Anaphylaxis due to liposomal amphotericin (AmBisome)

As patients with AIDS are living longer, increasing numbers are developing systemic infections with Cryptococcus neoformans necessitating intravenous amphotericin therapy.

Liposomal amphotericin B (AmBisome) is a recently introduced preparation and is claimed to be less commonly associated with adverse effects than conventional amphotericin B. It is therefore a reasonable alternative to use in patients with systemic fungal infection where conventional amphotericin B has been previously associated with renal toxicity.

Two cases of anaphylaxis due to liposomal amphotericin in patients who were not allergic to amphotericin have recently been described. We report a further case of anaphylaxis occurring in a patient being given his first injection of AmBisome for treatment of cryptococcal meningitis.

A 28 year old male patient who had been diagnosed HIV positive 9 years previously was admitted with a week's history of headache, photophobia and vomiting. Cryptococcal meningitis had been successfully treated 9 months previously with conventional intravenous amphotericin B. Subsequently, the patient was maintained on fluconazole but relapsed six months later. Initially, this was treated with intravenous amphotericin B. However, signs of renal toxicity, as shown by rising creatinine and urea, developed after two days and fluconazole was substituted. The patient recovered and again was maintained on fluconazole. After a further month this was changed to itraconazole because of nausea due to fluconazole.

On admission, medication included dapsone 50mg daily, pyrimethamine 50mg weekly, and itraconazole 400mg daily. CT of the brain was normal and examination of CSF showed 22 white blood cells/mm³ (the majority were lymphocytes) and two yeast cells. Both CSF and serum were positive for cryptococcal antigen. Relapse of cryptococcal meningitis was diagnosed and intravenous liposomal amphotericin B (AmBisome) at a dose of 1 mg/kg was commenced. Within seconds of starting the infusion the patient vomited and complained of epigastric pain and abdominal tightness. Bronchospasm, facial flushing and sweating were noted. The infusion was immediately discontinued and symptoms settled within 4 hours. Subsequent treatment comprised of fluconazole and itraconazole and the patient made an uneventful recovery.

It is well recognised that HIV positive patients have a higher incidence of adverse drug reactions compared with the general population and these cases further highlight the need for care to be taken when giving medication to this group of patients.

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Pre-treatment with hydration and electrolytes may prevent dose limiting toxicities during foscarnet induction therapy

Foscarnet (Foscavir, Astra Pharmaceuticals) has been used for the treatment of
cytomegalovirus (CMV) retinitis infection in acquired immunodeficiency syndrome (AIDS). However, the use of foscarnet is not without deleterious effects. In using foscarnet, the most frequently reported adverse events with electrolytes during five US controlled clinical trials were, (regardless of severity or relationship to foscavir), hypokalaemia (16%), hypocalcaemia (15%), hypomagnesaemia (15%) and seizures (10%). If left untreated depletion of these electrolytes result in neurological, cardiovascular and musculoskeletal sequelae.

Derey et al demonstrated, that adequate hydration prior to foscarnet infusion could negate nephrotoxicity almost completely. The electrolyte imbalances with foscarnet therapy are more complex. Concomitant replacement of electrolytes consisting of calcium, potassium, magnesium and phosphate could prevent potentially life threatening conditions. However, pre-treatment has not been reported before. As there are no definite guidelines on the doses of electrolytes to be used in pre-treatment, we conducted a non randomised, open label study on eight patients receiving induction therapy with foscarnet for CMV retinitis. The aim of the study was to assess the safety of pre-treatment with electrolytes, and to evaluate its effects on the dose-limiting electrolyte abnormalities seen with foscarnet induction therapy. The doses of electrolytes selected were based upon our previous experience with electrolyte replacement used in patients treated with foscarnet.

Eight patients with CMV retinitis needing foscarnet therapy were prospectively evaluated. All patients were infused with foscarnet 90 mg/kg every 12 hours for 2 weeks. The patients were hydrated with 2 l of 0-9% saline a day and received 1 g of MgSO₄ and 24 mMol of K₃PO₄ each day IV, and calcium carbonate 1 g PO each day for the first week. In the second week the K₃PO₄ was changed to KCl 20 meq/day. Patients on intravenous hyper-alimentation received similar replacements. Serum electrolytes were measured before foscarnet induction therapy, followed by twice a week during the induction period, and after completing induction therapy (table). All patients tolerated the therapy well and there were no dose limiting electrolyte abnormalities.

Foscarnet is effective against CMV and most other herpes viruses. It is also known to demonstrate some activity against human immunodeficiency virus type 1 (HIV-1). Most physicians treating CMV may be reluctant to use foscarnet because of the electrolyte abnormalities, and the resultant sequelae. The present observational study suggests, that electrolytes may be safely administered with induction doses of foscarnet, before electrolyte abnormalities occur, and may prevent dose limiting toxicities. Studies are presently underway to determine if the oral route may be substituted for intravenous, for hydration and electrolyte replacement.

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2 Foscarnet package insert.

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