O-12	LIPID-BASED AMPHOTERICIN B PREPARATIONS in CLINICAL PRACTICE

Jayesh Mehta

Amphotericin B is the drug of choice for the treatment of most fungal infections. However, conventional amphotericin B (CAB) results in systemic infusion-related adverse reactions and dose-dependent nephrotoxicity. Lipid dispersion of amphotericin attenuates its toxic effects on the mammalian cell membrane without impairing it's effect on the fungal cell membrane.

The three lipid preparations available currently, amphotericin B lipid complex (ABLC, Abelcet, The Liposome Company), amphotericin B colloid dispersion (ABCD, Amphotec, Sequus) and liposomal amphotericin (AmBisome, NeXstar) differ from one another significantly in their molecular structure because of differing lipid constituents (1).

The most important physical difference between these is their size with Abelcet being the largest and AmBisome being the smallest (Table 1). The most important chemical difference between them is that cholesterol, a highly stable molecule to which amphotericin binds avidly, is a constituent of AmBisome, Amphotec and CAB, but not of Abelcet.

These differences may underlie pharmacokinetic differences amongst these preparations. The peak plasma concentrations of amphotericin are lower after Abelcet and Amphotec, and higher after AmBisome compared with the concentration seen after CAB. The liver concentrations of amphotericin achieved with all 3 preparations are higher than CAB with whereas the kidney concentrations are similar. The most interesting difference however is in the lung tissue amphotericin concentrations where Abelcet appears to be highly concentrated (Table 2) (1-4).

Uncontrolled clinical data suggest that each of these preparations is effective in the treatment of confirmed fungal infections. Abelcet has been compared prospectively with CAB in the treatment of a confirmed fungal infection (candidiasis) showing equal efficacy overall, significantly superior efficacy with multiple species infections, and a significantly better safety profile (1,5,6).

Nephrotoxicity with each is less than with CAB. Systemic adverse reactions are less with Abelcet and AmBisome compared to CAB. The incidence of infusion-related toxicity is considerably higher with Amphotec, and ex-

Table 1. Size of the currently available lipid-based amphotericin compounds

Formulation	Particle size	Relative size
Abelcet	2-5 μ (2000-5000 nm)	25-62.5X
Amphotec	122 nm (+/- 48 nm)	1-2X
AmBisome	80 nm	1

Table 2. Pharmacokinetic characteristics of the currently available lipid-based amphotericin compounds which may affect their efficacy against pulmonary fungal infections

Formulation	Lung concentration compared to conventional amphotericin
Abelcet	Higher
Amphotec	Similar
AmBisome	Similar

ceeded that seen with CAB in one blinded study (7). The incidence of nephrotoxicity and infusion-related toxicity is higher with Abelcet than with AmBisome in but not significant enough to result in higher treatment discontinuation rates with Abelcet (8,9) except in one study (10). The latter was a toxicity/safety study (10) with a relatively low threhold for discontinuing the study drug which may account for the differences. The incidence of hepatotoxicity is significantly higher with AmBisome than with Abelcet (8).

Abelcet and AmBisome have been compared to each other in three studies; two prospective (8,10) and one retrospective (9). The efficacy of Abelcet was better than AmBisome in two studies (8,9) (Statistically significant in one despite higher AmBisome doses (8)). The two drugs were comparable in the third, which was designed to evaluate safety rather than efficacy (10).

All three preparations are considerably more expensive than CAB with the cost of AmBisome being approximately double that of the other two. The choice of the preparation to use should be based on efficacy, toxicity which may impair treatment delivery, and cost.

The use of these preparations needs to be explored earlier in the course of the illness when the performance status and organ function have not been compromised significantly and there may be a chance of improving survival.

REFERENCES

1. Mehta J. Do variations in molecular structure affect the clinical efficacy and safety of lipid-based amphotericin B preparations? Leuk Res 1997;21:183-8.
2. Janoff AS, Perkins WR, Saleton SL, Swenson CE. Amphotericin B lipid complex (ABLC): A molecular rationale for the attenuation of amphotericin B related toxicities. J Liposome Res 1993;3:451-72.
3. Wasan KM, Vadiei K, Lopez-Berestein G, Luke DR. Pharmacokinetics, tissue distribution, and toxicity of free and liposomal amphotericin B in diabetic rats. J Infect Dis 1990;161:562-6.
4. Olsen SJ, Swerdel MR, Blue B, Clark JM, Bonner DP. Tissue distribution of amphotericin B lipid complex in laboratory animals. J Pharmacy Pharmacol 1991; 43:831-5.
5. Anaissie EJ, White M, Uzun O, et al. Amphotericin B lipid complex (ABLC) vs amphotericin B (AMB) for treatment of hematogenous and invasive candidiasis: A prospective, randomized, multicenter trial. Proceedings of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, April 1995, San Francisco, p.330 (Abstr LM21).
6. Luke RG, Boyle JA. Renal effects of amphotericin B lipid complex. Am J Kid Dis 1998;31:780-5.
7. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998;27:296-302.
8. Fleming R, Kantarjian H, Husni R, et al. Randomized study of two lipid formulations of amphotericin B in the treatment of suspected or documented fungal infections in patients with leukemia. Proceedings of the 9th Focus on Fungal Infections Meeting, March 1999, San Diego, CA.
9. Clark AD, McKendrick S, Tansey PJ, Franklin IM, Chopra R. A comparative analysis of lipid-complexed and liposomal amphotericin B preparations in haematological oncology. Br J Haematol 1998;103:198-204.
10. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis 2000;31:1155-63.