IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
March 2020 Vol.:15, Issue:1

Currently Available Systemic Antifungal Drugs

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INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
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Jnanamba P*[1], Krishan Pal Singh[2], Raghavendra[3]

[1]Research Scholar OPJS University, Churu, Rajasthan, India

[2]Research Guide OPJS University, Churu, Rajasthan, India

[3]Research Scholar OPJS University, Churu, Rajasthan, India

Submission: 20 February 2020
Accepted: 27 February 2020
Published: 30 March 2020

Keywords: Antifungal agents, Therapy, systemic antifungal drugs

ABSTRACT

The recent trend or expansion of antifungal drug research has demonstrated that there is a critical need for new antifungal agents to treat these life-threatening invasive infections. Invasive fungal infections are critical in treating immune-compromised patients. The overview of the development of antifungal therapy discussed in this article reflects the increased interest in this area of infectious diseases. Although newer, less toxic, antifungal agents are available for clinical use, their clinical efficacy in some invasive fungal infections, such as aspergillosis and fusariosis, is not optimal. Thus, intense efforts in antifungal drug discovery are still needed to develop more promising and effective antifungal agents for use in the clinical arena.

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INTRODUCTION

POLYENES - AMPHOTERICIN B FORMULATIONS

Mechanism of action:

The polyenes (AmB, nystatin) are large (26–28 carbon molecules) macrolide structures, with many hydroxyl groups, which confer the amphipathic nature of the compounds (Fig No. 1). Of the initially discovered polyenes, only AmB is sufficiently benign to permit IV administration.[1,2] Amphotericin B is amphophilic and acts by binding through both hydrophilic hydrogen bonds and hydrophobic, non-specific van der Waals forces to ergosterol in fungal cell membranes.[3-5] Amphotericin B has a greater affinity to bind ergosterol and ergosterol-containing membranes than cholesterol or cholesterol-containing membranes.[2,6,7] Conformationally, compared to cholesterol, the chemical structure of ergosterol is more favorable for interactions governed by van der Waals forces.[3] The binding occurs within minutes of exposure and is followed by increasing leakage of intracellular ions out of fungal cells (i.e., potassium) and extracellular ions into cells, which leads to depolarization of the membrane and increased permeability to protons and monovalent cations.[4-6]. This osmotic disruption may not be the main mechanism of lethality to fungal cells, because polyenes also interfere with membrane-associated oxidative enzyme function, and this secondarily is thought to be lethal.[4,9]

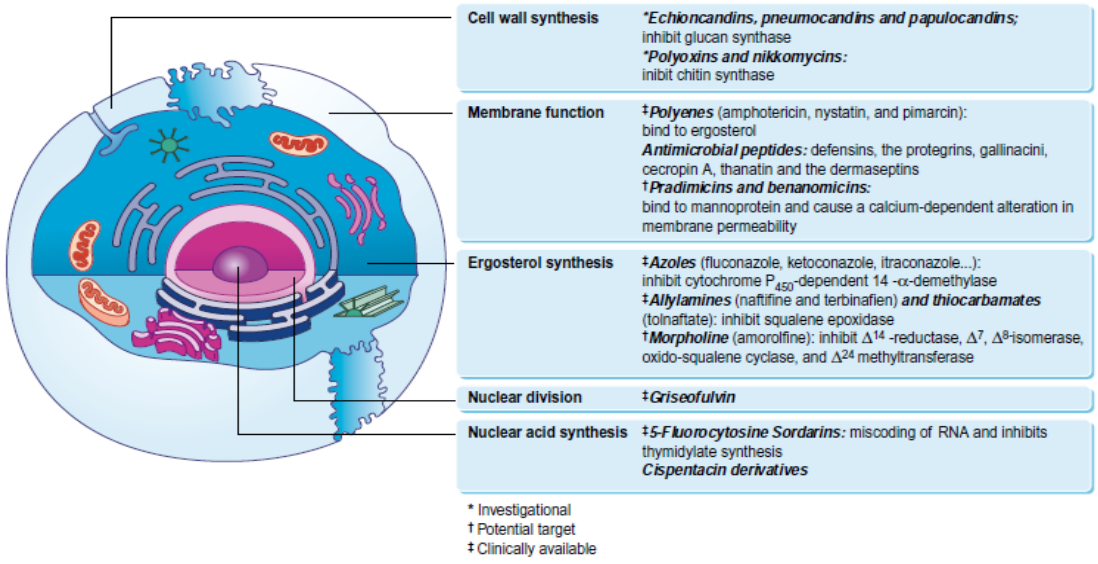

Figure No. 1: Site of action of antifungals

Although rapid lethal action is clearly shown in vitro against several fungal pathogens, neither polyenes nor any other antifungal drugs are lethal in vivo.[10-12] It is not clear whether this is due to a protected intracellular environment of some pathogens or limited access to fungal targets.

In addition to direct antifungal activity, AmB stimulates the release of cytokines such as tumor necrosis factor and interleukin-1 from mammalian phagocytic cells and also stimulates the release of macrophage superoxide ion, all of which may augment antifungal activity.[13-15]

Spectrum of activity:

The antifungal spectrum of AmB is extremely broad, it being easier to list the few exceptions than the targeted species. However, growing evidence suggests less than optimal activity against several *Candida* species.[16]*Candida lusitaniae* has long been recognized to develop resistance to AmB upon exposure to the drug. Moreover, increased minimum inhibitory concentrations (MIC) have been described for less common species including *C. guilliermondii* and *C. rugosa*, and rare mutants of *Candida* species, including *C. albicans*, *C. tropicalis*, and others.[17]Initial reports demonstrated that *C. guilliermondii* was capable of developing resistance to AmB; however, only 2% of bloodstream isolates from large global surveillance were resistant to the drug.[17,18] The diminishing susceptibility to AmB among more common *Candida* spp., including *C. glabrata* and *C. krusei*, is a growing concern.[19] Both *C. glabrata* and *C. krusei* exhibit decreased susceptibility to AmB compared with *C. albicans*.[20-22] More-over, AmB also exhibits delayed killing against these species when compared to its activity against *C. albicans*.[23]

Although AmB is active against most moulds, there is inter-species variability concerning amphotericin MICs. Among *Aspergillus* spp., *A. terreus*, *A. flavus*, and *A. nidulans* typically are less susceptible to AmB than other species.[24-26] Moulds other than *Aspergillus* spp., including certain zygomycetes, *Fusarium*, *Pseudallescheria* spp., *Scedosporium* spp., *Exophiala* spp., *Alternaria* spp., *Cladosporium* spp. and *Trichosporon asahii* (formerly *Trichosporon beigelii*), also exhibit high (2–32μg/ml) AmB MICs.[24-28]Table 7-2 describes the antifungal spectrum of AmB ac-cording to clinical response.

