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*Review Article*

# ECHINOCANDINS- A REVIEW

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## ABSTRACT

Echinocandins are considered to be large molecules from the perspective of drugs used for medical purposes.Echinocandins are able to kill most types Candida species, a type of yeast, and at least prevent the progression of growth of one type of mould called Aspergillusspp. They have modest activity against dimorphic fungi and have little activity against other types of moulds. The semisynthetic pneumocandinanalogs of echinocandins were later found to have the same kind of antifungal activity, but low toxicity. The different echinocandins have been evaluated and are currently used for the different diseases in humans. Poor absorption after oral administration limits use to the intravenous route. Dosing is once daily and drug interactions are few. Adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal liver function tests, and mild haemolysis. Absence of antagonism in combination with other antifungal drugs suggests that combination antifungal therapy could become a general feature of the echinocandins, particularly for invasive aspergillosis.

**Key words:** Echinocandins, caspofungin, micafungin, anidulafungin.

## INTRODUCTION

Screening natural products of fungal fermentation in the 1970s led to the discovery of echinocandins, a new group of antifungals with broad range activity against Candida species. Discovery of echinocandins stemmed from studies on papulacandins isolated from a strain of Papularia sphaerosperma, which were liposaccharide i.e., fatty acid derivatives of a disaccharide.

The first approved newer echinocandin was caspofungin and later micafungin, anidulafungin were also approved. All these preparations have low oral bioavailability, so must be given intravenously only. Several other echinocandin-like compounds have also been described, some of which are semisynthetic derivatives of the natural fermentation product, including enfumafungin, arbocandins, papulacandins, pneumocandin B, arundifungin and HMR 3270.

Many drugs have advanced the management of fungal infections, but failure rates still remain high and emergence of intrinsically resistant fungi is a growing problem. Echinocandins have now become one of the first line treatment for Candida before the species are identified and even as antifungal prophylaxis in hematopoietic stem cell transplant patients. Hence the emergence of echinocandins is therefore welcomed[1].

## CHEMISTRY

## ORIGIN OF THE ECHINOCANDINS

The lead compound for anidulafungin (LY303366;was identified in 1974. In 1989, the compound that led to caspofungin (MK991) was reported and the precursor of micafungin (FK463) was identified in1990. Several other echinocandin-like compounds have been described, some of which are semisynthetic derivatives of the natural fermentation product including enfumafungin, the arbocandins, the papulacandins, pneumocandin B, arundifungin and HMR 3270 (chemically derived from deoxymulundocandin). A less active echinocandin B analogue iscilofungin, this particular molecule was difficult to prepare and the formulation was toxic.

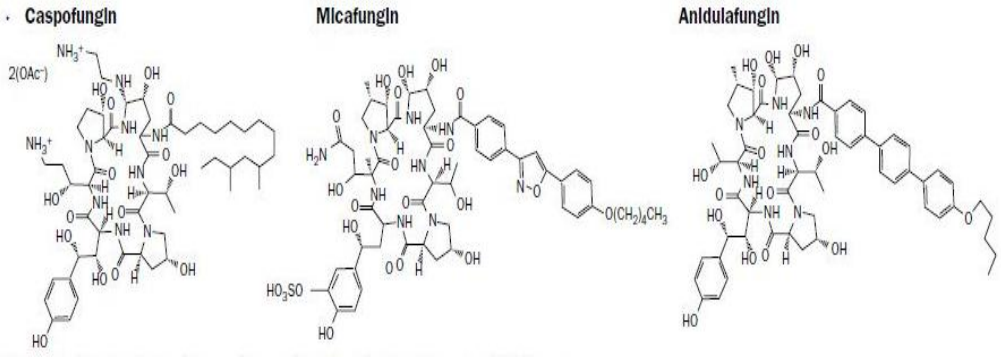


**Fig.1. Chemical Structures of Caspofungin, Micafungin and Anidulafungin**

Echinocandins are large lipopeptide molecules. All molecules in clinical use or development are amphiphilic cyclic hexapeptides with an N-linked acyl lipid side-chain and a molecular weight of about 1200. The aminoacid composition of these molecules is unusual since dihydroxyornithine, 4-hydroxyproline, dihydroxyhomotyrosine and 3-hydroxy-4-methylproline complement threoninein the peptidic nucleus. Caspofungin has a fatty-acid side-chain, micafungin has complex aromatic side-chain (3,5-diphenyl-substituted isoxazole), andanidulafungin has an alkoxytriphenyl(terphenyl) side-chain. Presumably, the side-chain intercalates with the phospholipid bilayer of the cell membrane. Caspofungin (acetate) is freely soluble in water, methanol and slightly soluble in ethanol. Micafungin is freely soluble in water whereas anidulafungin is not (Figure 1)

