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A REVIEW ON CASPOFUNGIN: STRUCTURE, METABOLISM AND PHARMACOLOGICAL USES

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ABSTRACT

Caspofungin is a drug in the echinocandins class of medications used to manage and treat several medical conditions. These illnesses include invasive candidiasis, esophageal candidiasis, febrile neutropenia, candida infections, and invasive aspergillosis. The current review was based on caspofungin: structure, metabolism and pharmacological uses. Caspofungin acetate is the first antifungal medication of the echinocandins class to receive marketing approval from the Food and Drug Administration (FDA). Caspofungin, along with other echinocandins, functions through noncompetitive inhibition of the enzyme beta-(1,3)-D-glucan synthase. This enzyme is essential for the formation of the fungal cell wall and is not found in mammalian cells. Caspofungin is metabolised in the liver through hydrolysis and delayed N-acetylation, resulting in the formation of two metabolites that are not active. Therefore, it is recommended to reduce the dosage in cases of severe liver dysfunction. Caspofungin has a brief initial half-life (t1/2) of 1 to 2 hours (with a volume of distribution of 9.7l) and a longer second half-life of 9 to 11 hours. Around 75% of a radioactive dosage is retrieved after a period of 27 days, with 41% excreted in urine and 35% excreted in faeces. Approximately 2% of caspofungin is eliminated in the urine without undergoing any changes. The most frequently documented adverse events consist of chills, fever, phlebitis/thrombophlebitis, tachycardia, nausea, vomiting, rash, hypokalemia,

increased plasma creatinine, pruritus, stomach discomfort, headache, and diarrhoea. It concludes that Caspofungin is an effective versatile antifungal drug with minimum side effects as compared to amphotericin-B.

KEYWORDS: Caspofungin, structure, pharmacokinetics, pharmacological uses, candida infections.

INTRODUCTION

Caspofungin is a drug in the echinocandins class of medications used to manage and treat several medical conditions.[1] These illnesses include invasive candidiasis, esophageal candidiasis, febrile neutropenia, candida infections, and invasive aspergillosis.[2][3] In order for an interprofessional team to manage and treat the conditions listed above, this activity evaluates the mechanism of action, adverse reaction profile, and other important elements (e.g., off-label usage, dose, pharmacodynamics, pharmacokinetics, monitoring, and pertinent interactions). Caspofungin acetate is the first antifungal medication of the echinocandins class to receive marketing approval from the Food and Drug Administration (FDA).[4] Its introduction was in 2001, approved for use in adults and pediatric patients (3 months of age and older).[5]

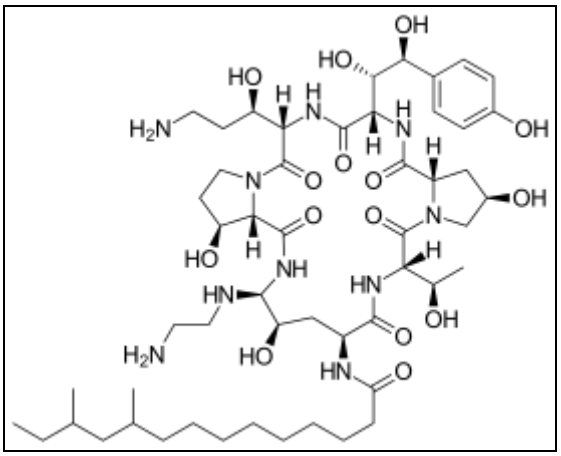

Fig. 1: Structure of Caspofungin.

Mode of action

Caspofungin, along with other echinocandins, functions through noncompetitive inhibition of the enzyme beta-(1,3)-D-glucan synthase. This enzyme is essential for the formation of the fungal cell wall and is not found in mammalian cells.

