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Pharmacology in Clinical Settings of Antifungal Drugs

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ABSTRACT:

In patients with severe underlying illnesses, invasive fungal infections have developed into significant sources of morbidity and mortality. Treatment options have been restricted to amphotericin B deoxycholate (AmB-D) with or without flucytosine for more than three decades. Only after the clinical advancement of itraconazole (ITC) and fluconazole (FLC) in the late 1980s did therapeutic options become available. The arsenal of antifungal agents, however, has significantly increased over the past ten years as a result of the introduction of less toxic AmB formulations, the improvement of antifungal triazoles, and the appearance of echinocandin lipopeptides, a new class of antifungal agents that target the fungal cell wall. In order to treat invasive fungal infections, this article discusses the clinical pharmacology of both licenced and investigational antifungal medications.

Keywords*:* Antifungal, micellar, candidiasis, plasma, hydration, meningitis, echinocandins

INTRODUCTION:

The pharmacology of topical and systemic medications is only used for therapeutic purposes. This page does not cover the topic of superficial dermatophyte infections of the skin and its appendages, as it has been covered elsewhere [1].

Polyene antibiotics

Amphotericin B deoxycholate: An internal ester, a free carboxyl group, seven conjugated double bonds, and a glycoside side chain with a main amino group make up the antibiotic amphotericin B, a naturally occurring polyene macrolide. It cannot be absorbed intramuscularly or orally. AmB has been solubilized with deoxycholate as a micellar suspension for parenteral usage.

Mechanism of action: Amphotericin B primarily acts by binding to ergosterol, the principal sterol in the cell membrane of most fungi, leading to the formation of ion channels and cell death. With less avidity, the compound also binds to cholesterol, the main sterol of mammalian cell membranes, which is believed to account for most of its adverse effects. A second mechanism of action of AmB may involve oxidative damage of the cell through a

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cascade of oxidative reactions linked to its own oxidation with formation of free radicals or an increase in membrane permeability [2,3].

Antifungal activity: Most fungi that are harmful to humans are active against by amphotericin B. Primary resistance has been linked to differences in the quality or quantity of membrane sterols, but it may also be connected to an increase in catalase activity and a reduction in the vulnerability to oxidative damage. Other than C lusitaniae, resistance is still rare in Cryptococcus neoformans and Candida species, while AmB appears to be less effective against nonalbicans Candida. The susceptibility of Aspergillus spp. and other opportunistic moulds to AmB tends to vary more than that of dimorphic fungi. At quantities that are safe for patients to receive, Aspergillus terreus, Fusarium spp., Pseudallescheria boydii, Scedosporium prolificans, a few other dematiaceous fungus, and Trichosporon beigelii may be resistant to AmB [4,5].

Pharmacodynamics: In time-kill assays, amphotericin B exhibits concentration-dependent fungicidal activity against susceptible Candida albicans, Candida neoformans, and Aspergillus fumigatus. It also exhibits an in vitro postantifungal effect that can last up to 12 hours against both Candida albicans and Candida neoformans. Cmax/MIC appears to best correspond with antifungal effectiveness in vivo, according to studies in laboratory animals with experimental disseminated candidiasis [7]. These results provide evidence in favour of the maximisation of peak concentrations and the need for large doses.

Pharmacokinetics: After being injected, AmB separates from its carrier and becomes heavily protein-bound before primarily distributing to the liver, spleen, bone marrow, kidney, and lung. With a terminal half-life of 15 days or longer and a b-half-life of 24 to 48 hours, clearance from plasma is sluggish [8,9]. Although concentrations in body fluids other than plasma are typically low, AmB is helpful in treating fungus infections of the central nervous system despite essentially undetectable amounts in the cerebrospinal fluid (CSF). The majority of drug disposal occurs in tissue accumulation. Patients with associated renal or hepatic impairment do not require a dose change of AmB. Hemodialysis usually has no effect on plasma concentrations of AmB due to its strong protein binding [10]. Children and infants appear to remove drugs from plasma more quickly than adults [1].