Table No. 1: Antifungal spectrum of amphotericin B by clinical response

Usually Effective (>60%)	Variably Effective to Resistant
Candida albicans	*Candida lusitaniae*
Candida krusei	*Candida rugosa*
Candida tropicalis	*Fusarium* spp.
Candida parapsilosis	*Pseudallescheria boydii*
Cryptococcus neoformans var. *neoformans*/var. *gattii*	*Scedosporium prolificans*
Histoplasma capsulatum var. *capsulatum*/var. *duboisii*	Various Phaeohyphomycetes
Paracoccidioides brasiliensis	*Aspergillus* spp.
Blastomyces dermatitidis	*Coccidioides immitis*
Penicillium marneffei	
Sporothrix schenckii	

Pharmacokinetics In humans, AmB primarily distributes to the liver and, to a lesser extent, a variety of other tissues including the spleen, kidneys, and heart.[2]Amphotericin B deoxycholate (D-AmB) is highly protein-bound (>95%), primarily to albumin and α_1-acid glycoprotein. The percentage of bound drug increases as the D-AmB concentration increases. This unique binding may be due to the low solubility of un-bound D-AmB in human plasma (<1 μg/ml), relative to the large binding capacity of plasma proteins.[29] Amphotericin B deoxycholate has a very large apparent volume of distribution (2–4 l/kg), suggesting that it distributes to tissues.[29-30]

Historically, D-AmB pharmacokinetics have been poorly understood, but over the years our understanding of how the human body handles D-AmB has greatly improved. Over 90% of the administered dose is accounted for 1 week after the administration of 0.6 mg/kg D-AmB to healthy volunteers, with most of the drug being excreted unchanged in the feces and urine.[30]Approximately two-thirds of D-AmB is recovered in the urine (20.6%) and feces (42.5%).[30] Urinary and fecal clearances of unchanged drug account for 75% of D-AmB total clearance.[30] Amphotericin B deoxycholate is cleared from its distribution sites very slowly, as reflected by its terminal half-life of approximately 127 hours.[30] The formulation of amphotericin B in a lipid vehicle significantly alters its distribution and elimination.[30]

The lipid amphotericin B formulations differ in composition and physicochemical properties. These differences produce subtle differences in amphotericin B pharmacokinetics among the

formulation. Following IV administration, lipid amphotericin B formulations are cleared from the circulation by macrophages or monocytes, Kupffer cells lining the hepatic sinusoids, reticular cells of the lymphatic tissue and bone marrow, spleen, and lung.[31] Physicochemical properties (size, surface charge, composition, and stability) of these compounds also determine how quickly they are cleared from the circulation. In general, the smaller the liposome or lipid complex, the longer it circulates. Also, positively charged or neutral liposomes or lipid complexes circulate longer than those of similar size that are negatively charged.[31,32] Lipid amphotericin B formulations can also be broken down in the serum or degraded by phospholipases. When amphotericin B is incorporated into liposomes or associated with lipid complexes, the lipids only influence its distribution in the body.

Amphotericin B lipid complex (ABLC) is 1.6–11 μm in size. Because of its size and surface charges, it is cleared rapidly from the circulation and distributes extensively to tissue. Consequently, compared to equivalent doses of the deoxycholate formulation, ABLC produces lower maximum serum concentrations and drug exposure while at steady state, and its volume of distribution and total clearance is higher.[33]

Liposomal amphotericin B (L-AmB) consists of spherical liposomes, 45–80 nm in size, with an aqueous core[34] Due to its small particle size distribution compared to other amphotericin B formulations, L-AmB is more slowly cleared from the blood-stream, has a longer circulation half-life, and achieves higher maximum plasma concentration and systemic drug exposure, but has a smaller volume of distribution.[35] Also, less than 10% of a dose is recovered in the urine and feces.[30]

Amphotericin B colloidal dispersion (ABCD) is a stable complex of amphotericin B and cholesteryl sulfate in a 1:1 molar ratio. This lipid formulation exists as disk-like structures averaging 75–170 nm.[32] The pharmacokinetics of this formulation are similar to those of the deoxycholate and lipid complex formulations.

Whether the subtle pharmacokinetic differences described above impact on clinical efficacy is still debatable. In addition to their physicochemical and pharmacokinetic properties, the in vivo activity of these formulations likely also depends on the amphotericin B concentration at the site of infection. However, there are very few published data describing amphotericin B disposition in human tissue following the administration of a lipid amphotericin B formulation. Data from autopsy material of patients who had been treated with L-AmB or

ABCD for suspected or proven invasive fungal infection suggest that individual differences in lipid amphotericin B formulation may influence amphotericin B penetration into the lung.[36] Amphotericin B lung concentrations in patients treated with ABCD significantly exceeded those of the liposomal amphotericin B-treated patients.[36] Both formulations produced high concentrations in the liver and spleen, and low concentrations in the myocardium and kidney. However, amphotericin B kidney concentrations in patients treated with ABCD significantly exceeded those of the liposomal amphotericin B-treated patients.[36]

Amphotericin B tissue concentrations following administration of lipid amphotericin B formulations have been compared to those following administration of the deoxycholate formulation in animal models. In these models, compared to the deoxycholate formulation, all lipid amphotericin B formulations produce higher amphotericin B concentrations in the liver, spleen and, in the case of ABLC, in the lungs.[37]

The central nervous system (CNS) disposition and antifun-gal efficacy of all the lipid amphotericin B formulations have also been studied in an animal model. Data suggest that amphotericin B delivery to the CNS following administration of a lipid amphotericin B formulation is a function of a concentration gradient between the plasma and CNS. The lipid amphotericin B formulations that do not achieve high and sustained concentrations of a free compound in the plasma may not be successful in eradicating species such as *C. albicans* from brain tissue.[115] Of the three lipid amphotericin B formulations, L-AmB achieves high and sustained concentrations of the free compound in the plasma and consequently, it was the most successful in eradicating *C. albicans* from brain tissue.[38]

The lipid amphotericin B formulations distribute similarly into bone marrow, liver, and fat tissue of uninfected animals. All of the lipid amphotericin B formulations achieve markedly higher concentrations in the bone marrow and liver than the D-AmB formulation, with ABCD demonstrating the greatest degree of distribution into these sites.[116] Amphotericin B lipid complex and L-AmB achieved concentrations 2–4 times and 2–5 times those of the D-AmB formulation in the liver and bone -marrow, respectively.[39]In contrast to liver and bone marrow, all lipid amphotericin B formulations accumulate poorly within fat tissue.[39]

Toxicity: The toxicities of D-AmB are dose and infusion-related. Immediately after administration, amphotericin B dissociates from the micelles and largely binds to low-density lipoprotein in the plasma.[40-42] Then it binds preferentially to fungal cell membrane ergosterol

but also binds less avidly to mammalian cell membrane cholesterol. High concentrations of amphotericin B can damage erythrocytes and other mammalian cells and cause osmotic leakage of hemoglobin and intracellular ions.[43]

Although hyperkalemia may occur with rapid infusions, administration of D-AmB normally leads to renal tubular potassium wasting and distal renal tubular acidosis, which can be treated with potassium and bicarbonate.[2]Other dose-related toxicities include nephrotoxicity, azotemia, electrolyte imbalance, cardiac arrhythmias, and anemia.[2] Amphotericin B deoxycholate-induced nephrotoxicity is the primary "dose-related" toxicity, and its incidence varies from 15% to 80%, depending on the population of patients.[2] With repeated dosing, amphotericin B also causes glomerular vasospasm and ischemia, resulting in decreases of glomerular filtration rate. Risk factors for D-AmB induced nephrotoxicity to include average daily dose, concomitant nephrotoxin (particularly ciclosporin) use, and elevated baseline serum creatinine.[44,45]

