH and increase the drug release at the elevated pH levels of the intestine. The absolute bioavailability for the oral delayed-release tablet of Posaconazole is 54%. An intravenous Posaconazole formulation cultivated as an aqueous solution containing the solubilizer sulfobutyl ether betacyclodextrin has also been approved. Dosage of Posaconazole varies with the treatment of different diseases. Luliconazole is used as topical agent only; it cannot be administered in any other formulations. Luliconazole 1% cream is applied in treatment of tinea pedis for two weeks (once daily), and of tinea cruris and tinea corporis for one week (once daily).

**Safety and Tolerability:**
New generation antifungal drugs are characterised by suitable toxicity profile and this is one of the major causes for their increasing use in the prophylaxis and management of invasive fungal infections in immune-compromised patients. Posaconazole has a very good safety and tolerability profile. Posaconazole shows a low occurrence of hepatotoxicity and cardiotoxicity and no clear relationship between treatment-related toxicity and Posaconazole exposure has been identified to date. The most commonly reported adverse events were fever, diarrhoea, nausea, vomiting and headache. Other notable adverse events included hypokalaemia, rash, thrombocytopenia and abdominal pain, which are manageable from a clinical perspective. The incidence of these adverse events was similar to that with Itraconazole and Fluconazole. Topical Luliconazole cream in different strengths has generally been well tolerated. Skin reactions, pruritus, and pain at the treatment site are the adverse effects of Luliconazole when applied topically.

**ANTIFUNGALS IN MANAGEMENT OF ORAL CANDIDIASIS**
Oral Candidiasis is one of the most common human fungal infections. The infection can occur due to certain predisposing factors like the use of dentures, xerostomia, and prolonged therapy with antibiotics, use of alcohol, local trauma, malnutrition, smoking and endocrine disorders. Oral candidiasis is one of the typical clinical features of those patients infected with the human immunodeficiency virus [HIV]; this manifestation was seen in up to 90% of individuals infected with HIV. Candidal infection may start as mild superficial mucosal involvement but in severe cases it can become fatal, like in immune-compromised individuals. Clinically it is present as creamy white lesion on tongue and buccal mucosa but can be present on floor of mouth, gingiva and palate also. In severe cases it is characterised by redness,
burning or soreness that may cause difficulty in eating or swallowing. Oral candidiasis is classified as acute, chronic and Candida-associated lesions, such as angular cheilitis, denture stomatitis and median rhomboidal glossitis. Pseudomembranous and erythematous candidiasis are forms of acute candidiasis, which can become chronic. Another chronic form is hyperplastic candidiasis. Diagnosis for oral candidiasis can be done only by clinical recognition of the oral lesions by the professional. This clinical diagnosis should be confirmed by microscopic identification of Candida in the appropriate clinical specimens. Antifungal treatment for oral candidiasis can be carried out topically or systemically, usually with oral formulations. Topical drugs treat limited infections. Systemic drugs are used when the infection is more widespread and cannot be controlled with the topical therapy. Nystatin and Miconazole are the most commonly used topical antifungal drugs in treatment of candidiasis. Both the drugs are very effective but require a long time of use to suppress the infection. Miconazole can be more suitable for patients but this drug may interact with other drugs. Other topical alternatives in management of oral candidiasis are Amphotericin B and Clotrimazole, but these drugs too have certain limitations. Oral Fluconazole and Itraconazole are effective in managing oral candidiasis that does not respond to topical management. Fluconazole is the drug of choice in systemic management of oral candidiasis as it had a significantly better clinical and mycological cure rate compared with Itraconazole. However, these drugs continue to have some crucial drawbacks. Fluconazole have shown limited activity against filamentous fungi and against variable isolates of Candida. The oral formulations, particularly capsules of Itraconazole have shown unpredictable absorption and the variability in the metabolism. New generation antifungal drugs exhibit satisfactory in vitro results against a large majority of Candida species including those with a reduced susceptibility to Fluconazole. New generation antifungal drugs like Posaconazole and Luliconazole have shown effective in vitro results against candida albicans. Posaconazole is used in the management of oropharyngeal candidiasis in HIV- positive patients.