**MECHANISM OF ACTION OF ECHINOCANDINS**

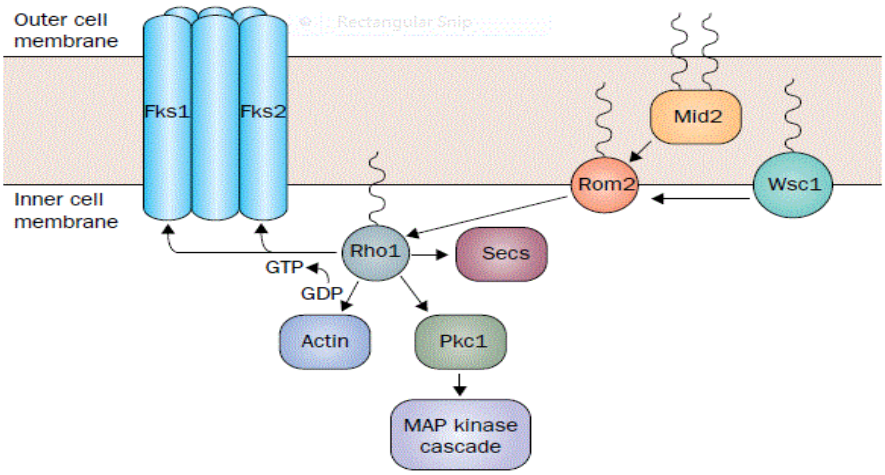


Figure 2: **Diagrammatic representation of the fungal cell membrane**
Proteins forming the β-(1,3)-D-glucan synthase complex (Fks1p and Fks2p) are shown, together with some proteins from the regulatory network.

**Fig.2.Diagramatic representation of the fungal cell memberane**

The target of the echinocandins is the synthetic cell-wall enzyme complex β-(1,3)-D-glucan synthase[2]. The gene encoding β-(1,3)-D-glucan synthase is Fks1. Diversity of phenotypes led to the cloning of a closely related gene Gsc2/Fks2. Mutations in Fks1 can confer caspofungin resistance.[3] Fks1 transcription is cell-cycle regulated and linked to cell-wall remodelling. Fks2 transcription is calcineurin-dependent. A key regulatory protein seems to be the product of Rho1, which interacts not only with Fks proteins but also with protein kinase C.[4] This protein is a well studied regulator of the mitogen-activated protein MAP kinase cascade and the actin

cytoskeleton assembly pathway in yeast. Rho1 seems to be dependent on guanine-nucleotide exchange factors, which are provided by Rom1 and Rom2 proteins. Rom2p is activated by the cell-wall-associated signaling glycoproteins Wsc1p and Mid2p. Because of the interaction with multiple proteins, Rho1p is thought to be a key switch, driving or arresting the synthesis of β-(1,3)-D-glucan. Activation of Rho1p not only activates β-(1,3)-D- glucan synthase but also results in activation of the MAP kinase cascade and affects actin synthesis. Echinocandins inhibit the enzyme β-(1,3)-D-glucan synthase and result in fungal cell death by cell cycle dysregulation. (Figure 2)

**FORMULATIONS**

All echinocandin preparations that have been used to date are for intravenous use only. Caspofungin is licensed for use in the USA and most of Europe and micafungin in Japan. Caspofungin is presented as a lyophylised white powder and excipients include sucrose, mannitol, acetic acid and sodium hydroxide. Once reconstituted, this formulation has a pH of 6·6 and is incompatible with dextrose. The drug is generally given by slow intravenous infusion over about 1h. Caspofungin can be stored(refrigerated) for up to 24 h after reconstitution and should be diluted before administration. Micafungin is prepared as a powder ready for reconstitution. Excipients include lactose, citric acid, sodium hydroxide and once reconstituted the pH of micafungin for infusion is 5–6hrs. Reconstituted micafungin solution is stable at room temperatures for 48 h, if protected from light. Micafungin can be administered with any intravenous infusion. Anidulafungin is provided as a lyophilized powder for reconstitution before infusion (Table 1)

**Table.1. Current status of availability of Echinocandins**

| Drug | Manufacturer | Current status |
|---|---|---|
| Caspofungin | Merck | Approved |
| Micafungin | Fujisawa | Approved |
| Anidulafungin | Vicuron | Phase 3 |
| HMR 3270 | Indevus | Phase 1 |
| Cilofungin | Lilly | Discontinued |

**RESISTANCE TO ECHINOCANDINS**

Prospective worldwide surveillance of clinical Candida isolates has revealed no evidence of emerging caspofungin resistance[5]. The molecular target of echinocandins is the Fks1 subunit of glucan synthase; predictably, mutations to this site confer varying degrees of resistance to the echinocandins. Fortunately, the echinocandins have proven to be worthy options in the treatment of azole-resistant Candida infections and clinical resistance remains a rare occurrence.

