USE OF LIPOSOMAL AMPHOTERICIN B IN THE TREATMENT OF DISSEMINATED COCCIDIOIDOMYCOSIS

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Disseminated fungal infection is an important cause of morbidity and mortality, especially in immunocompromised hosts. Amphotericin B is an important part of the therapy and treatment of invasive and life-threatening mycoses. We present a case of disseminated coccidioidomycosis in a patient who was successfully treated with liposomal amphotericin B (AmBisome®) on steroid therapy. It appears that liposomal amphotericin B may offer an alternative and safe option in the treatment of coccidioidomycosis when conventional amphotericin B cannot be used. (*J Natl Med Assoc.* 2003;95:982–985.)

Key words: amphotericin B ♦ coccidioidomycosis ♦ liposomal amphotericin B ♦ AmBisome®

INTRODUCTION

Coccidioidomycosis is a fungal infection caused by inhalation of the arthroconidia of the dimorphic fungus *Coccidioides immitis*. This infection is endemic in the southwestern United States (Arizona, New Mexico, Southern California, and Western Texas) and northern Mexico. Within these areas, the organism is commonly found in the soil, and infection is likely to occur in such situations as dry windy conditions or construction sites[1]. Sixty percent of healthy individuals will develop asymptomatic infection or symptoms of an upper respiratory tract infection when exposed to the spores of C. immitis. Most pulmonary C. immitis infections are self-limited, resolving in weeks to months without the use of antifungal medication[1,2]. Dissemination or extrapulmonary disease is more common in people infected with HIV, organ transplant recipients, diabetics, or patients receiving steroid treatment. Among people who become infected, women in their third trimester of pregnancy and people of African, Hispanic, and Filipino ancestry are at higher risk for disseminated coccidioidomycosis[3]. Dissemination occurs in 0.5–1% of the cases and usually involves a spread of infection to the skin, bone, joints, soft tissue, and meninges. Meningitis is a serious manifestation of disseminated coccidioidomycosis and occurs in 30–50% of the cases with a high mortality rate[2,3,4].

Until the advent of the azole group of drugs, such as fluconazole and itraconazole, amphotericin B deoxycholate (amB) had been the gold standard for the treatment of disseminated coccidioidomycosis. Unfortunately, drug-related toxicity is the most frequent limiting factor associated with amB[5]. As many as 80% of the patients treated with therapeutic doses of amB show evidence of renal impairment[6,7]. In an effort to improve the safety profile while retaining the pharmacological spectrum, new formulations of amB have been developed in a lipid emulsion. Examples of these lipid-based formulations are: liposomal B (AmBisome®), amB colloidal

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dispersion (ABCD), and amB lipid complex (ABLC)[7,8]. All three lipid formulations have different biochemical, pharmacokinetics, and pharmacodynamic properties. They share the same spectrum of amB deoxycholate, but they have been reported to be less nephrotoxic[9].

Several studies have reported the successful use of liposomal amB in the treatment of disseminated mycosis including: candidiasis, aspergillosis, cryptoccocal meningitis, and other difficult-to-treat mycoses—such as Fusarium and Zygomycetes[10]. These studies demonstrated that liposomal amB is as effective as conventional amB and has a superior safety profile[11-15]. However, there have been no published studies evaluating the use of liposomal amB in disseminated coccidioidomycosis.

We present a case of a disseminated coccidioidomycosis successfully treated with AmBisome® without any significant renal adverse effects. No evidence of recurrence of the disease was noted after a year.

CASE REPORT

We report a case of a 75-year-old Asian male with a history of uncontrolled hyperthyroidism who was being treated as an outpatient with beta-blockers, anti-thyroid medications, and because of unrelenting exopthalmos, was also placed on steroid therapy. He was started on prednisone 60 mg per day for several days and the progressively decreasing doses of prednisone over several weeks. During the period of tapering the dose of the steroid, the patient developed low-grade fevers ranging between 100°F and 101°F. This was also associated with a cough productive of a greenish sputum, malaise, and fatigue. He then gradually developed increasing shortness of breath to the point where he was unable to ambulate at all. He subsequently presented to the hospital for admission, at which time his temperature was 102.3°F, his blood pressure 122/60 mm Hg, his pulse 100 beats per minute, and his respiratory rate 24/mt. Physical examination revealed an elderly male in moderate respiratory distress on 2 liters of nasal oxygen. Mucous membranes were pale. Oral cavity was unremarkable; there was no significant adenopathy. There was evidence of proptosis. The chest revealed bilateral crackles and wheezes and decreased air entry bilaterally. The heart and abdominal examination was unremarkable.

The laboratory tests at the time of admission included a white blood cell count of $4.4x10^3/\mu l$, with 83% neutrophils, platelet of 234,000 Ul. The blood urea nitrogen was 37 mg/dl, and the creatinine was 1.1 mg/dl. The hemoglobin was 13.7 g/dl, the hematocrit 38.9%. Amino alanine transferase (ALT) was 234 U/l, the aspartate amino transferase (AST) was 245 U/l, and the bilirubin was 2.3 mg/dl. The magnesium was 2.1 mg/dl, and the potassium was 4.7 mmol/l. The chest x-ray at the time of admission revealed no infiltrates.