In some patient populations, the glomerulotubular flow may be augmented by acute infusion of isotonic saline before amphotericin B and may somewhat preserve renal function.[46] However, the usefulness of saline hydration may be offset by fluid restriction employed to manage the fluid status of critically ill patients. As renal failure progresses, synthesis of erythropoietin diminishes, which leads to anemia.[47] Most cases of D-AmB induced nephrotoxicity are mild to moderate in nature and reversible in patients at low risk for this complication.[48] Severe nephrotoxicity is uncommon but it too is often reversible.[48] Although D-AmB is nephrotoxic, renal dysfunction does not significantly impact its kinetics. Therefore, anephric patients may be treated with dosages similar to those given to patients with normal renal function. Initial decreases in renal function caused by amphotericin B may be improved by occasional interruption of therapy, switching to the lipid amphotericin B formulations that cause less nephrotoxicity or to a class of compounds such as the echinocandins or azoles that do not cause nephrotoxicity.

Amphotericin B deoxycholate causes "infusion-related" reactions, including hypotension, fever, rigors, and chills, in approximately 70% of patients.[44]These "infusion-related" reactions occur early in therapy and often subside with time. Pretreatment regimens consisting of diphenhydramine, acetaminophen, meperidine, and hydrocortisone are used to prevent "infusion-related" reactions. The "infusion-related" reactions are bothersome and may cause early discontinuation of D-AmB therapy or may interfere with the use of other

agents.

In addition to nephrotoxicity and infusion toxicities, amphotericin B produces local thrombophlebitis, nausea, and vomiting.[32,49] These toxicities may also be minimized to varying degrees by pretreatment regimens. Morphine and meperidine have also been used to relieve these symptoms.[44] Renal failure and anemia are the main toxicities that are significantly reduced by the use of lipid amphotericin B formulations.[50-52]

Commercially available lipid amphotericin B formulations represent a significant advance in antifungal therapy and their safety and efficacy have been extensively reviewed. [13,14] In empiric antifungal therapy settings, no significant difference in efficacy has been detected between lipid amphotericin B formulations and D-AmB.[15] However, all the lipid amphotericin B formulations lower the risk of D-AmB induced nephrotoxicity. Although ABCD is less nephrotoxic than D-AmB, a large double-blind randomized study demonstrated that infusion-related adverse events were significantly more common with ABCD than with D-AmB and 16 patients reported hypoxic events that were likely attributable to their study drug.[53] These events occurred primarily in patients who received ABCD, and the vast majority of these episodes were associated with required oxygen supplementation. In several patients, the hypoxic events resulted in the early discontinuation of ABCD therapy.[53] Because of these data, ABCD is not widely used. In contrast, ABLC and particularly L-AmB have reduced rates of infusion toxicities and nephrotoxicity (defined as doubling serum creatinine) compared with D-AmB.[52] This reduced toxicity allows increased doses of antifungal therapy to be utilized. With their superior safety profiles, ABLC and L-AmB are considered suitable alternatives to D-AmB.[54]

Amphotericin B deoxycholate is administered IV as a micelle mixture in 5% glucose. Admixture or infusion with saline must be avoided because it causes precipitation of the micelles. Pharmacy reconstitution instructions are different for each preparation and should be carefully followed. Although the drug may be administered as a rapid infusion (45–60 minutes), there is no medical reason for this and conventionally all formulations of amphotericin B are infused over 2–4 hours. The infusions should be much slower in patients with renal insufficiency.[2]

FLUORINATED PYRIMIDINE ANALOG[55]

Flucytosine

Mechanism of action: Flucytosine is the lone member of the group of fluorinated pyrimidine analog antifungal compounds. To exert its effect, flucytosine is taken up in susceptible fungi by the transport enzyme cytosine permease. This uptake can be competitively antagonized by adenine, hypoxanthine, and cytosine, which all share this transport system. Once inside the fungal cell, flucytosine rapidly undergoes intracellular conversion to 5-fluorouracil via cytosine deaminase. Fungi lacking cytosine deaminase are intrinsically resistant to flucytosine. [19] After intracellular conversion to 5-fluorouracil, the antifungal effect is exerted via one of two mechanisms. These mechanisms are independent of each other but whether both are responsible for flucytosine activity is unknown. First, through a series of phosphorylation reactions, 5-fluorouracil is ultimately converted to its triphosphate form, 5-fluorouridine triphosphate. The triphosphate form is incorporated into fungal RNA in place of uridylic acid, which alters the aminoacylation of tRNA and ultimately inhibits protein synthesis. A secondary mechanism ultimately leads to inhibition of DNA synthesis and involves the metabolism of 5-fluorouracil into 5-fluorodeoxyuridine monophosphate by uridine monophosphate pyrophosphorylase. The 5-fluorodeoxyuridine monophosphate is a potent inhibitor of thymidylate synthetase, which is critical to DNA biosynthesis. The importance of this secondary mechanism of activity is unclear.

Spectrum of activity: The antifungal spectrum of flucytosine is extremely narrow and is limited to *Candida* species and *C. neoformans*, although there are some anecdotal recommendations for aspergillosis and chromoblastomycosis. Because resistance to flucytosine may occur at multiple steps in its mode of action, including transport into the cell and deamination to the active compound, flucytosine is only used in combination with other agents, including amphotericin B and fluconazole.

Pharmacokinetics: Flucytosine is a small, very water-soluble molecule and therefore after oral administration it is rapidly and nearly completely absorbed from the intestine. The apparent volume of distribution of flucytosine approximates total body water and the drug distributes well into most body tissues and fluids, including cerebrospinal, vitreous and peritoneal fluids, and inflamed joints. Flucytosine is primarily eliminated by the kidneys via glomerular filtration. The drug is not secreted into the urine and does not undergo tubular

resorption; therefore flucytosine plasma clearance is closely related to creatinine clearance (CrCl). The half-life of flucytosine is approximately 3–4 hours in patients with normal renal function and is significantly prolonged with reductions in renal function. Dosage adjustment is necessary for patients with reduced renal function provides suggested dosage regimens in patients with varying degrees of renal function.

Therapeutic drug monitoring for flucytosine is beneficial and ideally, serum concentrations should be maintained between 25 and 100 μg/ml to minimize toxicity. Although several nomograms exist for dosing flucytosine based on CrCl in patients with renal dysfunction, they are based on serum creatinine measurements and should only be used with chronic renal dysfunction. They should also be used cautiously in elderly patients. During therapy, any necessary dosage adjustments should be based upon plasma concentrations. Lower flucytosine doses (75–100 mg/kg/day) to minimize its toxicity have been advocated and in vitro data suggest that antifungal efficacy would not be compromised by such dosing. Hepatic metabolism and protein binding of flucytosine is negligible.