**CLINICAL STUDIES**

**Posaconazole:**

The clinical effectiveness of Posaconazole in Oropharyngeal candidiasis (OPC) was investigated in a study done by Vasquez et al in 2006. This study was conducted in HIV-positive patients. In this study comparison between Posaconazole and Fluconazole was done to check their role in the management of OPC in HIV-infected patients. The clinical success (cure or improvement) was achieved on day 14. 329 patients were evaluated in the study. The effectiveness and safety of Posaconazole was investigated in a Phase III, study by Skiest et al in 2007. The study was conducted in 176 HIV-infected patients with oesophageal candidiasis or Oropharyngeal candidiasis who did not respond to Fluconazole or Itraconazole therapy or had resistant mucosal candidiasis. Posaconazole of 400 mg (twice daily for three days) was administered in 103 subjects, followed by administration of Posaconazole 400 mg (once daily for 25 days), and then Posaconazole 400 mg (twice daily for 28 days) in 96 patients. 75.3% of patients showed clinical response (cure or improvement) after receiving 28 days of Posaconazole treatment. Different patients with baseline isolates resistant to Fluconazole, Itraconazole, or both showed similar clinical responses.

A study was done in HIV-infected patients with azole-susceptible oropharyngeal candidiasis (OPC). After 14 days of treatment primary clinical success (defined as cure or improvement) was achieved. Patients were given Posaconazole or Fluconazole oral formulation (both Posaconazole and Fluconazole were administered in doses of 100 mg twice a day for one day followed by 100 mg once a day for 13 days). Posaconazole and Fluconazole showed similar clinical success rates at day 14 as well as four weeks after the completion of treatment. However, Posaconazole showed a significantly better mycological response rate than Fluconazole.

**Luliconazole:**

There are no clinical studies investigating the efficacy of Luliconazole in oral candidiasis infection, preclinical studies have shown such results.
Study was done to check the activity of Luliconazole against candida strains which were isolated from oral lesions of cancer patients in vitro\textsuperscript{16}. A total of 385 oral samples were collected from patients with different types of cancer and from patients who has undergone chemotherapy. By using PCR-RFLP method the yeast isolates were identified. The Minimal Inhibitory Concentration (MIC) values for Fluconazole and Luliconazole were determined using broth microdilution according to the M27-S3 protocol of the CLSI. The MICs, MIC\textsubscript{50}, MIC\textsubscript{90} and geometric mean (GM) values were evaluated for all the isolates. Totally, 36 yeast strains were isolated of which 72.7% found to be of candida albicans. The MICs for Luliconazole against all Candida isolates ranged from 0.007 μg/mL to 2 μg/mL; compared to 0.25 μg/mL to 128 μg/mL for Fluconazole. Compared to Fluconazole, Luliconazole showed more potent activity against all Candida species and potentially can be considered as capable antifungal drug alternative to Fluconazole\textsuperscript{16}.

Another preclinical study was done to check the activity of Luliconazole against candida strains in vitro\textsuperscript{17}. The strains were isolated from a dental plaque. During May 2015 to June 2016, 40 samples were collected from immune-competent patients with dental plaques. Candida isolates were identified using CHROM agar and PCR-RFLP test of which 37 samples were of Candida albicans (92.5%). The antifungal susceptibility profile of 8 antifungal drugs against Candida species were evaluated in vitro. Luliconazole showed more potent in vitro antifungal activity against all the candida isolates than Voriconazole (0.06 mg/ml), Amphotericin B (0.08 mg/ml), Anidulafungin (0.09 mg/ml), Miconazole (0.14 mg/ml), Caspofungin (0.24 mg/ml) Fluconazole (0.38 mg/ml) and Itraconazole (0.5 mg/ml), respectively. The study revealed that the Luliconazole has apparently superior in vitro antifungal activity compared to Amphotericin B, Caspofungin and other azoles against Candida isolates, suggesting that it can be a promising alternative drug for the treatment of oral Candidiasis\textsuperscript{17}.

**CONCLUSION**

Various drugs are available which are effective in the treatment oral candidiasis. But these drugs have some limitations and adverse effects. For management of oral candidiasis new formulations of antifungal drugs should be made which will be more potent, which will show little or no adverse effects and which will overcome all the limitations of available drugs. New generation antifungal drugs like Posaconazole and Luliconazole have shown promising in vitro results against candida species\textsuperscript{14, 16}. A proper use of these antifungal agents requires a careful knowledge in all aspects of the drug. Studies about their role in management of oral candidiasis are still going on. For now Posaconazole is approved only for treatment of oropharyngeal candidiasis in immune-compromised patients\textsuperscript{14}. Luliconazole and Posaconazole probably deserve further evaluation in specific clinical settings. Luliconazole and Posaconazole may emerge as capable and broad-spectrum antifungal agents in the future.

**REFERENCES:**


Mycological microbe, which is not always visible. Infections caused by these microorganisms can lead to various symptoms, including skin infections, respiratory infections, and serious systemic infections. posaconazole, an oral triazole, is a promising new antifungal agent.

- Posaconazole: an oral triazole with an extended spectrum of activity.