**PHARMACOKINETICS OF ECHINOCANDINS**

They have a low oral bioavailability, high protein binding, relatively low CSF and urine concentrations of parent drug. Since their urine concentrations are minimal, their clinical utility in treating urinary infections is poor. All display linear pharmacokinetics following administration of intravenous dosages and are degraded primarily by the liver by hydrolysis and N-acetylation. Following initial distribution, micafungin is taken up by RBCs and caspofungin and micafungin are taken up by liver. Excretion is slowly through bile.

Caspofungin is eliminated from the bloodstream with a half-life of 9 to 11 hours. Repeated administration of caspofungin (100 mg per day) has been well tolerated. Caspofungin utilizes the OATP-1B1 transporter, which also transports bile, rifampin and cyclosporine, thereby used in the treatment of candidal cholangitis.[6] Echinocandins are available only as parenteral formulations, are not dialyzable and do not require dosage adjustment in patients with renal insufficiency. Anidulafungin is eliminated exclusively by slow chemical degradation, has longer half-life and larger volume of distribution than the other two agents[7] (Table 2).

**Table.2. Pharmacokinetic parameters of Echinocandins in human subjects**

| **Pharmacokinetic parameters of Echinocandins in adult subjects** | | | |
|---|---|---|---|
| Variable | Caspofungin | Micafungin | Anidulafungin |
| $C_{max}$ | 7.64 | 4.95 | 2.07-3.5 |
| Bioavailability | | | 2%-7% |
| $t_{1/2}$ | 9-11 | 11-17 | 24-26 |
| $V_d$ | 0.14 | 0.215-0.242 | 0.5 |
| AUC | 87.9-114.8 | 111.3 | 44.4-53 |
| Protein binding | 96-97 | 99.8 | 84 |
| Metabolism | Slow peptide hydrolysis and N-acetylation. Also spontaneously degrades to inactive products | Catechol-O-methyltransfewrase pathway | Not metabolized. Undergoes slow chemical degradation to inactive metabolites |
| Cl | 0.15 | 0.185 | 0.26 |
| Elimination | 35%feces,41%urine | 40%feces,15%urine | Primarily feces |
| CSF penetration | low | low | <0.1% |
| Dosage adjustment in renal insufficiency | No dose adjustment needed | No dose adjustment needed | No dose adjustment needed |
| Dosage adjustment in renal insufficiency | Adjustment required as per Child-Pugh score | Adjustment required as per Child-Pugh score | No dose adjustment needed |

**PHARMACOKINETICS OF ECHINOCANDINS IN SPECIAL POPULATIONS**

**Hepatic insufficiency**: AUC of caspofungin is significantly increased in patients with moderate (Child- Pugh 7–9) hepatic insufficiency (maintenance dose has to be reduced to 35 mg). By contrast, decreased for micafungin; which is likely due to an increased volume of distribution and lower protein binding[8]. Decrease in AUC was observed in patients with severe hepatic insufficiency. Dosage adjustments are not suggested for patients with mild, moderate or severe hepatic dysfunction who are receiving anidulafungin.

**Pregnancy and lactation**: The echinocandins are all categorized as pregnancy Category C. There are no adequate and well-controlled studies in pregnant women; thus, echinocandins should be used only if the potential benefit justifies the risk to the fetus.

**Race and gender**: Pharmacokinetics are similar among Caucasians, Blacks, Asians and Hispanics. Dosage adjustments are not required based on race.

**PHARMACODYNAMICS OF ECHINOCANDINS**

They echinocandins exhibit concentration-dependent killing. Pharmacodynamic parameter to predict efficacy are AUC/MIC and Cmax: MIC (ratio of 3 indicates fungistatic activity, ratio of 10 indicates fungicidal activity). Caspofungin displays a significant post-antifungal effect[9].

**DRUG INTERACTIONS WITH ECHINOCANDINS**

The echinocandins are not substrates, inhibitors or inducers of cytochrome P450 nor do they interact with P-glycoprotein, thereby less drug interactions. 35% increase in the caspofungin AUC by cyclosporine. Rifampin has been shown to induce caspofungin metabolism. A dosage increase is recommended in patients receiving other enzyme inducers, such as efavirenz, nevirapine, phenytoin, dexamethasone and carbamazepine.

**INDICATIONS**

**Caspofungin**: In the treatment of esophageal candidiasis, invasive candidiasis in adult patients, invasive aspergillosis in patients refractory or intolerant to initial antifungal therapy and empiric therapy for presumed fungal infections in febrile, neutropenic patients.

