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## Antifungal agents with special references to antibiotics: A short review

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### Abstract

Clinical needs for new antifungal agents have steadily increased with the rise and alteration in spectrum several new options are now available for management of serious fungal infections. The aim of this review is to summarize the key features of the new antifungal agents and novel targets being investigated for the treatment of fungal infections, with special reference to its use in the treatment of chronic fungal infections. New triazoles have broad spectrum of activity with voriconazole presently being the drug of choice against invasive aspergillosis, and posaconazole is the possible first substitute of amphotericin B against zygomycosis. Echinocandins with new mode of action of inhibition of fungal cell wall polysaccharide synthesis are effective in treating candidemia and invasive candidiasis. Some of these agents are however, still awaiting FDA approval for their use in pediatric practice.

**Keywords:** Antifungal agents, Antibiotics, review

### Introduction

An antifungal medication is a pharmaceutical fungicide used to treat and prevent mycoses such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Such drugs are usually obtained by a doctor's prescription, but a few are available over-the-counter. Antibiotics are medications that can help to treat some infections and save lives. Antibiotics work on various types of infections caused by bacteria. Antibiotics are produced either from a mold, a fungus or synthetically. They include family medications such as, amino glycosides, macrolides, penicillins, tetracyclines, and cephalosporins. Some antibiotics are effective against only certain types of bacteria. Others can effectively fight a wide range of bacteria. Bacterial infections include strep throat, most (but not all) ear infections, and some sinus, bladder, and lung infections such as acute bronchitis. Antibiotics weaken or destroy bacteria. Antibiotics do this by interfering with protein formation processes of bacteria.

### New Azoles

Azoles exert their antifungal activity by binding to the ergosterol biosynthetic enzyme, lanosterol 14- $\alpha$  demethylase and inhibiting ergosterol synthesis. Earlier members of this group had a rather narrow spectrum of activity against some but not all yeasts, with itraconazole demonstrating some activity against molds. New generation triazoles have an expanded spectrum of action with cidal activity against a broad spectrum of molds and enhanced activity against *Candida* spp. and other yeasts. The new azoles that have been developed include voriconazole, posaconazole and ravuconazole; and isavuconazole and albaconazole are under study. While all azole derivatives share the common mechanism of action, each possesses a unique affinity for the various fungal cytochrome P450 enzymes and thus a unique spectrum of activity and safety profile. However, the common mechanism of action leads to cross-resistance among azoles.

### Voriconazole

It has been developed from fluconazole by adding  $\alpha$ -methyl group and substituting a fluoropyrimidine ring for one of the azole groups. This achieved fungicidal activity against *Aspergillus* and other molds but not against *Zygomycetes* [1]. United States Food and Drug Administration (FDA) approved it for the treatment of primary acute invasive aspergillosis and serious infections caused by *Scedosporium* spp. And *Fusarium* spp in 2002, and in 2005 approved its use for the treatment of candidemia in adult patients without neutropenia. It can be used as both oral and intravenous formulations and is currently available in India.

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Given orally on an empty stomach, the drug is rapidly and almost completely absorbed but food lowers the drug's bioavailability and delays absorption. The pharmacokinetics of voriconazole in children appears linear in contrast to non-linear pharmacokinetics in adults. This was based on single dose, open-label, two-center study involving children ages 2-11 years (mean 5.9 years); and a multi-dose, open, multicentric study in two age cohorts (age 2-6, and 6-12 years with mean age 6.4 years). These studies showed that a pediatric dose of approximately 11mg/kg administered every 12h are approximately bioequivalent to an adult dosage of 4mg/kg given every 12h [12]. Other variables such as CYP2C19 genotype, body weight, kidney and liver functions also affect plasma concentrations of the drug achieved after a given dosage. Selection of a fixed dose therefore yields a wide variety of plasma concentrations and there is a need of therapeutic drug monitoring for patients being treated with voriconazole [13, 14]. Though, voriconazole has not received FDA approval for use in children 2-11 years of age, it is approved in the European Union on the basis of compassionate use data [15]. Voriconazole has not yet been formally tested in neonates due to the visual adverse events reported in adults and children. There is a major concern over its effect on the developing retina [16]. Recently a case series of safe voriconazole use in critically ill newborn with cardiac disease has been reported from India [17]. No significant drug interaction despite use of several cardiac drugs or any side effect was observed.

