Effectiveness of Amphotericin B in Lipid Emulsion for Treating Fungal Septicemia in Granulocytopenic Patients

SIR—Liposomal formulations of amphotericin B (AmB) have been shown to have fewer toxic effects than do classic preparations (such as AmB deoxycholate), yet they have equivalent antifungal activity [1, 2]. Recently, it has been reported that AmB liposomal emulsion (AmBLE [Intralipid 20%]) reduces renal and infusion-related toxicity. When AmBLE has been used to treat mild fungal infections, reduced toxicity and efficacy similar to that of conventional preparations have been observed [3]. However, no data are available concerning the effectiveness of AmBLE in treating severe fungal infections. We report three cases of fungal septicemia in profoundly granulocytopenic patients who were successfully treated with AmBLE.

Case 1. A 9-year-old girl was admitted to the hospital for administration of a second cycle of salvage chemotherapy after a first relapse of non-Hodgkin's lymphoma. Seven days after chemotherapy was started, the patient had fever (temperature of 39°C) and hypotension, and her clinical condition had deteriorated. Findings on chest roentgenograms were normal. Progressive reduction in the total number of blood leukocytes was noted. Samples of blood for culture were taken before empirical antibiotic therapy with ceftazidime plus vancomycin was started.

Fever persisted for 4 days despite antibiotic treatment. However, findings on physical examination and on a repeated roentgenogram were normal. AmBLE was empirically added to the treatment regimen (2-hour infusion schedule at a dose of 0.6 mg/[kg · d]. The patient had mild chills and fever during the infusion despite having previously received therapy with iv meperidine and difenidramine. She did not have signs of renal toxicity during AmBLE therapy.

After antifungal therapy was begun, the patient defervesced and her clinical condition improved. Ten cultures of blood samples taken from a Hickman catheter and from a peripheral vein during the septicemic episode yielded *Candida tropicalis*. Because a quantitative method of culture was not available, we could not exclude the possibility that the septicemia was catheter-related. The Hickman catheter was removed and treatment with AmBLE was continued until the patient had received a total dose of 12 mg/kg.

The patient's clinical condition improved significantly. Findings on control tomograms of the thorax and abdomen and echocardiograms were normal. Culture of CSF and urine samples did not yield any organisms. The patient received one more cycle of salvage chemotherapy, and she underwent autologous bone marrow transplantation. She was well at a follow-up visit 11 months later.

Case 2. A 2-year-old boy with lymphoblastic leukemia who was in a second remission was admitted to the Bone Marrow Transplant Unit at our institution to receive a transplant of bone marrow from his HLA–identical brother. His conditioning regimen included total body irradiation and administration of cyclophosphamide and corticosteroids. Three days after the bone marrow infusion he developed fever and leukopenia (60 leukocytes/mm^3). Blood samples were taken for culture, and empirical antibiotic therapy with vancomycin plus ceftazidime was initiated. Because fever persisted after 2 days of therapy, AmBLE was administered (0.6 mg/[kg · d]); iv difenidramine was administered before infusion of AmBLE. He did not have side effects or evidence of renal toxicity.

Fever resolved after antifungal therapy was started. Cultures of three blood samples that were collected during the febrile episode yielded *Candida albicans*. No abnormalities were seen on echocardiograms or on computed tomograms of the thorax and abdomen. Cultures of CSF and urine did not yield any organisms. Treatment with AmBLE was continued until the patient had received a total dose of 10 mg/kg. The Hickman catheter was not removed. Control blood cultures remained negative for *Candida* species during the follow-up period. The patient was well at a follow-up visit 13 months later.

Case 3. A 65-year-old man with refractory non-Hodgkin's lymphoma was admitted to the hospital for administration of his first cycle of salvage chemotherapy. Ten days after treatment was begun he developed a fever, hypotension, and leukopenia (600 leukocytes/mm^3). Findings on chest roentgenograms were normal. Samples of blood were taken for culture. Empirical therapy with vancomycin plus ceftazidime was started, but fever persisted. Cultures of blood collected from an iv catheter and a peripheral vein yielded *Candida parapsilosis*. Therapy with AmBLE (0.6 mg/[kg · d]) was administered until the patient had received a total dose of 6 mg/kg. The patient defervesced, and his clinical condition improved. However, cultures of blood collected from the catheter remained positive for *C. parapsilosis*, which prompted us to remove the catheter.

No abnormalities were found on computed tomograms of the thorax and abdomen or on echocardiograms. Cultures of CSF, urine, and blood did not yield *Candida* species. Although the patient's infectious episode clinically resolved, he did not respond to salvage chemotherapy and died of progressive non-Hodgkin's lymphoma 5 months after the septic episode.

The findings of our report suggest that AmBLE is an effective treatment for fungal septicemia in severely granulocytopenic patients. The antifungal activity of AB deoxycholate and AmBLE has been shown to be similar in rabbits [4]. AmBLE has also been shown to be a safe and cost-effective treatment for oral candidiasis in patients infected with the human immunodeficiency virus [3].

AmB remains the standard treatment for severe fungal infections. However, its usefulness has been limited by its toxicity [1,2]. The exact mechanism by which the toxicity of AmB is reduced when it is in the form of AmBLE is not well understood; however, the fact that total body clearance is possible with AmBLE, which diffuses more readily than does AmB deoxycholate, may explain this effect. Moreover, lower serum levels of AmB have been found after infusion of AmBLE than after treatment with classic preparations of AmB [5, 6]. The increased tissue distribution of AmBLE may result in higher intracellular concentrations, which enhance antifungal activity.

Infusion-related toxicity could not be evaluated in the above

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