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An update on safety and efficacy of echinocandins in antifungal therapy

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ABSTRACT

The echinocandins are important and exciting agents because of their novel mechanism of action, low incidence of serious adverse effects, and low potential for drug–drug interactions. In vitro and in vivo, the echinocandins are rapidly fungicidal against most *Candida* species and fungistatic against *Aspergillus* species.It is also a treatment option for serious fungal infections. Pharmacokinetic–pharmacodynamic studies in animals have demonstrated superior efficacy, defined as maximal microbial kill, when compared to fluconazole. Anidulafungin exhibits a unique pharmacokinetic profile, and limited cases have shown a potential for activity in isolates with increased minimum inhibitory concentrations to caspofungin and micafungin. Caspofungin appears to have a slightly higher incidence of side effects and potential for drug–drug interactions. Micafungin appears to be very similar to caspofungin, with very few obvious differences between the two agents and also have similar safety and efficacy profile in patients with fungal infections. Adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal liver function tests, and mild haemolysis. Anidulafungin is economical and have dominant efficacy compared with micafungin and caspofungin in patients with candidemia and/or invasive candidiasis. All three echinocandins are generally well-tolerated. Echinocandins provide safe, uncomplicated and highly active therapy for invasive *Candida* infections with potentially superior efficacy versus fluconazole and better tolerability compared to formulations like amphotericin B, making them the agents of choice for moderate to severely ill patients with invasive candidiasis.

Keywords: Echinocandin, Anti-fungal therapy, Safety and efficacy, Drug interaction, Candidiasis.

INTRODUCTION

Candidemia and other forms of candidiasis, remain potentially fatal infections leading to morbidity, especially in patients who are critically ill and also immune compromised patients [(1)].Candida species causes a range of infections from non-life-threatening to life-threatening which can also be invasive in nature. These infections yet remain a major concern despite of advances in antifungal cascade [1, 2]

Within the fungal infections, *Candida albicans* is the commonly isolated specie, responsible for Candidemia and invasive Candidiasis. In the recent years, an increasing trend has been seen in isolation of non-albicans species too like *Candida glabrata, Candida parapsilosis, Candida tropocalis and Candida krusei.* These species also are as important as albicans species because *Candida glabrata* and *Candida krusei* isolates show resistance against Fluconazole [2].

In the treatment of candidemia, the commonly given antifungal agents are Fluconazole and the newer class of Echinocandins. Now-a-days, the Echinocandins have become an important part of the fungal infection treatment due to increasing incidences of fluconazole-resistant *non-Candida albicans* species [2]. Also, as echinocandins, don't exhibit cross-resistance to azoles derivatives, their usage is highly increasing. Their potentially low toxicity and minimal drug-drug interactions profile make them an excellent alternative choice [3, 4]

Echinocandins were discovered in the 1970s and were named as the pneumocandins but, they could not be used clinically due to their high risk of haemolysis. Later, the semisynthetic analogues of approved echinocandins were found to have similar antifungal activity with lower toxicity. The first approved drug from echinocandins was Caspofungin; later Micafungin and then Anidulafungin too were approved [4, 5]

Caspofungin got its final approval in 2001 by the USA and European regulatory authorities. It is mainly indicated in adults and paediatrics who are 3 months and older for empirical therapy in suspected fungal infections in febrile neutropenic patients, candidemia and few other candida infections like intra-abdominal abscesses and peritonitis. Also, observed to be useful in treatment of esophageal candidiasis and invasive aspergillosis [6]

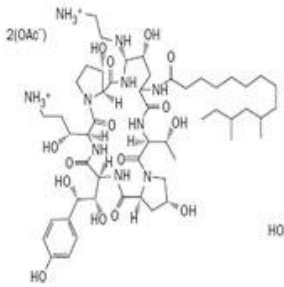
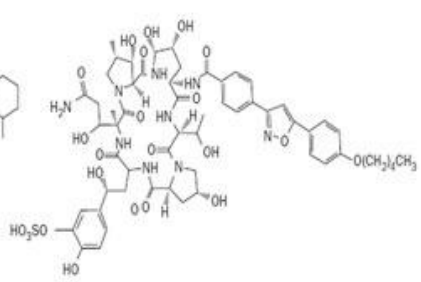
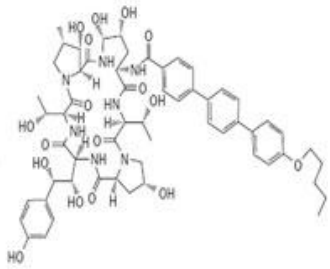
Micafungin after receiving approval in 2005, it was indicated for treatment of candidemia, acute disseminated candidiasis, abscesses and esophageal candidiasis. In January 2008, micafungin was also approved as a prophylactic treatment for candida infections in patients undergoing stem cell transplantation [5, 6]

