

## MEDIA BRIEF ON ANTIFUNGAL AGENTS

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Fungi are eukaryotic organisms that are not amenable to therapy with antibacterial antibiotics. With fungi, the situation exists where a eukaryotic organism (the fungus) is attacking a eukaryotic host (humans). This limits the number of avenues of basic biochemical differences that can be explored for the production of therapeutic agents. Although antifungal agents have been sought for decades, relatively few classes of drugs have been found.

Certain biochemical and physiologic characteristics that differentiate the fungus from other forms of life have to be exploited in administering antifungal therapy. Among these are the components of the fungal cell wall (beta-(1,3)-D-glucan), the fungal cell membrane (ergosterol formation and integrity), and finally, DNA synthesis in the fungal cell nucleus.

### POLYENE ANTIFUNGAL AGENTS

The earliest antifungal compounds used for the treatment of invasive fungal infections were the polyenes (parenteral amphotericin B). Amphotericin B exerts its effect on fungi by binding preferentially to the ergosterol moiety in the fungal cell membrane as compared with the cholesterol moiety in human plasma cell membranes. Its binding causes derangement of the membrane integrity punching holes in the membrane with subsequent leakage of cytoplasmic components. Nystatin exerts its antifungal effect in a similar fashion, but is only available as a topical agent treating topical forms of yeast infection. Amphotericin B and nystatin were licensed in the late 1950s and have remained mainstays of therapy for both invasive fungal infections (amphotericin B) and superficial fungal infections involving the mucous membranes and skin (nystatin).

Amphotericin B is available in a formulation with deoxycholate and in 3 lipid associated formulations. The active component of amphotericin B is produced by *Streptomyces nodosus*. As a lipophilic molecule, amphotericin B increases the fungal cell membrane permeability with loss of intracellular potassium and other molecules thus impairing fungal viability. This drug is fungicidal meaning that it kills fungi.

Amphotericin B has very broad activity against most fungi. Resistance to its effect may be caused by reduction in ergosterol biosynthesis and the synthesis of alternative sterols that lessen the ability of amphotericin B to interact with the fungal cell membrane. Resistance is common in *Aspergillus terreus*, *Candida lusitanae*, *Scedosporium apospermum* and *Trichosporon species*. In addition, certain organisms such *Aspergillus species* and zygomycetes require much higher doses of amphotericin B in order to be effective.

The other available lipid formulations of amphotericin B include: amphotericin B colloidal dispersion (Amphotec), amphotericin B lipid complex (Abelcet), and liposomal amphotericin B (Ambisome). These lipid associated formulations were prepared to lessen the side effects associated with amphotericin B deoxycholate.

The principal side effects associated with amphotericin B deoxycholate include renal toxicity secondary to a decrease in glomerular filtration rate; loss of potassium, magnesium, and bicarbonate; chills; fevers; rapid respiration; nausea; vomiting; anemia; and elevations in liver function tests.



## AZOLE ANTIFUNGAL AGENTS

As mentioned above, there is another group of antifungal agents that act by inhibiting the formation of ergosterol. These agents may be subdivided to the original imidazole compounds and the newer triazole agents. Both types of compounds exert their effect by inhibiting the demethylation of lanosterol in fungi through binding to one of the cytochrome P-450 enzymes leading to the accumulation of methylsterols and reduced concentration of ergosterol. All of the azoles are fungistatic, meaning that they do kill fungi but do it at a slower pace than the fungicidal agents.

The important azole compounds are: ketoconazole (only available as a topical agent), fluconazole, itraconazole, voriconazole, and posaconazole were synthetically produced starting with ketoconazole in 1980. Thereafter, fluconazole became available in 1990 with itraconazole, voriconazole and posaconazole thereafter. Fluconazole, and voriconazole are available in both an oral and an intravenous preparation. In contrast itraconazole and posaconazole are currently only available in oral preparations. Ketoconazole is now only available as a topical preparation.