Toxicity: The primary toxicities of flucytosine are myelosuppression, gastrointestinal intolerance, and hepatic toxicity. The underlying mechanism of myelosuppression associated with flucytosine is unknown. However, the conversion of flucytosine to 5-fluorouracil is believed to be one possible mechanism. Patients treated with flucytosine have detectable 5-fluorouracil serum concentrations that are comparable to those associated with toxicity in 5-fluorouracil treated patients. The conversion of flucytosine to 5-fluorouracil is thought to occur at least in part via bacterial intraluminal pain) that occur in an estimated 6% of treated patients.[114] The incidence of flucytosine-associated hepatotoxicity or clinically significant transaminase/phosphatase abnormalities varies from 0% to 41% depending on the definitions employed. The underlying mechanism of flucytosine-associated hepatotoxicity or clinically significant transaminase/ phosphatase abnormalities is unknown. This adverse effect often occurs when concentrations exceed 100 mg/l but this toxicity may also occur below this threshold concentration.

Mechanism of action: The azoles exert a fungistatic effect by dose-dependent inhibition of CYP-dependent 14α-demethylase, which ultimately depletes ergosterol and compromises cell wall integrity. The first clinically useful azoles (clotrimazole, ketoconazole) have excellent activity against *Candida* species. Because of a lack of systemic effect, clotrimazole is used only for mucosal infections. Ketoconazole, the first systemic azole, has largely been

supplanted by the other agents in the class and is more commonly used in the developing nations, where its low cost is a major advantage; thus it will not be addressed in this chapter. The systemic azoles developed after ketoconazole- include fluconazole, itraconazole, voriconazole, and posaconazole.

Among species, the systemic triazoles vary in their 14α-demethylase inhibition, which may in part explain the differences in antifungal activity in this class. The triazoles also secondarily target other steps in the ergosterol biosynthesis pathway. Depending upon the genus, the affinity for these secondary targets varies among the agents. For example, in fluconazole-susceptible *C. albicans* fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, whereas voriconazole completely inhibits both ergosterol and obtusifoliol synthesis. Similarly, in *C. krusei*, both voriconazole and fluconazole completely inhibit obtusi-foliol synthesis, but voriconazole inhibits ergosterol synthesis to a greater extent than does fluconazole. Itraconazole and -fluconazole may also inhibit 3-ketoreductase, which catalyzes the reduction of the 3-ketosteroid obtusifolione to obtusifoliol in *C. neoformans*. The resultant accumulation of the 3-ketosteroid obtusifolione and other methylated sterol pre-cursors increases the fragility of the cell membrane. However, in *Histoplasma capsulatum* var. *capsulatum*, it is hypothesized that of these two agents, only itraconazole significantly inhibits 3-ketoreductase. This may explain why itraconazole is more active than fluconazole against this pathogen. All azoles act much more slowly than polyenes. Thus they are used less often than polyenes in the treatment of fulminating fungal infections.

Spectrum of Activity As a class the azoles have a broad spectrum of activity against a variety of yeasts and moulds. However, as this therapeutic class expands, differences in the spectrum of activity among the individual agents emerge. As discussed above, the differential spectrum of activity exhibited across the class likely reflects variation in the inhibition of 14α-demethylase and secondary targets among species.

Table No. 2: Clinically antifungal activity of the azoles

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Yeasts				
Candida species				
C. albicans	++	++	++	++
Flu/itra resistant	-	-	+	+
C. glabrata	+/-	+/-	+?	+?
C. parapsilosis	++	++	++	++
C. tropicalis	++	+	++	++
C. lusitaniae	++	++	++	++
C. krusei	-	+/-	++	++
C. guilliermondii	+/-	+	++	++
Crytococcus neoformans	++	+	++	++
Trichosporon asahii	++	+	++	++
Dimorphic fungi				
Coccidiodes immitis	+	++	++	++
Histoplasma capsulatum	+/-	++	++	NA
Blastomyces dermatitidis	+/-	++	++	NA
Sporothrix schenckii	+	++	++	NA
Paracoccidioides brasiliensis	+	++	NA	++
Penicillium marneffei	+	++	++	NA
Moulds				
Aspergillus spp.	-	++	++	++
Fusarium spp.	-*	-*	+/-*	NA*
Zygomycetes	-	+/-**	-	+/-**
Scedosporium apiospermum	+/-	++	++	NA
Scedosporium prolificans	-	-	-	-
Phaeohyphomycetes	+	+/++	+/++	+/++

+ moderate activity; ++ excellent activity; +/- variable activity; - no clinical activity; flu/itra, fluconazole, itraconazole; NA, insufficient data on clinical activity, probably effective.
**Fusarium solani* is resistant to all azoles; variable susceptibility of other species.
**Variable susceptibility: species and organism dependent; *Rhizopus* spp. more susceptible than other species.

Fluconazole: The in vitro activity of fluconazole is generally considered fungistatic and its relatively narrow spectrum of activity is essentially limited to yeasts. Specifically, 8.5-year

global surveillance of susceptibilities of *Candida* species and other yeasts demonstrated that fluconazole is very active against *Candida* species including *C. albicans, C. parapsilosis, C. tropicalis,* and *C. lusitaniae*. However, fluconazole is much less active against other *Candida* spp. *C. krusei* is inherently resistant, and species such as *C. glabrata* and C. *guilliermondii* have reduced susceptibilities to fluconazole. Fluconazole also has activity against *C. neoformans* and *Coccidioides immitis*. In general, fluconazole seems to be moderate to severely less active milligram for milligram than other azoles against *H. capsulatum, Paracoccidioidesbrasiliensis, Sporothrix schenckii, Blastomyces dermatitidis,* and *Penicillium marneffei*. Fluconazole has no activity against *Aspergillus* spp., *Fusarium* spp. and the agents of zygomycosis-.

Itraconazole: Itraconazole exerts fungicidal activity against filamentous fungi and some strains of *C. neoformans* and is generally fungistatic against many yeasts. Except for *C. glabrata,* itraconazole is moderate to very active against most medically important fluconazole-susceptible and -resistant *Candida* species. However, given the withdrawal of the IV formulation from the marketplace and the variable serum concentrations produced by the oral itraconazole formulations, this agent is not considered a viable option for the treatment of systemic candidiasis.

Itraconazole has modest activity against *C. neoformans*; however, the poor central nervous system penetration of this drug limits its usefulness for treating cryptococcosis. Itraconazole has also excellent in vitro activity against common di-morphic or endemic fungi including *C. immitis, H. capsulatum, B. dermatitidis,* and *S. schenckii*. It has good activity against many *Aspergillus* spp. but it has variable activity against *Fusarium* spp. and very limited activity against the agents of zygomycosis. Also, itraconazole is unique in that hydroxyitraconazole, its primary metabolite in humans is bio-active. Data suggest that hydroxyitraconazole activity against *C. pseudotropicalis* was nearly twice that of itraconazole but its activity against *A. fumigatus, A. terreus, C. neoformans,* and *C. immitis* was the same as that of itraconazole. How much hydroxyitraconazole contributes to the activity of itraconazole in vivo is unknown.

Voriconazole: Voriconazole exerts fungicidal activity against most yeasts and certain opportunistic fungi, and fungicidal activity against some non-*albicans Candida* spp. and *C. neoformans*.Voriconazole possesses a very broad spectrum of activity against dermatophytes, yeasts, and moulds. This agent is active against all *Candida* spp., including fluconazole-

resistant *C. albicans, C. glabrata,* and *C. krusei*. Except for *C. tropicalis,* voriconazole is more active than fluconazole against medically important *Candida* spp. It is very active against other yeasts, including *C. neoformans* and most *Trichosporon* spp., including *T. asahii,* but it is not very active against *T. beigelii*/*T. cutaneum*.