Caspofungin demonstrates a lethal effect on Candida species, including those that are resistant to triazole drugs, and a growth-inhibiting effect on Aspergillus species. The pharmacokinetics exhibited by this presentation are triphasic and nonlinear. Following the drug's first intravenous delivery, there is a swift decline in plasma concentrations caused by the dispersion of the drug into tissues. This is then followed by a gradual release of the drug from the tissues outside of blood vessels, as well as slow metabolism in the liver.[6],[7] The substance is metabolised in the liver through hydrolysis and delayed N-acetylation, resulting in the formation of two metabolites that are not active. Therefore, it is recommended to reduce the dosage in cases of severe liver dysfunction.[8] Caspofungin also spontaneously disintegrates into an open-ring compound.[9]

Pharmacokinetics

It is advisable to decrease the dosage in cases of hepatic insufficiency, taking into consideration the Child-Pugh (C-P) score. Nevertheless, it is imperative not to decrease the dosage in critically ill patients until there is clear indication of liver cirrhosis.[10] Renal impairment does not require a reduction in dosage. The flow of echinocandin across the membranes appears to be limited due to its high protein binding, specifically 97% to albumin.[11] Furthermore, it is advised to raise the maintenance dose of caspofungin when it is taken together with strong inducers of cytochrome P450 3A4 (CYP3A4) metabolism. Several agents that may be included are rifampin, nevirapine, efavirenz, carbamazepine, dexamethasone, and phenytoin.[6] The simultaneous administration of caspofungin and cyclosporine has been associated with an elevated risk of caspofungin-induced liver damage. However, some case reports have documented patients who received both medications without experiencing any significant signs or symptoms of liver toxicity.[12][13][14]

The pharmacokinetics of caspofungin exhibit a higher accumulation with increasing dosage, and there is a dose-dependent relationship in the time it takes to achieve a stable state when administered numerous times. Hence, it is necessary to administer an initial high dose followed by a smaller dose once a day in order to achieve the desired therapeutic level of the drug in the bloodstream and prevent excessive drug buildup. This method yields a minimum trough concentration of 1mcg/ml (the desired concentration for treating invasive infections, determined through laboratory testing of Candida spp.).[15]

Caspofungin has a brief initial half-life (t1/2) of 1 to 2 hours (with a volume of distribution of 9.7l) and a longer second half-life of 9 to 11 hours, which follows a logarithmic pattern. In

contrast to the other phases, the gamma-phase half-life (t1/2) of 40-50 hours exhibits nonlinearity and is accountable for the gradual buildup of caspofungin over a period. Caspofungin is removed from the bloodstream at a sluggish rate, with a clearance of 10 to 12 ml/minute. Around 75% of a radioactive dosage is retrieved after a period of 27 days, with 41% excreted in urine and 35% excreted in faeces. Approximately 2% of caspofungin is eliminated in the urine without undergoing any changes.[16]

Adverse drug reactions

Caspofungin exhibits a relatively low frequency of negative effects. The most frequently documented adverse events consist[17]:

- ✓ Chills
- ✓ Fever
- ✓ Phlebitis/thrombophlebitis
- ✓ Tachycardia
- ✓ Nausea
- ✓ Vomiting
- ✓ Rashes
- ✓ Hypokalemia
- ✓ Increased plasma creatinine
- ✓ Pruritus
- ✓ Stomach discomfort
- ✓ Headache
- ✓ Diarrhoea.

There are also reports of a slight increase in aminotransferases.

Caspofungin has been discovered to induce cutaneous erosions that resemble those observed in toxic epidermal necrolysis (TEN). In a case report authored by Lee et al., it is detailed that an 86-year-old man with widespread Candida krusei infection developed a rash consisting of erythematous macules and plaques. This rash rapidly advanced to the formation of blisters and skin erosions following the administration of caspofungin.[18]

Contraindications

The primary contraindication is a documented hypersensitivity reaction to caspofungin acetate or any other components present in the formulation. Insufficient data is available on

the use of caspofungin in pregnancy, hence doctors should use caution while using it. Amphotericin B is the primary treatment for systemic fungal infections during pregnancy, however other drugs can be used as alternatives.[19]

