Nephrotoxicity of Amphotericin B Desoxycholate

Sir—We read with great interest the study of Bates et al. [1], which assessed the mortality and financial cost of acute renal failure associated with use of amphotericin B desoxycholate at a single tertiary-care hospital. Among 707 adults admitted to the hospital and given parenteral amphotericin B therapy, 30% had acute renal failure. For patients with acute renal failure, the mortality rate was significantly higher, the hospital stay was 8.2 days longer, and the total cost of treatment was $30,000 greater than for the patients who did not have renal failure. These findings offer important points for discussion in the debate about whether new antifungal drugs should be used as alternatives to inexpensive treatment with conventional amphotericin B. The first, obvious observation would be that any antifungal agent that reduces the frequency of severe complications may be more expensive but still cost-effective.

We report our experience with the use of amphotericin B at our hematologic center during 1996–2000. During this period lipid formulations of the drug were available at the hospital pharmacy. All hospitalized patients received iv hydration that contained at least 1 L of 0.9% saline daily during the whole period of amphotericin B treatment. Ambulatory patients received 1 L of 0.9% saline administered iv during 1.5 h before receipt of amphotericin B. The drug was administered over 2 h at a dosage of 1 mg/kg/day (higher dosages were given only occasionally). In the event of infusion-related side effects, premedication with steroids, acetaminophen, antihistamines, and/or meperidine was administered. Serum electrolyte concentrations, biochemical parameters of renal function, and fluid balance were monitored frequently. Electrolyte supplements sodium, potassium, magnesium, calcium, and phosphorus) were administered as clinically indicated on the basis of laboratory test findings. Amphotericin B was replaced with a lipid formulation of the drug (usually liposomal amphotericin B) in the event of acute renal failure, which was defined by serum creatinine level that increased 50% from the baseline level and peaked at >2.0 mg/dL for 2 consecutive days.

During the 5-year study, 235 patients received amphotericin B treatment. The average total amphotericin B dose received by the patients was 980 mg (range, 50–2800 mg). The average total duration of administration was 14 days (range, 1–55 days). Twenty patients (8.5%) had acute renal failure that required amphotericin B to be discontinued and replaced with a lipid formulation of the drug. For another 3 patients, amphotericin B was replaced with liposomal amphotericin B because of severe infusion-related side effects. Creatinine levels decreased after discontinuation of amphotericin B in all cases, and no patient underwent dialysis.

The frequency of acute renal failure during conventional amphotericin B treatment was minimal compared with that reported by other centers. However, there has been a wide range in the incidence of amphotericin B–associated acute renal failure reported in the literature [1–6]. The occurrence of side effects of amphotericin B therapy could be influenced by several factors: the selection of the patient population, the underlying clinical conditions of the patients, the characteristics of the fungal infection, and the use of concomitant drugs, which could account for the varying frequency of nephrotoxicity in the various studies. However, there is some evidence that the schedule of administration of the drug may be very important for the prevention and/or management of nephrotoxicity. Salt depletion during amphotericin B treatment has been shown to be associated with renal accumulation of the drug and with histopathologic evidence of patchy degradation of the tubular cytoplasm in animal models [7]. It has been reported that a safe and effective means of reducing the risk of amphotericin B nephrotoxicity—and reversing it—is administration of supplemental sodium chloride (by means of iv saline) and avoidance of dehydration [6–9].

However, despite this experimental and clinical evidence, most studies that have either evaluated amphotericin B toxicity or compared amphotericin B with other antifungal drugs have not considered the possible role of salt depletion in the development of acute renal failure; in addition, information on sodium supplementation has not been available [1–4]. To our knowledge, a schedule of amphotericin B administration that includes specific indications for hydration and electrolyte supplementation has not been standardized. We think that there is a risk that the safety of conventional amphotericin B, which continues to be the “gold standard” among antifungal drugs, will be inadequately investigated, compared with that of other drugs. In our opinion, prospective clinical trials are needed that focus on the improvement and the standardization of all procedures that can reduce the severe side effects of amphotericin B.
Two Distinct Patterns of Central Nervous System Complications Due to Mycoplasma pneumoniae Infection

Str—We read with great interest the article by Soćan et al. [1] that appeared in a recent issue of the journal (electronic edition only). The authors described 13 patients with CNS complications due to Mycoplasma pneumoniae infection. Of these 13 patients, 9 had CSF samples that were positive for M. pneumoniae by culture and all 13 had CSF samples positive for M. pneumoniae by PCR. Most strikingly, the CSF samples from the 8 patients who had acute-onset CNS infection soon after respiratory symptoms appeared were all positive by culture, which was in sharp contrast to the finding that culture results were positive for only 1 of the 5 patients whose neurological symptoms began gradually and lasted longer. (However, the authors did not mention the exact number of days from the onset of respiratory symptoms to the onset of CNS infection.) This finding is quite important with respect to the etiology of CNS complications due to M. pneumoniae infection and is fairly consistent with our previous PCR findings [2], to which, unfortunately, Soćan and colleagues did not refer.

In our study, using PCR, we detected M. pneumoniae DNA in CSF samples at a significantly higher rate for patients with early-onset encephalitis (defined as onset of CNS disease ≤7 days after the onset of fever) than for patients with late-onset encephalitis (defined as onset of CNS disease ≥8 days after the onset of fever) [2]. Recent reports from institutions other than ours have also supported this finding—describing both early-onset, PCR-positive cases [3–5] and late-onset, PCR-negative cases [6].

On the basis of these findings and those of Soćan et al. [1], it seems clear that there are 2 distinct patterns of CNS complications due to M. pneumoniae infection: early-onset encephalitis, in which the presence of the organism (which must be viable?) in the CNS is a prerequisite for the development of disease, and late-onset encephalitis, in which the presence of the organism in the CNS might not be essential when the disease occurs. We believe that Soćan and colleagues should have discussed this matter. In this context, it is rather unexpected that the CSF samples from the 4 patients with possible late-onset encephalitis were negative for M. pneumoniae by culture but still were positive by PCR. The authors also should have mentioned the sensitivity of the PCR system they used.

In addition, the route of invasion of the CNS by M. pneumoniae is a matter of concern. We have also reported that, when using PCR, hematogenous dissemination is possible [7]. It would be interesting to know whether Soćan and colleagues tested or will test serum samples from patients with CNS complications.

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References