Use of Intralipid as a Vehicle for Amphotericin B in the Treatment of Cryptococcal Meningitis in a Renal Transplant Recipient

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Dear Sir,

Cryptococcosis is an uncommon opportunistic infection which may occur in renal transplant recipients. Amphotericin B, the treatment of choice for cryptococcosis, is invariably nephrotoxic, and in an attempt to reduce this nephrotoxicity, a liposomal form of the drug has been developed [1-3]. Recently amphotericin administered mixed with intralipid has also been shown to reduce the nephrotoxicity [4]. We describe a patient who developed cryptococcal meningitis shortly after kidney transplantation and demonstrate the effectiveness of the amphotericin B-intralipid mixture in treating this infection.

A 34-year-old man underwent a cadaver kidney transplant for end-stage renal failure due to chronic glomerulonephritis. Prior to the transplant he had been on maintenance haemodialysis for a period of 3 months. Preoperatively his HIV antibody status was negative, and a chest radiograph revealed no abnormalities. The immunosuppression protocol consisted of ciclosporin (10 mg/kg/day), azathioprine (2 mg/kg/day), and prednisone (30 mg/day). The postoperative course was complicated by acute tubular necrosis, and the patient required haemodialysis on two occasions. The graft function improved after the 5th postoperative day. The urine output increased daily, and the serum creatinine concentration fell as the acute tubular necrosis resolved. The patient did not experience any rejection episodes and, therefore, did not receive any bolus intravenous doses of steroids. On the 14th posttransplant day the patient became pyrexial with a leucocytosis of 14,000. Urine cultures and chest radiograph were normal. On the 19th postoperative day he was mildly confused, and a lumbar puncture was performed. The opening pressure was elevated at 21 cm water. There were no cells in the cerebrospinal fluid, and the biochemistry was normal, but encapsulated yeasts were demonstrated on Indian ink staining. The cryptococcal antigen titre in the cerebrospinal fluid was 1:8. A blood culture was positive for cryptococcus, and the cryptococcal antigen titre in the blood was 1:8,000. A computerized tomography scan of the head showed no abnormalities. His renal function showed urea 16 mmol/l and creatinine 338 µmol/l with a creatinine clearance of 15 ml/min. The patient was commenced on flucytosine (dosage adjusted according to blood concentrations) and amphotericin B. In an attempt to reduce the nephrotoxicity, amphotericin B was mixed in 250 ml
of intralipid and administered daily at a dose of 0.6 mg/kg/day via a peripheral line over a period of 6 h. Immunosuppression therapy was maintained.

The patient became apyrexial 48 h after starting treatment, and there was an associated improvement in his mental state. The cerebrospinal fluid cryptococcal antigen titre was undetectable 7 days after commencing treatment. The HIV antibody status remained negative. Measurement of the urinary chemistry parameters after 2 weeks on treatment showed an improvement in his creatinine clearance from 31 to 81 ml/min. Urinary β2-microglobulin and total protein concentration remained unchanged, but urinary potassium increased from 85 to 150 mmol/l on a fixed diet. The urine volumes increased to 3-4.5 litres daily. Both potassium and magnesium required supplementation. The patient recovered well and was discharged after 4 weeks of treatment. The serum creatinine level was 88 µmol/l and the clearance 86 ml/min.

Cryptococcosis is an uncommon opportunistic infection which carries a significant morbidity and mortality in renal transplant patients. The reported prevalence rate is approximately 3.6% and it is associated with an overall mortality of 31% [5]. Cryptococcal infection usually manifests after several months of immunosuppression. Shaariah et al. [5] found that the mean period on immunosuppression prior to infection occurring in renal transplant patients was 48 months. The case presented is, therefore, unusual in that the presentation was so soon after transplantation. This would suggest that the patient already had a cryptococcal focus (presumably pulmonary in origin).

The treatment of cryptococcal infections is also associated with significant morbidity as a result of deterioration in renal allograft function attributed to amphotericin. The incorporation of amphotericin into liposomes has been shown to reduce the renal toxicity, allowing larger doses to be administered and thereby increasing its efficacy in both experimental and clinical studies [1-3]. These formulations are now commercially available (AmBisome from Vestar), but are expensive.

Experimentally, a delivery system of deoxycholate amphotericin B emulsified in 20% intralipid (Kabi), a fat emulsion used for total parenteral nutrition, was found to be more effective than deoxycholate amphotericin B dissolved in glucose in the treatment of systemic cryptococcosis in mice [6]. Moreau et al. [4] have shown that amphotericin B mixed with intralipid improves its clinical tolerance as well as reducing nephrotoxicity in humans. In this case we achieved an excellent clinical response with double the recommended dose of amphotericin B (0.6 mg/kg/day) despite the patient having severely impaired renal function. There was, however, evidence of some renal tubular toxicity which was manifested by increased urinary volumes, a potassium leak, and hypomagnesaemia requiring supplementation. However, the creatinine clearance increased during treatment.

The use of lipid vehicles to administer poorly water-soluble drugs is not a new concept. Patients who are unable to be treated with conventional amphotericin B due to renal toxicity can safely tolerate amphotericin B in lipid vehicles. Furthermore, improvement of the renal function is possible despite a prolonged course of treatment [7]. Deoxycholate amphotericin B mixed with intralipid is an effective and easily ad-ministrable method of treatment which to a large extent abrogates the renal toxicity usually associated with this drug.
References


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Cryptococcal Meningitis Treatment in Renal Transplantation Recipient