Subtherapeutic Ocular Penetration of Caspofungin and Associated Treatment Failure in Candida albicans Endophthalmitis

G. M. Gauthier1, T. M. Nork2, R. Prince4, and D. Andes1,3

1Department of Medicine, Section of Infectious Diseases, 2Department of Ophthalmology, and 3Department of Medical Microbiology and Immunology, University of Wisconsin–Madison, Madison, and 4College of Pharmacy, University of Houston, Houston, Texas

Candida endophthalmitis represents the most serious ocular complication of candidemia. The pharmacokinetics and pharmacodynamics of fluconazole, amphotericin B, and fluconazole are fairly well established in endophthalmitis therapy. There remains a paucity of clinical data regarding the utility of new antymycotic agents in the treatment of fungal chorioretinitis and endophthalmitis. We report a case of clinical failure of caspofungin in the management of Candida albicans endophthalmitis associated with poor vitreous penetration.

Endogenous Candida chorioretinitis and endophthalmitis are the most common ocular complications of candidemia and, on the basis of prospective studies, occur in 3.7%–28% of patients with candidemia [1–5]. Significant risk factors include indwelling vascular catheters, broad-spectrum antimicrobials, surgery, malignancy, and injection drug use (IDU) [5–7]. Management is based on the severity of ocular involvement. Treatment guidelines suggest that chorioretinitis and mild vitritis can be managed with systemic antifungal therapy in conjunction with serial ophthalmologic examinations [8]. Moderate-to-severe vitreous involvement frequently warrants surgical intervention (i.e., vitrectomy), systemic antifungal therapy, and consideration for intravitreal amphotericin B therapy. The rationale for antifungal drug choice is based on small case series and antymycotic vitreous penetration. Currently, limited published data are available regarding echinocandin vitreous penetration and the utility of echinocandin antifungals in the management of ocular fungal infections. We detail the inadvertent use of caspofungin monotherapy in a patient with candidemia and associated chorioretinitis, ocular treatment failure, and measurement of serum and vitreous caspofungin concentrations during vitrectomy.

Case report. A 33-year-old man with a diagnosis of stage I nonseminomatous mixed germ cell testicular cancer was treated with left orchiectomy and retroperitoneal lymph node dissection. His course was complicated by a small bowel obstruction requiring the initiation of total parenteral nutrition via a peripherally inserted central catheter (PICC).

Two months later, he presented to his primary care physician with a 1–2 week history of bilateral floaters, a 1–2 day history of bilateral decreased vision, and fevers of up to 40.6°C. Cultures of blood samples obtained at admission (including samples obtained through the PICC and peripheral blood samples) and cultures of the PICC tip grew Candida albicans. Ophthalmologic examination revealed 3+ anterior chamber cell and flare, moderate swelling of the optic nerves, obscuration of the retinal vessels, and yellow, fluffy chorioretinal lesions with associated hemorrhage (figure 1A). CT of the chest showed lesions consistent with multiple bilateral septic pulmonary emboli. A tranesophageal echocardiogram did not reveal vegetations. The patient was treated with both caspofungin and fluconazole. Cultures of blood samples showed rapid clearance of infection, and serial dilated ophthalmoscopy demonstrated improvement of the ocular inflammation.

Unfortunately, because of a medication-dispensing error, the patient was discharged from the hospital after 5 days with a prescription for caspofungin (50 mg per day) but without fluconazole. Three days later, his visual acuity decreased secondary to progression of disease (figure 1B). The left eye required immediate vitrectomy, endolaser photocoagulation, and intravitreal amphotericin B deoxycholate (5 μg per 100 μL). Intraoperative vitreous sampling showed an undetectable caspofungin concentration by high-performance liquid chromatography (lower limit of detection, 50 ng/mL). Concomitant serum concentration was 3.3 μg/mL. After the surgical procedure, the patient received 4 weeks of therapy with amphotericin B lipid complex (5 mg/kg per day). His visual acuity returned to normal, and there has been no evidence of relapse for 8 months.

Discussion. During the past 2 decades, the number of available antifungal agents has significantly increased, most recently with the addition of voriconazole to the triazole family and the development of the echinocandin class, consisting of caspofungin monotherapy in a patient with candidemia and associated chorioretinitis, ocular treatment failure, and measurement of serum and vitreous caspofungin concentrations during vitrectomy.

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Reprints or correspondence: Dr. D. Andes, 600 Highland Ave., Rm. H5/572, Madison, WI 53792 (dand@medicine.wisc.edu).

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fungin, micafungin, and anidulafungin. Caspofungin is fungicidal to Candida and has been documented to be as effective as amphotericin B for the treatment of candidemia in a randomized prospective study [4]. However, its role in the management of Candida chorioretinitis and endophthalmitis has yet to be fully defined. Among the >200 patients in the aforementioned study, 7 patients received a diagnosis of endophthalmitis, but the authors do not report whether caspofungin was utilized to treat these patients [4]. Caspofungin has been successfully used in 2 of 3 patients as part of dual therapy with voriconazole, a drug with good vitreous penetration that appears to be effective for primary endophthalmitis therapy [9, 10]. To date, the utility of caspofungin monotherapy for Candida endophthalmitis is limited to a single patient with mild vitreitis and a solitary retinal lesion, who, after 28 days of therapy, had complete resolution of his ocular infection [11]. Our patient experienced failure of caspofungin monotherapy while having undetectable vitreous caspofungin levels. This report represents the only known data regarding caspofungin vitreous concentrations in either humans or animals. The other echinocandins also appear to have limited vitreous penetration. Micafungin vitreous penetration is dose dependant and ranges from undetectable levels to 0.034 μg/mL in the noninflamed rabbit eye [12]. In a disseminated candidiasis rabbit model, micafungin reduced vitreous C. albicans burden; however, drug entry into the vitreous may have been affected by Candida meningioencephalitis [13]. Similar to micafungin, anidulafungin vitreous penetration is dose dependant and ranges from undetectable to 0.184 μg/mL in neutropenic rabbits with disseminated candidiasis [14]. Our report of undetectable vitreous caspofungin levels after 9 days of therapy with progression of culture-proven Candida endophthalmitis after the accidental cessation of fluconazole suggests that caspofungin may not be useful monotherapy for fungal endophthalmitis. Further pharmacokinetic and clinical outcome data are needed to determine the role of caspofungin and of the other echinocandins in the management of ocular fungal infections.

**References**