Approval for Anidulafungin was gained by Pfizer in February 2006. It is known to have similar safety profile as that of Caspofungin [7, 8]

Chemistry of Echinocandins

Echinocandins are large lipopeptide molecules which are synthetically modified from various fungi and their fermentation broths. They are amphiphilic cyclic hexapeptides with N-linked acyl lipid side-chain, having a molecular weight of about 1200 [5, 9]

Table no1: Molecular weight, Solubility and Chemical structure of Echinocandins

	Caspofungin	Micafungin	Anidulafungin
Molecular formula	$C_{52}H_{88}N_{10}O_{15}\cdot 2C_2H_4O_2$	$C_{56}H_{70}N_9NaO_{23}S.$	$C_{58}H_{73}N_7O_{17}$
Solubility	freely soluble in water and methanol, and slightly soluble in ethanol	freely soluble in water	freely soluble in water
Chemical structure	Caspofungin 	Micafungin 	Anidulafungin 

Pharmacology of Echinocandins

Echinocandins are noncompetitive inhibitors of 1, 3-β-D-glucan synthase, an enzyme needed for the formation of 1,3-β-D-glucan. Glucan synthase is not found in mammalian cells, and therefore, can be easily targeted by the antifungal agents. Glucan is an essential component for growth and maintenance of fungal cell wall, its shape, rigidity and resistance to osmotic pressure. All fungal species have varying amounts of chitin, glucans and other cell wall constituents, making them more susceptible to the echinocandins than others. 1, 3-β-D-glucan is a major cell wall component of Candida and Aspergillus species, rendering them more vulnerable to agents found in this drug class [10]

In vitro activity of Echinocandins

Within the echinocandins, Micafungin exhibits in vitro activity against Aspergillus species & Candida species, including *Candida albicans, glabrata, krusei, parapsilosis,* and *tropicalis*.Caspofungin shows in vitro activity against Aspergillus species including *Aspergillus fumigatus, flavus, and terreus* and *Candida* species including *Candida albicans, glabrata, guilliermondii, krusei, parapsilosis,* and *tropicalis*. Anidulafungin has in vitro activity against *Candida* species including *Candida albicans, glabrata, parapsilosis, tropicalis, famata, rugosa, stellatoidea*; *Aspergillus*species (*A. fumigatus*) and other molds (*Bipolaris spicifera*, *Exophiala jeanselme; Fonsecaea pedrosoi, Madurella spp., Penicillium marneffei, Phialophoraverrucosa, Pseudallescheria boydii andWangiella dermatitidis*) [11]

One important note about echinocandins is that, they are concentration dependent agents i. e. more the concentration, more is the fungicidal activity. Hence, Micafungin, Caspofungin and Anidulafungin are not active at certain concentrations against Zygomycetes, Cryptococcus neoformans, Fusarium spp., or Trichosporon spp. This characteristic is different from the azoles, as they display time-dependent activity or in other words, there is increased antifungal activity with increased exposure to the drug [11, 12]

All the echinocandins have inconsistent oral absorption and hence, they are available only for intravenous use.

Caspofungin

The dosage of caspofungin acetate for candidemia, invasive aspergillosis and febrile neutropenia is a single loading dose of 70mg IV on day 1 and to be followed by 50mg IV once daily thereafter. Recommended Dosing of Caspofungin in Paediatric Patients [3 months to 17 years of age] for all indications is 70 mg/m^2 IV loading dose on day 1 followed by 50 mg/m^2 once daily further. The maximum dose of Caspofungin is 70mg in both loading and daily maintenance dose and should not exceed regardless the patient's calculated dose [13]. Dosing in paediatric patients should be based on the patient's body surface area (BSA) as calculated by the Mosteller Formula:

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times weight\ (kg)}{3600}}$$

Patients with Hepatic Impairment

For adultpatients with mild hepatic impairment, no dosage adjustment is required. For patients with moderate hepatic impairment, caspofungin 35 mg daily is recommended. However, the loading dose of 70mg remains the same on day 1 [13, 16]

Patients with renal dysfunction

Adult patients with renal insufficiency, no dosage adjustment is necessary for caspofungin.