Adverse effects: The nephrotoxicity of AmB and responses to infusions are significant issues that frequently restrict therapy. The production of cytokines from monocytes in response to the medication is thought to mediate infusion-related responses (fever, rigours, chills, myalgias, arthralgias, nausea, vomiting, and headaches). Up to 73% of individuals can have them after the first dose, however they frequently become better as the treatment goes on [11]. Slowing the infusion rate or pre-medicating with acetaminophen (10 to 15 mg/kg), hydrocortisone (0.5 to 1 mg/kg), or meperidine (0.2 to 0.5 mg/kg) will reduce the severity of infusion-related responses. Rapid infusion (60 minutes) may result in cardiac arrhythmias and cardiac arrest brought on by sudden potassium release, particularly if there is pre-existing hyperkalemia or renal impairment. Real allergy responses are uncommon [10]. Azotemia and

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the loss of potassium and magnesium are the hallmarks of AmB-associated nephrotoxicity; tubular acidosis and reduced urine concentration capacity are rarely clinically significant [12].

Replacement of hypokalemia can be difficult unless hypomagnesemia is treated. Azotemia is frequent. In a sizable prospective clinical trial, 34% of 344 unstratified patients taking AmB for empirical treatment of fever and neutropenia had baseline serum creatinine levels that had increased by more than 100% [11]. Renal toxicity associated with the use of AmB has the potential to result in renal failure and dialysis [13], but azotemia often stabilises on therapy and is typically reversible after the drug is stopped. Azotemia can be made worse by concurrent nephrotoxic agents, in particular by cyclosporine and tacrolimus. A normal saline loading (10 to 15 mL 0.9% NaCl/kg/d) and avoiding concurrent nephrotoxic medications may minimise the risk and severity of azotemia [10].

AmB may also cause flushing, vestibular problems, hypotension, hypertension, normocytic, normochromic anaemia, and other potentially serious side effects [14]. Because AmB causes skin irritation, infusion should be done through a central line.

Drug interactions: For AmB, there are no known medication interactions brought on by similar metabolic pathways. Corticosteroids have the potential to make hypomagnesemia worse, and cancer patients with platinum-associated nephropathy are at an increased risk of developing severe hypomagnesemia. The toxicity of medications that are removed by the kidneys may increase as a result of AmB therapy. Last but not least, concurrent granulocyte infusion has been linked to acute pulmonary responses and needs to be avoided [10].

Indications and dosing: Historically, amphotericin B deoxycholate has been regarded as the medicine of choice for the first management of the majority of life-threatening infections brought on by susceptible microorganisms. This idea may be evolving due to the improved efficacy-toxicity profile of AmB lipid formulations, novel triazoles, and echinocandins. The recommended daily dosage ranges from 0.5 to 1.5 mg/kg/d given over 2 to 4 hours as tolerated, depending on the kind of infection and the host. 0.5 to 0.6 mg/kg/d is the usual dosage for empirical therapy in chronically febrile neutropenic individuals [15,16]. For candidiasis, the dosage is 0.6 mg/kg/d for Candida albicans, 1 mg/kg for Candida glabrata, Candida tropicalis, and Candida krusei [17], and 1.0 to 1.5 mg/kg/d for aspergillosis or zygomycosis [18]. Although clinical experience is limited, AmB-D continuous infusion may be less harmful [19]. At this time, the dosage recommendations for all paediatric age groups are the same as for adults [1]. To enable rapid intervention for infusion-related responses, treatment should begin at the full target dosage with thorough bedside monitoring during the first infusion [10].

Therapeutic monitoring: Because the associations between plasma and tissue concentrations and clinical efficacy or toxicity have not been well defined [6,] monitoring of AmB concentrations in plasma or CSF appears to be of limited utility.

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Amphotericin B lipid formulations: Three novel AmB formulations, including AmB colloidal dispersion ([ABCD] Amphocil or Amphotec), AmB lipid complex ([ABLC] Abelcet), and a tiny unilamellar vesicle liposomal formulation, have been approved in the past few years in the United States and much of Europe ([L-AmB] AmBisome). These substances enable the delivery of greater dosages of amphotericin B (AmB) due to their lower nephrotoxicity in comparison to amphotericin B deoxycholate (AmB-D). For equal antifungal activity, higher doses are needed [20,21].

Flucytosine:

Flucytosine (5-fluorocytosine [5-FC]) is a low-molecular-weight watersoluble synthetic fluorinated pyrimidine analogue. It is taken up by the fungus-specific enzyme cytosine permease and converted in the cytoplasm by cytosine deaminase to 5-fluorouracil, which causes RNA miscoding and inhibits DNA synthesis [37]. 5-FC is relatively nontoxic to due to cytosine deaminase's lack of action or very low activity in mammalian cells. Only an oral formulation of 5-FC is available in the United States; outside of the US, a few nations offer an intravenous formulation.