The patient was placed on appropriate broad-spectrum antimicrobial therapy at the time of admission to the hospital with the presumptive diagnosis of community-acquired pneumonia. He did not improve and continued to have progressive dypsnea. By day 3, the chest x-rays showed bilateral pulmonary infiltrates with the suggestion of pulmonary nodules that were not present prior to admission. Because of progressive respiratory distress, he was transferred to the intensive care unit and placed on the ventilator. A bronchoalveolar lavage and biopsy were then performed—both showing evidence of coccidioidomycosis. Serological analysis by complement fixation showed a titer of 1:2000. A bone marrow aspiration and biopsy, also consistent with disseminated coccidioidomycosis, were done. The patient was empirically started on intravenous high-dose fluconazole. However, he had to be switched to liposomal amphotericin as opposed to conventional amphotericin because his age, history of hypertension, possible septic shock syndrome, and the presence of early renal insufficiency. The patient was started on AmBisome® at 3 mg/kg per day, which was continued throughout the six-week period, as he seemed to tolerate the dosage with a good clinical response and no evidence of renal toxicity. Repeated chest x-rays showed slow but significant clearing of pulmonary infiltrates over a period of four to six weeks. The complement fixation titers had dropped to 1:250. He was then switched to oral fluconazole at 400 mg once a day to complete a total course of nine months. The steroid therapy had been stopped by the end of the fourth week of hospitalization. The chest x-ray and the complement titers had returned to normal at the end of nine months of therapy and has since been discontinued without any evidence of recurrence. Follow-up two years later revealed no evidence of recurrence of the coccidioidomycosis.

DISCUSSION

During the last decade, disseminated and highly re-incident fungal infections have become a major cause of morbidity and mortality. Despite remarkable advances in detection and therapy, coccidioidomycosis remains a persistent threat to both immunocompromised and immunocompetent hosts[4]. As mentioned previously, pregnant women, immunocompromised hosts, and people of Filipino, African, Hispanic, or Asian ancestry are at greater risk for disseminated coccidioidomycosis[4].

Since the mid-1960s amB has been the drug of choice for systemic fungal infections due to its broad activity against a wide spectrum of life-threatening and invasive mycoses. However, the clinical use of amB is limited due to infusion-related therapy (hyperpyrexia, hypotension) and nephrotoxicity[7]. AmB is a polyene macrolide, which acts by binding to ergosterol in the fungal cell membrane, leading to formation of pores. This, in turn, causes a disruption of the fungal cell membrane and thereby cell death[16]. Despite the effective nature of this drug, its use has been limited due to the toxic side effects. Consequently, use of amB is often a compromise between efficacy and toxicity.

Recent advances in drug delivery technology have led to the development of amB-lipid formulations. New lipid-based formulations include: amB colloidal dispersion (ABCD), amB lipid complex (ABLC), and liposomal amB (AmBisome®). All these lipid-based formulations contain amB but differ in shape, size, reticuloendothelial clearance, and visceral diffusion. AmBisome®, the only true liposome, consists of amB intercalated in a liposomal membrane[9,10]. Liposomes are closed spherical vesicles formed as a result of mixing phospholipids and cholesterol arranged in concentric bilayer membranes when hydrated in aqueous solutions. The encapsulated amphotericin leads to decreased nephrotoxicity, fever, chills, hypokalemia, and cardiorespiratory events, such as hypertension[8,16]. Because of its small size and its ability to incorporate cholesterol, AmBisome® is also associated with a lower plasma clearance rate[16,17]. In addition, several studies consistently showed that AmBisome® effectively targets fungal cells inhibiting in vivo replication of a wide variety of fungi[9]. Since the advent of liposomal amB, patients who have severe disseminated infections can be treated fairly aggressively with high doses of amphotericin without any significant sequelae of renal or liver dysfunction[7].

Several studies have been published on the use of liposomal amB in the treatment of neutropenia, disseminated aspergillosis, cryptococcal meningitis, and candidiasis[11-15,18]. These studies demonstrated that liposomal amB is as effective as conventional amphotericin but is associated with fewer side effects. Salvage therapy for zygomycosis has been demonstrated in one patient.

To our knowledge, so far there have been no published studies demonstrating the use of liposomal amB in the treatment of disseminated coccidioidomycosis. This paper, therefore, presents several interesting points in the use of liposomal amB, which still need definitive answers: 1) Total dose needed to treat disseminated coccidioidomycosis, 2) use of this drug intrathecally versus systemically in CNS coccidioidomycosis, 3) Treatment of coccidioidomycosis in AIDS patients or patients with hepatic dysfunction 4) Combined treatment for other unusual and/or resistant fungal infections needing a combination of an azole and amB.

In conclusion, we present a case of disseminated coccidioidomycosis successfully treated with liposomal amB with no evidence of relapse. Our findings concur with the literature in that AmBisome® is as effective as conventional amB deoxycholate but without the adverse effects. Further studies need to be done to assess the exact duration of treatment, optimal dosing of liposomal amB, and the use of combination therapy in patients with significant disease. New drugs, such as voriconazole and caspofungin, are now available, and there is some limited in vitro and in vivo data on its use in coccidioidomycosis and other rare fungi[19]. It appears that lipid-based formulations of amB—although a much more expensive drug—may prove to be an alternative and safe treatment for coccidioidomycosis, if conventional amphotericin or the azoles cannot be utilized.

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