Voriconazole exhibits excellent in vitro activity against *Aspergillus* spp. and is highly active against *A. fumigatus, A. flavus,* and *A. terreus*. However, over time *A. fumigatus* isolates have become slightly less susceptible to several antifungal agents, including voriconazole.[132] Voriconazole has a very potent activity against the dimorphic fungi including *C. immitis, H. capsulatum, B. dermatitidis,* and *S. schenckii*. It is active against many amphotericin-resistant moulds, including certain strains of *Scedosporium apiospermum* (asexual state of *Pseudallescheria boydii*) and *P. boydii,* but it has variable activity against *Fusarium* spp. Similar to fluconazole, voriconazole has poor or no activity against the agents of zygomycosis-.

Posaconazole: Posaconazole exerts fungicidal activity against non-*albicans Candida* species including *C. krusei, C. inconspicuous* and *C. lusitaniae,* but is fungistatic against. *albicans, C.glabrata, C. tropicalis, C. guilliermondii,* and *C. parapsilosis*.Like voriconazole, posaconazole demonstrates *in-vitro* fungicidal activity against *Aspergillus* spp and *C. neoformans*. It is more active than itraconazole and fluconazole against all *Candida* spp. and *C. neoformans*.

In vitro, posaconazole is the most active azole against *Aspergillus* spp. and is highly active against *A. fumigatus, A. flavus,* and *A. terreus*. Posaconazole has very potent -activity against the dimorphic fungi including *C. immitis, H. capsulatum, B. dermatitidis,* and *S. schenckii*. It also demonstrates variable activity against many amphotericin-resistant molds, including certain strains of *Scedosporiumapiospermum* (asexual state of *Pseudallescheria boydii*) and *P. boydii,* but is not active against *Fusarium* spp. Posaconazole has variable activity against the agents of zygomycosis.

Pharmacokinetics The systemic azoles differ in chemical properties, which form the basis of the pharmacokinetic differences between the agents and the propensity of this class to interact with other medications. These properties can limit the use of these agents, particularly itraconazole. The pharmacokinetic properties of the commonly used systemic azoles are provided in Table 3.

Table No. 3: Summary of oral azole dosing and pharmacokinetics

		Itraconazole			
	Fluconazole	**Cap**	**Soln**	**Voriconazole**	**Posaconazole**
Absorption					
Rate	Rapid (1–3 h)	Slow	Rapid	Rapid	Slow
Bioavailability (%)	>93	≈30	≈55	≈96	–
Food effect	No	Yes	Yes	Yes	Yes
Increase (↑)/ Decrease (↓)	None	↑	↓	↓	↑
Distribution					
Protein binding (%)	Minimal (<10)	Significant (99.8)		Moderate (60)	Significant (>95)
VD (L/kg)	0.7–0.8	10.7		4.6	Very large
CNS/CSF penetration	60–80%	<1%		>50%	–
Metabolism					
CYP substrate	Yes (moderate)	Yes (major)		Yes (major)	Yes (mild)
Isoform (s)	2C9/19; 3A4	3A4		2C19; 3A4; 2C9	3A4
CYP inhibitor	Yes	Yes		Yes	Yes
Isoform (s)	2C9/19; 3A4	3A4		2C9; 2C19; 3A4	3A4
Phase II substrate	No	No		–	Yes
Isoform	–	–		–	UGT1A4
Phase II inhibitor	Yes	No		–	–
Isoform	UGT2B7	–		–	–
Other pathway(s)	–	–		–	–
Transporters					
P-gp substrate	No	Yes		No	Yes
P-gp inhibitor	No	Yes		No	Yes
Other transporters	–	–		–	–
Transport protein	–	BCRP (I)		–	–
Elimination					
Urine	Yes (89%)	No (<1%)		No (<5%)	No (<14%)
Bile/Feces	No	Yes		Yes	Yes (77%)

– unknown/not applicable; Cap, capsule; Soln, solution; VD, volume of distribution; UGT, UDP-glucuronosyltransferase; COMT, catechol-O-methyltransferase; OATP, organic anion transporting polypeptide; BCRP (I), breast cancer resistance protein inhibitor.

Fluconazole: The oral formulations of fluconazole are rapidly and nearly completely absorbed. With a bioavailability of over 93%, serum concentrations after oral dosing approximate those achieved with IV dosing. The IV formulation should be used only when oral intake is not possible or when oral absorption cannot be assured. In general, administering fluconazole through an enteral feeding tube does not appreciably impact its systemic availability. However, serum concentrations achieved with standard doses administered via an enteral feeding tube may be inadequate to treat *C. glabrata* infections. Fluconazole absorption is not dependent on gastric acidity or the presence of food. Fluconazole binds minimally to plasma proteins (11%) and circulates primarily as a free drug. Therefore the drug readily distributes into the CSF and urine, as well as hepatic, renal and CNS tissues.

Measurement of fluconazole serum or cerebrospinal fluid concentrations is rarely needed unless there is concern regarding patient compliance, inadequate response to therapy or possible drug-drug interaction.

The chemical properties of fluconazole allow it to circumvent much of the intestinal and hepatic metabolism required by itraconazole or voriconazole for elimination. Increases in fluconazole dosage produce proportional (i.e., linear) changes in serum concentration and systemic exposure. Fluconazole is metabolized by an as yet unidentified CYP and a glucuronidase in the liver to two inactive metabolites. Approximately 91% of an orally administered fluconazole dose is excreted in the urine, mostly (80%) as parent drug, and the two inactive metabolites account for the remaining 11%. Fluconazole undergoes minimal CYP-mediated metabolism but it does weakly inhibit CYP3A4. However, it also more strongly inhibits several other CYP enzymes. Fluconazole binds non-competitively to CYP, and because it circulates largely as a free drug, its ability to inhibit CYP in vitro may not reflect it's *in-vivo* inhibitory potential.

Dosage adjustment is necessary for patients with reduced renal function. A 50% dose reduction is recommended for a CrCl between 11 and 50 ml/mn. Patients undergoing hemodialysis should receive one dose after each dialysis session.

Itraconazole: Itraconazole is available as 100 mg capsules and solubilized in a 40% HP-βCD 10 mg/ml solution for oral use. The IV formulation containing HP-βCD has been withdrawn from the marketplace. Itraconazole absorption from the capsule form is slow and incomplete, and the drug undergoes significant “first-pass” metabolism in the intestines and liver before reaching the systemic circulation. In capsule form, absorption is variable and itraconazole is better absorbed under acidic gastric conditions or in the fed state. In contrast, HP-βCD significantly enhances the solubility of itraconazole. The oral solution requires no dissolution so its absorption is not influenced by gastric pH and is rapid. Thus, high concentrations of itraconazole are delivered to the intestinal epithelium, which may cause transient saturation of intestinal CYP3A4. The oral solution undergoes less “first-pass” metabolism and therefore produces higher and more consistent serum concentrations. In this form, itraconazole is better absorbed in the fasting than the fed state. Higher peak plasma concentrations of itraconazole and its primary metabolite, hydroxyitraconazole, are achieved more rapidly following administration in the fasted state compared to non-fasting conditions. Compared to the capsule, the oral solution produces a pharmacokinetic profile with less inter- and intrapatient

variability. Although the oral solution is optimally absorbed under fasting conditions, even in the fed state it produces higher serum concentrations than the capsule. The absolute bioavailability of the oral solution is higher than that of the capsule, but the two formulations are considered bioequivalent.