Antifungal activity: The antifungal spectrum of 5-FC in vitro encompasses Candida spp, C. neoformans, Saccharomyces cerevisiae, and selected dematiaceous molds. 5-FC has no or weak activity against Aspergillus spp and other hyaline molds [14,37]. Synergistic or additive effects in combination with AmB have been observed against Candida spp, and in combination with AmB or fluconazole against C neoformans. Extensive reviews of its pharmacology and pharmacodynamics have been published recently [10,37,38].

Indications and dosing: 5-FC is typically not used as a single agent because of the potential for secondary resistance [39,40]. The induction therapy for cryptococcal meningitis is a recognised indication for its usage in combination with AmB-D [41,42]. For the treatment of Candida infections affecting deep tissues, AmB-D and 5-FC can also be advised, especially in critically ill patients and when non-albicans Candida species are present [40]. It is not advised to use 5-FC as an empirical treatment for neutropenia because it has been shown to prolong haematological recovery following cytotoxic chemotherapy [43]. When therapy with AmB is not possible, the combination of 5-FC and fluconazole may be utilised for cryptococcal meningitis or other invasive Candida infections. Currently, the authors advise a starting dose of 100 mg/kg per day, divided into three or four doses, for both adults and children.

Therapeutic monitoring: To prevent toxicity, plasma concentrations must be closely monitored. Peak plasma levels between 40 and 60 lg/mL at 2 hours after dose correspond with antifungal activity and are infrequently linked to hematologic side effects [38,40].

Antifungal triazoles: To prevent toxicity, plasma concentrations must be closely monitored. Peak plasma levels between 40 and 60 lg/mL at 2 hours after dose correspond with antifungal activity and are infrequently linked to hematologic side effects [38,40].

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Echinocandin lipopeptides: anidulafungin, caspofungin, and micafungin

A unique class of semi-synthetic amphiphilic lipopeptides called echinocandins is made up of a cyclic hexapeptide core connected to a variety of lipid side chains. Echinocandins work by inhibiting 1,3-b-glucan production, a polymer found in the cell walls of many pathogenic fungus. The ropy glucan fibrils, along with chitin, are in charge of giving the cell wall its strength and shape. They are critical for cell division and cell growth as well as preserving the osmotic integrity of the fungal cell. Anidulafungin (VER002, formerly LY303366, Versicor, Freemont, CA) and Micafungin (FK463, Fujisawa, Deerfield, IL) are two additional medications that are in advanced stages of clinical development. One of these medications, caspofungin (MK-0991, Merck, Rahway, NJ), has already received FDA approval as a third-line treatment for invasive aspergillosis. The echinocandins have the potential to be used in combination regimens with currently accessible conventional antifungal drugs due to their unique mode of action.

The present echinocandins appear to share several pharmacologic characteristics. The antifungal efficiency of all three drugs against these organisms in vivo has been proven in a number of animal models. All three compounds have potent and broad-spectrum fungicidal in vitro activity against Candida spp. and potent inhibitory activity against Aspergillus spp. The present echinocandins are ineffective against the majority of hyalohyphomycetes, Zygomycetes, C neoformans, and T beigelii and have erratic efficacy against dematiaceous and endemic mould. Additionally, in animal models of Pneumocystis carinii pneumonitis, all echinocandins have shown both therapeutic and preventative action [4]. Resistance-induction experiments have shown a modest potential for secondary resistance in Candida spp., while primary resistance to echinocandins in otherwise vulnerable fungal yeast species is uncommon. There are no studies on the prevalence of primary echinocandin resistance among clinical isolates of Aspergillus spp. or the production of secondary resistance in vitro.

Future directions

In the past ten years, there has been a significant increase in the study of antifungal medications as well as the clinical development of a number of novel substances and tactics for the treatment of invasive fungal diseases. AmB-D is a suitable substitute for ITC, voriconazole, and liposomal AmB in neutropenic fever. The more recent triazoles tantalisingly hint at the prospect of treating mould infections orally and appear to be a good alternative to AmB in many aspergillosis cases. Echinocandins plus triazoles or AmB are already being considered as a combination therapy. Although invasive fungal infections will probably continue to be a common and serious complication in immunocompromised patients, a wider range of drugs, a better understanding of the mechanisms underlying resistance, the integration of pharmacokinetic and pharmacodynamic relationships, and combination therapies give hope for further significant advancements in prevention and treatment.

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