Elderly patients

No systematic dosage adjustment is required.

Micafungin

The dosage of micafungin sodium for the prophylaxis of Candida infections is 50 mg IV daily. For treatment of esophageal candidiasis, a dosage of 150 mg IV daily is required. 85% of steady-state concentration is achieved after three daily doses; therefore, no loading dose is required for micafungin [14]

Patients with renal dysfunction

Dosage adjustment is not required for micafungin in patients with renal insufficiency. Since micafungin is highly bound to protein, it cannot be dialyzed.

Patients with hepatic dysfunction

Micafungin does not require dosage adjustment for patients with mild or moderate hepatic dysfunction (Child-Pugh score, 7-9) [16]

Pediatric patients

The safety and efficacy of micafungin are not established in pediatric patients [14, 15, 17]

Anidulafungin

Studies carried out for Anidulafungin showed its efficacy in Candidemia and invasive candidiasis.

A loading dose of 100mg IV on day 1 followed by 50mg thereafter, loading dose of 150mf IV on day 1 followed by 75mg once and a loading dose of 200mg IV on day 1 and 100mg thereafter are few regimens practiced [17, 18, 19].

Pharmacokinetics

Echinocandins have many pharmacokinetic similarities like low oral bioavailability, all are highly protein bound, and relatively have low concentrations in CSF and urine**.** Echinocandins are poorly absorbed when administered orally. When administered by injection, their distribution in all body tissues and organs is very well. After distribution, a sufficient concentration of drug is available which is capable of treating systemic as well as localised fungal infections. Anidulafungin, caspofungin, and micafungin differ most importantly, by the manner they are eliminated from the human body. Anidulafungin has a slower elimination rate via chemical degradation while micafungin is primarily eliminated by the liver by hydrolysis. Caspofungin is eliminated partly through chemical degradation and partial hydrolysis in the liver. Very little of these drugs is eliminated by the kidneys [9, 10, 19]

Pharmacokinetics of echinocandins in special populations

Echinocandins	Special population	Pharmacokinetics
Caspofungin	Patients with renal insufficiency	No dosage adjustment is required
	Hepatic insufficiency	AUC of Caspofungin is significantly increased in patients with hepatic insufficiency and hence, it is suggested that, the dose of Caspofungin be decreased from **50mg to 35mg** daily in patients with moderate hepatic insufficiency
	Pediatrics	Weight-based dosing in children resulted in lower plasma concentrations as compared to adults whereas dosing based on body surface area ($mg/m^2/day$) resulted in steady plasma state concentration same as adults, receiving a 50mg dose.
	Nursing mothers	Caspofungin was found in the milk of lactating drug treated rats and hence, should be exercised with caution when echinocandins are administered to a nursing woman
	Pregnancy	Categorized as Pregnancy Category C and should be used only if the potential benefit justifies the risk to the fetus
	Geriatric use	No dosage adjustments are required
Anidulafungin	Patients with renal insufficiency	No dosage adjustment is required
	Hepatic insufficiency	Dosage adjustments are not suggested for patients with mild, moderate, or severe hepatic dysfunction who are receiving Anidulafungin
	Pediatrics	Concentrations and exposures following administration of maintenance doses of 0.75 mg/kg/day and 1.5 mg/kg/day were similar to those observed in adults following maintenance doses of 50 mg/day and 100 mg/day, respectively.
	Nursing mothers	Anidulafungin was found in the milk of lactating drug treated rats and hence, should be exercised with caution when echinocandins are administered to a nursing woman
	Pregnancy	Categorized as Pregnancy Category C and should be used only if the potential benefit justifies the risk to the fetus
	Geriatric use	Range of clearance is similar in elderly and nonelderly subjects.