Itraconazole is highly lipophilic. In the serum, it is highly bound (99.8%) to albumin and consequently, the unbound concentrations in body fluids (i.e., CSF, saliva, urine) are very low. Itraconazole distributes widely throughout the body and has a high affinity for tissues (i.e., vaginal mucosa, horny layer of nails, etc.). It can persist in these tissues long after the serum concentrations are undetectable. Increases in itraconazole dosage produce disproportional (i.e., non-linear) changes in drug levels. Itraconazole is extensively metabolized and several metabolites are sequentially formed only by CYP3A4, including hydroxyitraconazole, ketoitraconazole, and *N*-dialkyl-itraconazole. The principal metabolite, hydroxy itraconazole, is formed primarily during gut wall metabolism and is bioactive.

Voriconazole: Voriconazole is available as an IV and oral formulation. The IV formulation consists of powder for reconstitution containing 200 mg voriconazole solubilized with sulfonyl ether β-cyclodextrin (SE-βCD). When reconstituted, the final solution contains 10 mg/ml. The oral tablets contain either 50 or 200 mg of voriconazole. Voriconazole dissolution is not affected by altered gastric pH. Following oral dosing, voriconazole absorption is rapid and nearly complete, with a relative bioavailability approaching 90%. Peak serum concentrations are achieved within 2 hours of oral dosing. Voriconazole is moderately bound to plasma proteins and is widely distributed throughout the body. In the case of reports, CSF concentrations achieved with standard dosing have been approximately 30–60% of plasma concentrations. Voriconazole concentrations in brain tissue are higher than those in the CSF.

In adults, increases in voriconazole dosage produce disproportional (i.e., non-linear) changes in drug levels. In contrast, increases in voriconazole dosage in children given low-dose voriconazole produce proportional (i.e. linear) changes in drug levels. Moreover, higher doses are required in children. Voriconazole is metabolized by several CYP enzymes including CYP2C19, 2C9, and 3A4. The primary voriconazole metabolite in man is formed by CYP2C19, CYP3A4, and, to some extent, CYP2C9. Both CYP2C19 and CYP2C9 exhibit genetic polymorphisms that add to the complexity of voriconazole pharmacokinetics. Therefore age-related differences- are probably due to the saturation of CYP enzymes in

adults, polymorphisms or age-related differences in CYP expression. However, at higher dosages data suggest that voriconazole exhibits non-linear pharmacokinetics in children.

Because clearance of SE-βCD excipient is reduced four-fold in moderate to severe renal impairment (CrCl 30–50 ml/ min), it is recommended that the IV route be avoided if CrCl <50 ml/min unless the benefits outweigh the risk. No dose reduction is needed when using the oral formulation. It is also recommended that the maintenance dose of voriconazole be reduced by 50% in the presence of moderate hepatic cirrhosis; however, a standard loading dose should still be used in this setting.

Posaconazole: Posaconazole, a highly lipophilic weak base, is chemically similar to itraconazole. Posaconazole is available only as an oral suspension. It is systemically available and eliminated slowly, with consistent pharmacokinetic values at specific dose levels following single and multiple doses given to healthy volunteers as tablets or the marketed oral suspension. Healthy volunteer studies indicate that posaconazole systemic availability is optimized with the oral suspension and that increases in dosage up to 800 mg/day produce proportional (i.e., linear) changes in drug levels. Posaconazole oral suspension administered in the fed state, particularly after a high-fat meal, provides optimal oral drug exposure. Based on drug exposure and maximum serum concentration values, relative oral bioavailability estimates are fourfold and 2.6-fold greater following administration of the posaconazole oral sus-pension with a high-fat and non-fat meal, respectively.

The oral administration of 600–800 mg/day in divided doses (200 mg 3 times/day or 400 mg twice/day) maximizes posaconazole exposure.

In neutropenic hematopoietic stem cell transplant recipients, increasing dosing frequency and doses up to 800 mg/day produced dose-related but less than dose increases in maximum serum concentrations and exposure. The reasons for this finding are unclear, but likely related to the poor nutritional intake, vomiting, and diarrhea common to this population. While mucositis reduced exposure, the effect was not significant and was lessened with increasing total dose up to 800 mg/ day and administering it in divided doses. From a pharmacokinetic standpoint, there is no benefit to administering total daily doses over 800 mg singly or in divided doses.[158] Posaco-nazole is metabolized less than itraconazole or voriconazole. In contrast to itraconazole and voriconazole, posaconazole is only minimally metabolized by CYP. Most posaconazole metabolites are glucuronide conjugates formed by uridine

diphosphate glucuronosyltransferase (UGT) pathways.

Toxicity: The azoles are a relatively safe class of drugs and are associated with few serious adverse effects. The advent of fluconazole and subsequent agents greatly improved the safety of this class. All the azoles are associated with gastrointestinal intolerance, transient transaminitis, hepatic toxicity, rashes, dizziness, and psychosis. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) are the most common side effects associated with this class, particularly with the oral itraconazole solution. These effects are usually encountered with high doses of these compounds, but the symptoms are rarely severe enough to necessitate discontinuation of therapy.

Clinically significant transaminitis occurs commonly with all azoles. In general, patients experiencing azole-associated transaminase abnormalities are asymptomatic, but these increases can, on rare occasions, evolve into fatal drug-induced hepatitis. Consequently, clinicians should obtain baseline liver function tests before starting azole therapy. Moreover, patients receiving azoles should periodically be monitored for evidence of drug-induced hepatitis.

The azoles can also produce allergic skin rashes that are generally mild and subside with discontinuation of the drug. The azoles produce teratogenic effects in mice and therefore their use should be avoided in pregnancy (Category C).

Fluconazole: Fluconazole is the safest azole and doses4–5 times over the recommended daily dose have been well tolerated. Gastrointestinal symptoms associated with fluconazole use rarely occur and when they do, they are frequently considered mild. Fluconazole may also produce transient transaminase abnormalities, but progression to severe drug-induced hepatitis is exceedingly rare. Fluconazole does not inhibit human steroidogenesis. Nonetheless, it has produced alopecia in up to 20% of patients receiving at least 400 mg/day for more than 2 months. This alopecia is reversible and resolves within 6 months of stopping therapy or reducing the dose by 50%.

