The Solubility Ceiling: A Rationale for Continuous Infusion Amphotericin B Therapy?

Sir—We read with interest the recent open-label study by Imhof et al. [1] reporting the tolerability of high-dose amphotericin B (AmB deoxycholate (AmB-d)) administered by continuous infusion. Similar to previous reports [2, 3], continuously infused AmB-d was found to result in a lower rate of nephrotoxicity and fewer infusion-related reactions than did a 4-h infusion of AmB-d at the same daily dose. Despite these promising findings, the practice of administering AmB-d by continuous infusion has not been widely adopted by clinicians for 3 reasons: (1) comparative data supporting the efficacy of continuously infused AmB-d are still limited; (2) dedication of venous access solely to the administration of AmB-d is often unfeasible, especially in critically ill patients; and (3) the concentration-dependent pharmacodynamic characteristics of AmB suggest that less-frequently administered, higher daily doses would be more active than the same daily dose of AmB-d administered by continuous infusion [4, 5].

As pointed out in the accompanying editorial by Hiemenz [6], comparative clinical trials involving humans have provided little clear-cut evidence of a steep dose-response curve for AmB, despite there being previous descriptions of concentration-dependent pharmacodynamics in vitro and in vivo [4, 5, 7]. The unusual biopharmaceutical properties of AmB may explain this discrepancy. AmB exhibits nonlinear, concentration-dependent binding to proteins in serum and tissue [8, 9]. Unlike most drugs, for which the percentage of bound drug decreases with saturation of protein binding sites, AmB protein binding in plasma increases with increasing drug concentrations, from ~95% bound at 0.6 µg/mL to >99% bound at 65 µg/mL [8]. This unique pattern of protein binding is probably a result of the drug’s “amphoteric” properties (i.e., poor solubility at a neutral pH) [8]. Therefore, higher dosages of AmB-d are unlikely to increase the fraction of microbiologically active AmB in plasma or tissue once this solubility threshold is reached.

So what is the solubility threshold of AmB in humans? Using ultrafiltration and equilibrium dialysis, Bekersky et al. [8] estimated that the maximum free-drug solubility of unbound AmB in human plasma was <1 µg/mL. When AmB-d was added at higher concentrations, unbound concentrations of AmB did not substantially increase. In tissue, a similar pattern of protein or lipid binding seems to occur. Colette et al. [10] examined the tissue concentrations, bioactivity, and tissue fungicidal/fungistatic titers of organ specimens recovered from patients with cancer who had received AMB-d therapy. Although high concentrations of AmB were measured by high-performance liquid chromatography (HPLC) in the liver, spleen, and lung (mean concentration, 27.5, 5.2, and 3.2 µg/mL, respectively), AmB concentrations measured by bioassay were, on average, <20% of concurrent concentrations measured by HPLC. Of interest, the highest relative fraction of bioactive AmB was found in the kidney (>40%). None of the organ homogenates demonstrated fungicidal activity against Candida albicans or Aspergillus fumigatus. In a similar study, Christiansen et al. [9] documented high AmB concentrations in the liver, spleen and lungs of patients with cancer who had received AmB-d therapy. Viable Candida and Aspergillus isolates (MIC, <0.4 µg/mL) could be recovered, despite organ-tissue concentrations of 2.5–166 µg of AmB per gram of tissue [9]. If only a small and saturable proportion of AmB is bioavailable in tissue, than dosage escalation with either conventional or lipid formulations of AmB would seem to have limited benefit for patients for whom AmB regimens are failing. However, higher dosages could still be beneficial in anatomical sites in which AmB penetration/saturation is limited (e.g., the brain, the heart, and the vitreous humor).

Figure 1. Model of protein-bound (shaded) and free (unbound) fraction of amphotericin B (AmB) concentrations in plasma after a 4-h infusion (A) or continuous infusion (B). Arrows represent binding and/or distribution equilibrium. RES, cells of the reticular endothelial system.
Changes in protein binding can significantly alter the distribution and elimination of drugs in humans. Dose-dependent alterations in protein binding and distribution of AmB may explain why nephrotoxicity has less frequently been observed among patients who received AmB-d by continuous infusion. On the basis of the analysis by Bekersky et al. [8] and available pharmacokinetic data [11, 12], 4-h infusions may produce a larger fraction of protein-bound AmB per daily dose than does a continuous infusion (figure 1). This could result in more rapid and extensive distribution of AmB to deep-tissue sites, such as the kidney, resulting in higher rates of clinically observed nephrotoxicity.

Clearly, comparative pharmacokinetic and tissue distribution studies of rapidly versus continuously infused AmB would be necessary to explain the differences in toxicity observed between the 2 dosing strategies. As less-toxic, effective alternatives to AmB-based therapy are introduced, the likelihood of such an extensive pharmacokinetic trial being completed is diminishing. We hope that the pharmacodynamics of these newer agents will prove to be less enigmatic than those of AmB-d.

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References