The azole compounds are highly active against yeast including *Candida species* and cryptococcus. In addition, itraconazole, voriconazole, and posaconazole are not only active against *Candida species*, but have excellent activity against *Aspergillus species*. In particular, voriconazole is also active against *Fusarium species*, while posaconazole is also active against the zygomycetes. Itraconazole is also potent against histoplasmosis and blastomycosis. The azoles are fungistatic agents meaning that they inhibit fungal growth. As a result of their activity against commonly encountered fungi and their ability to be administered both orally and intravenously, the azoles have become the mainstays for prophylaxis (prevention) of invasive fungal infection in immunocompromised patients.

In addition, there are imidazole compounds that are only available for topical application (miconazole and clotrimazole). As a result, they are used to treat cutaneous and mucosal superficial *Candida* infections.

The adverse effects related to the azole compounds occur secondary to their metabolism in the liver resulting in drug interactions with a number of other pharmaceutical products and their direct effect on the liver. This is particularly true for itraconazole, voriconazole and posaconazole. In contrast, fluconazole is excreted by the kidney and poses fewer drug interactions. It may, however, cause some nausea and vomiting.

## ALLYLAMINE ANTIFUNGAL AGENTS

Another chemical group that is active against a number of fungi is the allylamines. Members of this group once again interfere with ergosterol biosynthesis by inhibiting the enzyme squalene epoxidase. One of the enzymes necessary for the production of lanosterol, an intermediate compound in the formation of ergosterol. In addition, lanosterol is an intermediate in mammalian human cholesterol synthesis but the fungal enzyme is many times more sensitive. The allylamines are available in both topical and oral formulations. As a result, they are effective in treating superficial fungal infections of the skin and nail infections. Their main side effects relate to nausea and vomiting, as well as liver function abnormalities when given orally.

## FLUOCYTOSINE

Fluocytosine is a fluorine analog of a normal body constituent cytosine. This agent is administered orally and is water-soluble. Absorption from the gastrointestinal tract is rapid and approximately 90% of the compound is excreted in the urine.



Fluocytosine works by deamination to 5-fluorouracil. It is 5-fluorouracil that is then converted to other compounds that interfere with DNA synthesis.

Fluocytosine is highly active against *Candida species* other than *Candida krusei*. It is also active against *Cryptococcus neoformans* and has some activity against certain isolates of *Aspergillus species*. However, its use is limited by its side effect profile that includes leukopenia, thrombocytopenia, and diarrhea.

#### ECHINOCANDIN ANTIFUNGAL AGENTS

The echinocandin class of antifungal agents act by inhibiting the synthesis of beta 1,3-D-glucan. This compound is a major component of the fungal cell wall and is synthesized by the enzyme glucan synthase. The echinocandins bind to a subunit of the gene that produces glucan synthase. The echinocandins are fungicidal agents. Caspofungin was the first of the echinocandins to be marketed in 2001. There are currently 3 available echinocandins: anidulafungin, caspofungin, and micafungin. The spectra of activity of these agents are similar. They are broadly active against all *Candida species* including isolates resistant to other agents, and *Aspergillus species*. However, against the latter pathogens their activity is limited to growing and dividing hyphal elements; resting forms are not killed. It should be noted that the echinocandins are not active against other yeasts such as *Cryptococcus*.

In general, the echinocandins are very safe agents. Both caspofungin and micafungin are excreted via the liver and as a result dosage reduction are necessary for caspofungin. Some drug interactions may occur with caspofungin (cyclosporine, tacrolimus, rifampin, and phenytoin) and micafungin (sirolimus). In contrast, anidulafungin is broken

down slowly in the bloodstream and no drug interactions occur with it. Minor elevations in liver function tests may occur with all of the echinocandins.

Future development of antifungal agents will probably be directed at other inhibitors of fungal cell wall formation. In addition, other new azole compounds directed at ergosterol formation are also under development. The latter agents will have broad spectrum of activity to include both *Candida species* and the molds. The objective the development of these newer agents will be to minimize their toxicity while enhancing their clinical utility.