Itraconazole: When administered in dosages of 400 mg/day or less, itraconazole generally produces little toxicity. However, the incidence of adverse effects increases with prolonged courses of at least 400 mg/day but rarely does the toxicity require drug discontinuation. Like all azoles, transient transaminase abnormalities and gastrointestinal adverse effects, particularly nausea, abdominal pain, and diarrhea, are common with itraconazole

administration. These symptoms are generally described as mild by patients receiving the capsule form. However, with the oral solution, they occur more frequently and are more severe. In clinical trials in patients with AIDS who received the oral solution, gastrointestinal adverse events were so severe that 810% of patients discontinued the drug. Diarrhea associated with the oral solution is generally attributed to an osmotic effect of the HP-βCD in the GI tract. Itraconazole on rare occasions can produce yet to be explained life-threatening reactions (liver failure, CHF). Even though these adverse effects are very rare, their risk of occurrence should be considered when using itraconazole to treat non-life threatening infections of the skin and nail beds. When used in the recommended dosages, itraconazole has little or no inhibitory effect on human steroidogenesis. However, patients may experience a mineralocorticoid excess syndrome manifested by hypokalemia, hypertension, and edema with doses over 400 mg/day, especially with protracted courses.

Voriconazole: Voriconazole is generally well tolerated. In addition to the gastrointestinal and dermatologic adverse effects seen with other azoles, voriconazole produces visual disturbances and clinically significant transaminase abnormalities in approximately 30% and 12.7% of patients, respectively. These adverse effects are typically benign and rarely lead to discontinuation of therapy. The visual disturbances are acute and include changes in color discrimination, blurred vision, photophobia, and the appearance of bright spots. These disturbances generally require little or no therapy and diminish shortly into a course of therapy without producing lasting retinal damage. The underlying mechanism for this adverse effect is unknown.

Like the other azoles, the transaminase abnormalities associated with voriconazole are common and mild but on rare occasions, life-threatening hepatitis has been described. Whether voriconazole is more hepatotoxic than other azoles or whether this adverse effect is correlated with voriconazole dose or serum concentrations is debatable. Data suggest that transaminase ab-normalities increase with voriconazole dose. Furthermore, transaminase abnormalities or liver failure developed in six of 22 (27%) patients with invasive aspergillosis who had voriconazole serum concentrations greater than 6 μg/ml. However, in phase 2 and 3 clinical trials, voriconazole frequently produced transaminitis, yet the majority of cases were mild to moderate in severity and rarely (≈3%) resulted in drug discontinuation. A retrospective longitudinal logistic regression analysis provides compelling data suggesting that factors other than elevated serum drug concentrations contribute to transaminase

abnormalities in patients receiving voriconazole. In voriconazole, clinical studies allergic skin rashes occurred in approximately 20% of patients. These reactions were generally considered mild in severity and did not interrupt therapy.

Posaconazole: Compared to other azoles, there is much less clinical experience with this agent. Consequently, its safety ˉprofile may not be fully realized. Nonetheless, to date, the common adverse effects associated with posaconazole use have been similar to those observed with other agents in the class (i.e., gastrointestinal, transient transaminase abnormalities).

Echinocandins: Caspofungin, micafungin, anidulafungin

Table No. 4: Summary of oral azole dosing and pharmacokinetics

		Itraconazole			
	Fluconazole	**Cap**	**Soln**	**Voriconazole**	**Posaconazole**
Absorption					
Rate	Rapid (1–3 h)	Slow	Rapid	Rapid	Slow
Bioavailability (%)	>93	≈30	≈55	≈96	–
Food effect	No	Yes	Yes	Yes	Yes
Increase (↑)/ Decrease (↓)	None	↑	↓	↓	↑
Distribution					
Protein binding (%)	Minimal (<10)	Significant (99.8)		Moderate (60)	Significant (>95)
VD (L/kg)	0.7–0.8	10.7		4.6	Very large
CNS/CSF penetration	60–80%	<1%		>50%	–
Metabolism					
CYP substrate	Yes (moderate)	Yes (major)		Yes (major)	Yes (mild)
Isoform (s)	2C9/19; 3A4	3A4		2C19; 3A4; 2C9	3A4
CYP inhibitor	Yes	Yes		Yes	Yes
Isoform (s)	2C9/19; 3A4	3A4		2C9; 2C19; 3A4	3A4
Phase II substrate	No	No		–	Yes
Isoform	–	–		–	UGT1A4
Phase II inhibitor	Yes	No		–	–
Isoform	UGT2B7	–		–	–
Other pathway(s)	–	–		–	–
Transporters					
P-gp substrate	No	Yes		No	Yes
P-gp inhibitor	No	Yes		No	Yes
Other transporters	–	–		–	–
Transport protein	–	BCRP (I)		–	–
Elimination					
Urine	Yes (89%)	No (<1%)		No (<5%)	No (<14%)
Bile/Feces	No	Yes		Yes	Yes (77%)

– unknown/not applicable; Cap, capsule; Soln, solution; VD, volume of distribution; UGT, UDP-glucuronosyltransferase; COMT, catechol-O-methyltransferase; OATP, organic anion transporting polypeptide; BCRP (I), breast cancer resistance protein inhibitor.

Mechanism of action: The echinocandins are synthetic lipopeptides that are derived from fermentation products from several different fungi. These compounds disrupt cell wall synthesis by inhibiting a novel target, β1,3-d-glucan synthase, which blocks β1,3-d-glucan synthesis. This enzyme is present in most fungal pathogens but is not present in mammalian cells and its inhibition ultimately produces osmotic lysis of the cell. β1,3-d-glucans are critical components of most fungal cell walls and provide morphology and structural integrity.

Spectrum of activity: These agents bind rapidly and irreversibly to β1,3-d-glucan synthase and cause rapid death in certain pathogens. The echinocandins possess a narrow antifungal spectrum that is restricted to *Candida* spp. and *Aspergillus* spp. and there is little difference among the individual drugs. All the echinocandins exert fungicidal activity against *Candida* spp.; however, in *Aspergillus* spp. these compounds do not usually cause complete inhibition of growth but instead induce abnormal morphologic hyphal growth. Therefore these agents are considered to be fungistatic against *Aspergillus* spp.

***In-vitro*:** The echinocandins are highly active against *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. dubliniensis*, and *C. krusei*.They are slightly less active against *C. parapsilosis*, *C. guilliermondii*, and *C. lusitaniae* and MIC values aretypically- higher for these pathogens than other *Candida* spp. In general, the echinocandins are very active against *A. flavus*, *A. fumigatus*, and *A. terreus*. Inhibition of growth is observed at very low concentrations, but the in vitro activity can be influenced by inoculum size and media composition. Therefore there may be subtle differences in the in vitro activity of the individual echinocandins against *Aspergillus* spp. that currently can be difficult to discern. The echinocandins are also active against *Pneumocystisjirovecii*. *In-vitro*, this class also has modest activity against dimorphic fungi including *C. immitis*, *H. capsulatum*, and *B. dermatitidis*, but this activity is not considered to be clinically useful. The echinocandins have little or no activity against *C. neoformans*, *Trichosporon* spp., *Fusarium* spp. or any agents of zygomycosis.

Pharmacokinetics: Due to their molecular size all the echinocandins are available only as IV formulations. The echinocandins differ little in their chemical properties; thus, following IV administration they demonstrate similar pharmacokinetic behavior. The pharmacokinetic properties of the echinocandins are summarized in Table 10. The primary difference between the agents lies in how they are metabolized and how they distribute throughout the body, which influences their elimination half-lives. Increases in the dosage of all the echinocandins pro-duce proportional (i.e., linear) changes in serum concentration and systemic exposure. The echinocandins are not appreciably metabolized by CYP.