**Dose**: It is administered intravenously once daily over 1 hour. In candidemia and salvage therapy of aspergillosis, the initial dose is 70 mg, followed by 50 mg daily. The dose may be increased to 70 mg daily in patients failing to respond. Esophageal candidiasis is treated with 50 mg daily.[10]

**Micafungin**: In the treatment of esophageal candidiasis, prophylaxis of candida in hematopoietic stem cell transplant patients

**Anidulafungin**: In the treatment of esophageal candidiasis, candidemia and other forms of candida infections, intra-abdominal abscess and peritonitis.

For Caspofungin and Micafungin liver function tests have to be carried out at baseline and periodically whereas for anidulafungin, infusion related reactions should be looked for.

**ADVERSE EVENTS AND TOXIC EFFECTS**

Headache is a frequent side-effect with all three compounds. Local irritation at the infusion site, fever, liver toxic effects- rise in alanine aminotransferase, patchy hepatic necrosis, abnormal liver-function seen more with patients receiving caspofungin.

Histamine-like reactions are seen after rapid anidulafungin administration.

**ADVANTAGES OF ECHINOCANDINS:**

- Broad range (especially against all Candida), thus can be given empirically in febrile neutropenia and stem cell transplant
- Can be used in case of azole-resistant Candida or use as a second line agent for refractory aspergillosis
- Long half life (polyphasic elimination: alpha phase 1–2 hours + beta phase 9–11 hours + gamma phase 40–50 hours)
- Low toxicity: only histamine release (3%), fever (2.9%), nausea and vomiting (2.9%), and phlebitis at the injection site (2.9%), very rarely allergy and anaphylaxis
- Not an inhibitor, inducer, or substrate of the cytochrome P450 system, or P-glycoprotein, thus minimal drug interactions
- Lack of interference from renal failure and hemodialysis
- No dose adjustment is necessary based on age, gender, race
- Better (or no less effective) than amphotericin B and fluconazole against yeast infections

**DISADVANTAGES OF ECHINOCANDINS:**

- Embryotoxic (category C) thus cannot be used in pregnancy
- Needs dose adjustment in liver disease
- Poor ocular penetration in fungal endophthalmitis

**Table.3. Echinocandin- containing combination antifungal therapy (invitro and animal data)**

| **Echinocandin- containing combination antifungal therapy (invitro and animal data)** | | |
|---|---|---|
| Caspofungin | Candida species<br><br>Aspergillus species<br><br>Mucormycosis | Invitro combination with fluconazole yielded generally indifferent results and showed potential benefit in animal study<br>Invitro and animal combination with amphotericin B and triazoles generally synergistic. Antagonism is not seen.<br>Combination with amphotericin B showed survival benefit in animal model |
| Micafungin | Aspergillus species<br><br><br><br>Candida species | Invitro and animal models, the combination of amphotericin B and triazole antifungals was generally synergistic , decreased $EC_{90}$<br>Of voriconazole against A.fumigatus and A.terreus but not A.flavus<br>Voriconazole combination indifferent in 97% isolates, most |

| | | |
|---|---|---|
| | Scedosporium and fusarium solani species | likely due to already low MICs with micafungin. Combination with amphotericin B required to eradicate C.Glabarata infection in immunosuppressed mice<br>Combination with voriconazole synergistic in 64% of isolates. Antagonism not noted. |
| Anidulafungin | Aspergillus species<br><br>Candida species | Invitro combination with amphoterisin is antagonistic whereas combination with voriconazole+itraconazole showed synergy<br>Invitro combination with amphotericin B,itraconazole, ketoconazole, 5-fluorocytosine generally show additivity or indifference. Antagonism noted in all strains of C.tropicalis with combination of ketoconazole and anidulafungin |

**Table.4.Indications of Echinocandins and their monitoring**

| Agent | Indication | Monitoring |
|---|---|---|
| Anidulafungin | Candidemia and other forms of candida infections, intra abdominal abscess and peritonitis.<br>Esophageal candidiasis | Infusion related reactions if administered quickly |
| Caspofungin | Empiric therapy for presumed fungal infections in febrile, neutropenic patients.<br>Treatment of esophageal, invasive candidiasis in adult patients.<br>Treatment of invasive aspergillosis in patients refractory or intolerant to initial antifungal therapy | Liver function tests at baseline and periodically |
| Micafungin | Prophylaxis of candida in hematopoietic stem cell transplant patients<br>Esophageal candidiasis | Liver function tests at baseline and periodically |

## CONCLUSION

In terms of safety, all three echinocandins demonstrate superior safety compared to amphotericin B and its formulations. They also present a safer drug interaction profile when compared to azole antifungals.

Overall, anidulafungin, caspofungin, and micafungin demonstrate similar efficacy compared to other antifungals for the prevention and treatment of invasive fungal infections and offer a superior profile for certain aspects of safety. For these reasons, they are considered as first or second line therapy in several different indications for many patients.

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