	Patients with renal insufficiency	**No dosage adjustment is required**
Micafungin	Hepatic insufficiency	In patients receiving micafungin, dosage adjustments are not recommended for patients with moderate hepatic dysfunction.
	Pediatrics	According to dose-escalation study in pediatric patients, an increase in the clearance of micafungin was noted in patients 2–8 years of age. Hence, recommended that a dosage of 1.5 times that of the adult dosage be utilized in this population
	Nursing mothers	Micafungin was found in the milk of lactating drug treated rats and hence, should be exercised with caution when echinocandins are administered to a nursing woman
	Pregnancy	Categorized as Pregnancy Category C and should be used only if the potential benefit justifies the risk to the fetus

Drug interactions

Drug interactions play a major role in pharmacotherapy. Drug-drug interaction has contributed as a major factor for mortality all over the world. Echinocandins being newer antifungals, their interaction profile has been charted in Tableno.2 respectively.

Echinocandins	**Interacting drug**	**Effect**
Caspofungin [21, 22, 23, 24, 25]	Cyclosporin	Current use of cyclosporin increases the AUC of caspofungin by 35%
	Efavirenz, Phenytoin, Nevirapine, Carbamazepine, and Dexamethasone,	Slight increases in caspofungin clearance
	Voriconazole	Synergistic interactions
	Rifampicin	Excretion of caspofungin through the biliary system, resultsin additional exposure to both compounds
	Tacrolimus	Caspofungin increases The trough levels of tacrolimus
	Amphotericin B	There is synergistic interactions between Amphotericin B and Caspofungin
	Posaconazole	Posaconazole exhibits in vitro synergy with caspofungin or FK506 against the C. albicans isolates tested
Micafungin[26, 27, 28]	cyclosporin	Cyclosporin also increases the AUC of micafungin by 13%
	Itraconazole, Sirolimus and Nifedipine	Micafungin increasesthe exposures of itraconazole, sirolimus and nifedipine, requiring monitoring and dose reduction
	Farnesol	Farnesol has a synergistic or additive interaction with micafungin,
Anidulafungin[29, 30]	Cyclosporin	Cyclosporin also increases the AUC of anidulafungin, by 21%
	Voriconazole	Shows synergistic mechanism

Safety and efficacy

Tolerance of echinocandins overall is quite good. Since, all three agents differ in their chemical and pharmacokinetic properties, amongst these three; Caspofungin has been in the market for a long time compared to Micafungin and Anidulafungin. When it comes to its usage in vulnerable patients like paediatrics, Caspofungin and Micafungin exhibit a similar safety profile in paediatric patients, whereas, safety and efficacy of Anidulafungin has not been established. The most common contraindication for all echinocandins is any known hypersensitivity to any component of the drug. Compared to other antifungals, they have a relatively favourable safety profile. As the echinocandins are available in injectable form, infusion related reactions may occur but, the response of these reactions to antihistamines is well established. Amongst the three echinocandins, Caspofungin shows a slightly higher frequency of liver-related laboratory abnormalities (1-15%) compared to the other two drugs [31]. Nausea, vomiting, diarrhoea and other mild gastrointestinal symptoms are possible, but rare. Micafungin also is well tolerated. Hyperbilirubinemia (3.3%), nausea (2.4%), and eosinophilia have been reported [38, 39]. Patients receiving Micafungin have shown local phlebitis like reactionsat the injection site. From the overall reported ADRs of 46%, only 5% were directly associated with Anidulafungin. The most common adverse events included hypotension (13%), vomiting (13%), constipation (11%) and nausea (11%) but none are dose dependent [32, 33]

CONCLUSION

The echinocandins are newer and important agents due to their novel mechanism of action, lesser serious adverse effects, and low potential for drug–drug interactions. Being antifungal class, they demonstrate potent activity against Candida species. Echinocandins have shown their potent activity against infections like invasive candidiasis, esophageal candidiasis and candidemia. In addition, Micafungin and Caspofungin are remarkably similar. They have similar spectrum of activity with only minor difference in pharmacokinetics, pharmacodynamics, adverse effects and drug interactions. All the three echinocandins when compared with other azole derivatives like Fluconazole, have shown similar spectrum of activity and thus proving a better choice as they have minimal side effects and also low resistance. Echinocandins can also serve as a choice of treatment when other antifungals prove to be resistant in the infections. Convenient dosing, a favourable safety profile, and limited drug interactions make echinocandins a welcome addition to the antifungal armamentarium.

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