Table No. 5: Summary of echinocandin pharmacokinetics

	Caspofungin	Micafungin	Anidulafungin
Distribution			
Protein binding (%)	Significant (97)	Significant (99)	Significant (84)
VD (l/kg)	0.15	0.4	0.6
CNS/CSF penetration	Minimal	Minimal	–
Metabolism			
CYP substrate	No	No	No
Isoform(s)	–	–	–
CYP inhibitor	No	No	No
Isoform(s)	–	–	–
Phase II substrate	No	No	No
Isoform	–	–	–
Phase II inhibitor	No	No	No
Isoform	–	–	–
Other pathway(s)	*N*-acetylation Peptide hydrolysis	Arylsulfatase COMT hydroxylation	Chemical degradation
Transporters			
P-gp substrate	No*	No	No
P-gp inhibitor	No*	No	No
Other transporters	Yes	–	–
Transport protein	OATP1B1	–	–
Elimination			
Urine	Yes (41%)	No (<1%)	No (<1%)
Bile/Feces	Yes (35%)	Yes (71%)	No (<10%)

*,only at concentrations in excess of those achieved clinically; – unknown/not applicable; VD, volume of distribution; COMT, catechol-O-methyltransferase; OATP, organic anion transporting polypeptide.

Caspofungin: The distribution of caspofungin is complex and involves several distinct phases. Following IV administration, caspofungin is extensively bound to albumin and thus initially it largely distributes only to the plasma and extracellular fluid. Subsequently, it slowly distributes into the tissue, primarily the liver, via an active transport process involving the organic anion transport proteins (OATP), specifically OATP1B1. This is a very slow process that influences the subsequent elimination half-life of the drug. Caspofungin is slowly metabolized in the liver via *N*-acetylation and peptide hydrolysis to inactive metabolites, which are excreted in the bile and feces.

In the presence of moderate hepatic impairment, the maintenance dose of caspofungin should be reduced to 35 mg per day. However, a standard loading dose of 70 mg should still be used in this setting.

Micafungin: The distribution and metabolism of micafungin are not completely understood. Following IV administration, micafungin is extensively bound to plasma proteins, primarily albumin, and, to a lesser extent, to α1-acid glycoprotein and its apparent volume of distribution is larger than that of caspofungin. Micafungin is metabolized to several metabolites that are formed by hepatic reactions catalyzed by arylsulfatase, catechol-O-methyltransferase, and to a minor extent ω1-hydroxylation via CYP. Very little (<1%) of a micafungin dose is eliminated as unchanged drug in the urine. Approximately 70% of an administered dose is eliminated as parent drug and metabolite(s) in feces.

Anidulafungin: The distribution and metabolism of anidulafungin are not fully understood. Following IV administration, anidulafungin is less bound to plasma proteins, has a larger volume of distribution and achieves lower peak serum concentrations than caspofungin or micafungin. Anidulafungin primarily undergoes slow non-enzymatic degradation in the plasma to a peptide breakdown product, which is enzymatically degraded and excreted in the feces and bile. Very little anidulafungin is excreted in the feces or urine as unchanged drug.

Toxicity: The echinocandins are well tolerated and their use is associated with very few significant adverse effects. Common adverse effects include irritation at the injection site, phlebitis, and transient transaminase abnormalities. Other less common non-specific adverse effects include nausea, vomiting, diarrhea, fever, and headache.

Allylamines

Terbinafine

Mechanism of action: Terbinafine reversibly inhibits squalene epoxidase, an enzyme that acts early in the ergosterol synthesis pathway. This inhibition produces both the fungistatic and fungicidal effects on fungal cells.

Spectrum of activity: In vitro, terbinafine demonstrates excellent fungicidal activity against many dermatophytes including *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis* and *Epidermophyton floccosum*. How-ever, terbinafine demonstrates

variable and somewhat poor in vitro activity against many yeasts. It generally demonstrates fungicidal activity against *C. parapsilosis* but it is fungistatic against *C. albicans* and other *Candida* spp. The in vitro spectrum of activity also includes *Aspergillus* spp., some dimorphic fungi, *S. schenckii*, and others. Initial animal studies in mice showed no activity in vivo against systemic pathogens, and the drug was abandoned for these indications.

Pharmacokinetics: Terbinafine is well absorbed after oral administration, but it undergoes significant "first-pass" metabolism and its resulting apparent bioavailability is only 45%. It is metabolized to ten metabolites by at least seven different CYP enzymes, the most important being CYP2C9, CYP1A2, and CYP3A4. Terbinafine binds extensively to plasma proteins. Of note, it distributes extensively to poorly perfused tissues (i.e., skin and ungual bed). Terbinafine is extensively metabolized by the liver and 15 metabolites have been identified.

Toxicity: Terbinafine produces few adverse reactions, including perversion of taste perception and occasionally abnormal liver function.

OTHER NOVEL TARGETS UNDER DEVELOPMENT

Other potential targets, including protein synthesis pathways, have been identified in fungi, although few antifungal compounds have been synthesized to take advantage of them. One target that has been studied for many years is elongation factor 2(EF2). The ordains are the most studied class of compounds directed at this target. These derivatives are specific inhibitors of fungal translation factor EF2, which catalyzes the translocation of tRNA and mRNA after peptide bond formation.[133,134]. The *N*-myristylation of fungal proteins is also a potential target to exploit. *N*-myristoyl proteins, also known as ADP- ribosylation factors, are essential to fungal growth and potent inhibitors are fungicidal.[133,135,136]. Protein *N*-myristoyl transferase is critical for the *in-vitro* viability of *Candida albicans* and *C. neoformans*.[133]. The naturally occurring cationic peptides and their synthetic derivatives are potentially promising agents. These peptides include the defensins, the protegrins, gallinacin, cecropin A, thaumatin and the dermaseptins. There are other novel targets including intracellular organelles, specific enzymes involved in the sphingolipid biosynthesis pathway, to name a few. However, whether investigations into these targets will yield clinically useful antifungal agents remains to be seen.

CONCLUSION

The discovery of new molecular targets in both yeasts and filamentous fungi that will render these organisms susceptible to novel antifungal drugs is likely to continue because of the major challenge by systemic fungal infections in clinical medicine today. Also, we need to learn more about combination antifungal therapy, e.g. about the effects of the sequential blockade at two or more sites, and about the combination of antifungal agents with cytokines in an attempt to augment the inflammatory and immune responses of patients. This overview of new antifungal drug development reflects the increased interest in this field of infectious diseases and demonstrates that, although some progress has been made, further efforts are necessary to develop more promising agents against invasive fungal disease.

The recent trend or expansion of antifungal drug research has demonstrated that there is a critical need for new antifungal agents to treat these life-threatening invasive infections. Invasive fungal infections are critical in treating immunocompromised patients. The overview of the development of antifungal therapy discussed in this thesis reflects the increased interest in this area of infectious diseases. Although newer, less toxic, antifungal agents are available for clinical use, their clinical efficacy in some invasive fungal infections, such as aspergillosis and fusariosis, is not optimal. Thus, intense efforts in antifungal drug discovery are still needed to develop more promising and effective antifungal agents for use in the clinical arena.

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