#### Posaconazole

An oral 2nd generation azole, was approved by the FDA in 2006 for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients at increased risk for these infections due to hematopoietic stem cell transplant, graft versus host disease, and hematological malignancies with prolonged neutropenia from chemotherapy. This drug is not yet commercially available in India. Posaconazole is similar in structure to itraconazole and has a broad-spectrum of activity in vitro against a wide array of yeasts, moulds, and especially the *Zygomycetes*, for which treatment options are limited. Unlike voriconazole, absorption is better when administered with fatty meals with extensive distribution in the tissues. It is only used as a compassionate release agent in oral formulation. It is active in vivo in several experimental models of pulmonary, cerebral, and disseminated aspergillosis [18, 19]. Randomized comparative studies of efficacy and safety of posaconazole in HIV-infected adults with oropharyngeal candidiasis indicate that it is as effective as fluconazole and well tolerated. A 40-80% response rate has been shown in patients with a wide variety of IFIs including cryptococcosis, candidiasis, phaeohiphomycosis, aspergillosis and fusariosis [15, 20, 21]. Limited efficacy data are available in children. Posaconazole plasma levels were compared between juvenile (aged 8-17 years) and adult (aged 18-64 years) patients participating in an open-label phase III study. Posaconazole, 800 mg/ day was given as salvage therapy for proven or probable IFI, refractory to standard antifungal therapy. Posaconazole concentrations in plasma were similar for juvenile and adult patients, suggesting that clinical outcomes are expected to be similar in adults and juvenile group with refractory invasive fungal infection [22]. There is no data available on the safety and efficacy of posaconazole in neonates.

#### Ravuconazole

It is a derivative of fluconazole with potent activity against *Candida* spp., *Aspergillus* spp., *C. neoformans*, *H. capsulatum* and *C. immitis* in vitro. It is fungicidal, has 47-74% bioavailability with linear pharmacokinetics, and possesses long half-life of approximately 100h. Activity of ravuconazole against *Fusarium* and *Scedosporium* is less than that of voriconazole and cross-resistance between fluconazole and ravuconazole has been observed with *Candida glabrata* and other *Candida* spp [23]. The drug has no activity against *Rhizopus* or *Mucor* spp. The safety and tolerability of ravuconazole has been tested in a handful of adult patients and was found to be similar to that of fluconazole. Unfortunately, no pediatric data is available.

#### BAL-8557

It is the water-soluble pro-drug that gets cleaved to BAL-4815 (isavuconazole). This new azole has very high (98%) plasma protein binding in humans and has potent *in vitro* activity against *Aspergillus* spp. including *A. fumigatus*, *A. flavus*, *A. terreus* and *A. niger*. It has lower MIC and MIC50 values than those of voriconazole for the majority of *Candida* spp. tested, including *C. glabrata* and *C. krusei*, and exhibits activity against dermatophytes and *Zygomycetes* [24, 25, 26]. Several randomized clinical trials are evaluating the safety and efficacy of this drug for the treatment of invasive *Candida* infections [23]. Additional triazoles such as albaconazole are undergoing early clinical evaluation and their future is uncertain. For all new triazoles, concerns about emerging drug-resistant fungi and the problem of management of breakthrough infections will dictate their role in future antifungal prophylaxis and treatment.

#### B. Echinocandins:

This is an entirely new class of antifungal agents that exert their activity by noncompetitive inhibition of 1, 3- $\beta$ -D-glucan, an essential fungal cell wall polysaccharide. Structurally, they are characterized by a cyclic hexapeptide core linked to a lipid side chain that is variably configured. Echinocandins are fungistatic (due to blockade of cell wall synthesis) against *Aspergillus* and fungicidal (due to loss of cell wall integrity) against *Candida* activities. The unique mechanism of action has dual benefit: fewer side effects as cell walls are lacking in human cell, and possibility of successful combination with agents acting on cell membrane as combination therapy. All drugs in this group have poor bioavailability and have to be administered intravenously.

#### Conclusion

The advances in antifungal therapy have been impressive in the last few years and new therapeutic strategies have had significant impact on the mortality of IFI [30]. This has great implications in the field of chronic antifungal therapy, especially since the number of children receiving chemotherapy and HSCT continue to increase. However there is need for more clinical trials to study the use of these new agents and their efficacy in different clinical conditions, specifically in the pediatric age group.

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