ECHINOCANDINS FOR THE TREATMENT OF SYSTEMIC FUNGAL INFECTIONS

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Echinocandins are considered to be large molecules from the perspective of drugs used for medical purposes. Compounds in this class are all composed of a similar core which allows them to be soluble in different types of solutions (oil or water). Attached to this core is a lipid side chain which is characteristic for each of the different agents of this class. **Anidulafungin, caspofungin**, and **micafungin** are semi synthetic compounds that are currently licensed for use. These agents inhibit an enzyme necessary for the formation of fungal cell wall components. This inhibition compromises the integrity of the cell wall which then fails and eventually leads to cell death. Targeting this structure unique to fungal cells and non-existent in mammalian cells provides an important advantage of minimizing adverse effects compared to antifungal agents of other classes. Also, because of this different target site, pathogens resistant to other classes of antifungals are unlikely to be resistant to echinocandins.

Echinocandins are poorly absorbed when administered orally. When administered by injection they will reach most tissues and organs with concentrations sufficient to treat the localized and systemic fungal infections. Anidulafungin, caspofungin, and micafungin differ most importantly by the manner they are eliminated from the human body. Anidulafungin is eliminated slowly by chemical degradation throughout the body while micafungin is primarily eliminated in the liver by hydrolysis, a process seldom involved in drug interactions. Caspofungin is eliminated partially through chemical degradation and partially through the liver by hydrolysis. Very little of these drugs is eliminated by the kidneys.

Fungus can be further classified into yeast, molds, and dimorphic agents. Echinocandins are able to kill most types *Candida* spp., a type of yeast, and at least prevent the progression of growth of one type of mold called *Aspergillus* spp. They have modest activity against dimorphic fungi and have little activity against other types of molds. All three echinocandins have shown similar efficacy in different animal models. However, because they show variability in the way they concentrate in different tissues in humans affected with different disease states it is essential to evaluate each agent in clinical trials in order to assess efficacy and safety before mandating their respective use for specific indications.

The different echinocandins have been evaluated and are currently used for the different diseases in humans (see table below for approved indications). Invasive fungal infections in patients with immune deficiencies are quite rare but can be deadly. Early initiation of antifungals as prevention or in

patients who remain febrile despite antimicrobial therapy may improve survival. Because echinocandins have a very good safety profile they have a significant advantage over other antifungals which may harm a several number of patients for the benefit of a few. Micafungin is effective for the prevention of fungal infections in patients undergoing hematopoietic stem cell transplant. Caspofungin is effective for treatment of suspected invasive fungal infections in patients who are feverish and have an immune deficiency called neutropenia. Note that when rare molds are a concern in certain institutions other antifungals may be a more appropriate choice for this indication.

Echinocandins are also used for treatment of yeast infections associated with *Candida* spp. when it invades the oral cavity and esophagus, or when it invades the blood stream and other organs. Caspofungin is now considered by some to be the first line agent for treatment of candidemia. Micafungin and anidulafungin have also been found to effective in this situation.

Echinocandins are used for the treatment of mold infections associated with *Aspergillus* spp. when it invades the blood stream and other organs as alternatives to first-line agents. Caspofungin is the most extensively studied molecule of this class for this indication. Micafungin seems to offer similar efficacy to caspofungin. Anidulafungin has yet to be evaluated. It is important to recognize that *Aspergillus* spp. disease can be very difficult to treat and is associated with a very high rate of mortality. Therefore, the combination of an echinocandin with other antifungal agents such as amphotericin B or voriconazole (see azoles) is considered in certain cases to hopefully achieve better results than with monotherapy.

In terms of safety, all three echinocandins demonstrate superior safety compared to amphotericin B and its formulations. General monitoring parameters are presented in table 1. 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.

Suggested reading:

Wagner C, Graninger W, Presterl E, Joukhadar C. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. Pharmacology. 2006;78:161-77

Thirion DJG, Sheppard D. Echinocandins for fungal infections: a review and practical considerations. EJHP Practice 2007;2:41-6

TABLE 1: APPROVED INDICATIONS FOR USE IN NORTH AMERICA AS OF 2008*

AGENT	INDICATION	MONITORING
Anidulafungin	Candidemia and other forms of *Candida* infections intra-abdominal abscess, and peritonitis Esophageal candidiasis	Infusion related reactions if administered to quickly
Caspofungin	Empiric therapy for presumed fungal infections in febrile, neutropenic patients Treatment of esophageal candidiasis Treatment of invasive candidiasis in adult patients 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 Esophageal candidiasis	Liver function tests at baseline and periodically

*Additional indications may be approved with further research and development