Pharmacological Uses

- **Febrile neutropenia:** A fever above 101 F (or 38 C) for 1 hour is considered as the defining characteristic. This is accompanied by either an absolute neutrophil count (ANC) of 500 cells/microliter or less, or an ANC of 1000 cells/microliter or less with a projected lowest point of 500 cells/microliter or fewer. The Infectious Diseases Society of America (IDSA) recommends empiric antifungal medication for high-risk patients with persistent febrile neutropenia despite broad-spectrum antibiotic therapy. Among various antifungals, caspofungin is included.[20]
- **Invasive candidiasis:** In a double-blind, randomised experiment comparing the effectiveness of caspofungin and amphotericin B in patients with invasive endocarditis, 73.4% of those who received caspofungin had a more favourable outcome, while only 61.7% of those who received amphotericin B had a similar outcome.[21] In the initial management of candidemia, the use of echinocandins is recommended above azoles in the following situations: when there is confirmation or suspicion of either C. glabrata or C. krusei infection, or when the patient's candidemia does not respond to therapy with an azole drug.[22]
- **Candida infections:** candidemia, intra-abdominal abscesses, peritonitis, and pleural space infections.
- **Esophageal candidiasis:** Multiple investigations have demonstrated that caspofungin exhibits a favourable treatment response that is equivalent to fluconazole.[23][24] In 2002, Villanueva et al. conducted a double-blind, randomised trial with 177 HIV patients diagnosed with esophageal candidiasis, one year following the launch of caspofungin. The patients were allocated randomly into two groups: one receiving caspofungin (50mg IV) and the other receiving fluconazole (200mg IV). Both medications were administered once daily for a duration of 7-21 days. After stopping the treatment, there was a simultaneous improvement in symptoms and endoscopic findings within 5 to 7 days. The treatment response rates were 81% and 85% for the patients in the caspofungin and fluconazole groups, respectively.5 In the same year, Kartsonis et al. conducted a retrospective analysis that showed the efficacy of caspofungin in treating esophageal candidiasis that is resistant to or does not respond to fluconazole. Out of the 14 patients

with in-vitro resistant isolates, the treatment was successful in 11 of them. Additionally, out of the 11 patients with refractory illness, the treatment was successful in 7 of them. Caspofungin seems to have fewer adverse effects compared to intravenous amphotericin B when used to treat esophageal candidiasis.

- **Invasive aspergillosis:** Caspofungin has FDA approval to treat invasive aspergillosis in patients who are refractory to or intolerant of voriconazole, the primary antifungal agent.[25][26][27] Echinocandins are not recommended as first-line therapy.

Toxicity

While infrequent, the echinocandins have been associated with clinically severe cases of hepatitis, hepatomegaly, hyperbilirubinemia, and even hepatic failure. It is recommended to periodically monitor hepatic aminotransferases during caspofungin therapy.[28] Due to the hepatotoxic side effects linked to caspofungin, it is crucial to monitor liver function. Caspofungin has been observed to induce the release of histamine in peripheral blood cells, increasing the likelihood of patients having histamine-mediated symptoms that can range from severe to fatal anaphylaxis.[29] To reduce the risk of morbidity and death, it is crucial to closely monitor patients for anaphylaxis, rash, or histamine-related symptoms such as face swelling, bronchospasm, and a sensation of warmth.[30]

CONCLUSION

Caspofungin has demonstrated efficacy in the treatment of fungal infections caused by Aspergillus and Candida species. It belongs to the echinocandin family, which is a novel group of antifungal drugs that have a wide range of effectiveness against all species of Candida. When compared to fluconazole or amphotericin B, it has shown to be highly effective or superior in specific clinical situations such as invasive Candida infections, Candida esophagitis, and candidemia. It concludes that Caspofungin is an effective versatile antifungal drug with minimum side effects as compared to amphotericin-B.

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CONFLICT OF INTEREST

None.

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