such life threatening infections, as systemic fungosis. In such patients, we have often used successfully, de-escalting standard doses of liposomal Amphotericin B (Ambisome®). This could be the reason behind compromised efficacy with the novel preparation in this study.

7. Also three of the authors of the current study are the manufacturers of this new molecule. So surely there would be a conflict of interest in reporting the results of this pilot study.
8. In our own experience of significant and severe fungal infections in immunocompetent and immunocompromized patients, the use of coventional Amphotericin B has been fraught with serious nephrotoxicity or adverse effects during administration of the drug, invariably forcing us to go back to standard liposomal Amphotericin B (Ambisome®).
9. As a small noncomparative phase 2 trial, these results do not provide any proof that this liposomal preparation of Amphotericin B is comparable in safety or efficacy to the currently available Amphotericin B products. Larger, controlled prospective trials in both children and adults, against a variety of clinically relevant fungal pathogens, comparing this agent to both Amphotericin B deoxycholate and the standard liposomal Amphotericin B product (Ambisome®) are needed in order to fully assess the relative merits of this new fungal formulation.

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REFERENCE

1. Kotwani RN, Bodhe PV, Kirodian BG, Mehta KP, Ali US, Kshirsagar NA. Treatment of neonatal candidiasis with Liposomal Amphotericin B CL-AMP-LRC-1). Phase II Study. Indian Pediatr 2003; 40: 545-550.

Reply

Our response to the letter is as follows:

1. In the liposomal amphotericin formulation, amphotericin (which is lipid soluble) is intercalated in the lipid which form the liposome. Aqueous phase is normal saline. There is no incompatibility(1).
2. LD50 of Ambisome is 175mg/kg and LD50 of Indian liposomal amphotericin is 14-17 mg/kg(2). However, LD50 values are from animal studies. Dose, efficacy and safety in clinical studies should be considered for comparing Ambsiome with Indian liposomal amphotericin.
3. The assessment criteria used and followed were as per the previous studies done(3-7), which were modified and were made more stringent. Accordingly, those babies who died before a week of therapy were considered non assessable. The incomplete treatment will not give complete clearing of fungal infection.
4. Our study clearly shows the efficacy of Indian liposomal amphotericin B against systemic Candida albicans infection in neonates, which is the most common fungal infection seen in NICUs. The liposomal preparation used is easy to use, can be given over one hour with no thrombophlebitis, has no nephrotoxicity, safe even in preterm, is less expensive

than the liposomal preparation currently available. It is difficult to get similar kind of comparison but larger comparative studies with other amphotericin B preparation and studies for efficacy against other Candida species and fungi need to be undertaken.

5. Anemia with fall in PCV is very common in sick premature neonates due to sepsis (bacterial or fungal), repeated blood collections and hypoactive bone marrow (Erythropoetin deficiency).

   Repeated blood transfusions is important supportive treatment even in those in whom liposomal amphotericin B was not given. Although twelve babies required blood transfusion it is not possible to say whether this was an adverse effect of the prepration used as all these babies were preterm and septic, which could have contributed to the fall in PCV and need for transfusions. Not a single baby showed a rise of creatinine above the baseline. Hypokalemia was the main significant side effect noted in five patients and required monitoring and therapy. In another study (unpublished) comparing plain amphotericin with Indian liposomal amphotericin, fall in Hb and blood transfusions given were comparable in plain amphotericin and liposomal amphotericin group.

6. Liposomal amphotericin B was used in sick, preterm neonates with immature kidneys, hence a cautious approach with initial small dose which also helped in detecting hypersensitivity reactions. Step up is from 0.1 mg/kg to 0.4 mg/kg and then 1 mg/kg is continued.

7. It is to be clarified that liposomal amphotericin was jointly developed by Department of Clinical Pharmacology, Seth G.S. Medical College and KEM Hospital, Parel, Mumbai 400 012 and Department of Biochemistry, University of Delhi South Campus, Benito juarez Road, New Delhi 110 021; with funding from Department of Biotechnology, Government of India, New Delhi. The study is carried out independently by neonatologist of B.J. Wadia Children's Hospital, Parel, Mumbai 400 012, who were involved in the drug administration, assessment as well as patients care. These investigators are the co-authors of this article. Therefore, there is no such conflict of interest.

8. We would like to know the reader's experience in sick preterm neonates with Candida albicans infections. We fully agree that conventional amphotericin B is fraught with the risks of nephrotoxicity and other adverse effects. The other available preparations such as "Ambisome" and the lipid preprations have less toxicity but are prohibitively expensive for the majority of patients. One of the advantages of L-AMP-LRC-1 is no need of reconstituting the drug and neutral charge.

9. One of the other comparative study with plain amphotericin and Indian liposomal amphotericin carried out in patients with systemic fungal infection showed that L-AMP-LRC-1 was better tolerated t han conventional amphotericin. Also, 100% complete response was observed in patients treated with LAMP-LRC-1 group compared to 82.35% response rate observed in patients treated with conventional amphotericin(8).

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REFERENCES

1. Ahmad I, Sarkar AK and Bachhawat BK. Effect of cholesterol in various liposomal compositions on the *in vivo* toxicity, therapeutic efficacy and tissue distribution of amphotericin B. Biotechnol Appl Biochem 1990; 12: 550-556.
2. Gokhale PC, Kotwani RN, Dange SY, Kshirsagar NA, Pandya SK. Preclinical and pharmaceutical testing of liposomal amphotericin B. Indian J Medical Research 1993; 98: 75-78.
3. Lopez-Brestein G, Fainstein V, Hopfer R, Mehta K, Sullivan MP, Keating M. Liposomal amhotericin B for the treatment of systemic fungal infections in patients with cancer: A preliminary study. J Infec Dis 1985; 151: 704-710.
4. Weber RS, Lopez-Berstein G, Houston TX. Treatment of Aspergillus sinusitis with Liposomal amphotericin B. Laryngoscope 1987; 97: 937-941.
5. Sculier JP, Coune A, Meunier F, Branssinae C, Laduron C, Hallaert C, *et al*. Pilot study of amphotericin B entrapped in sonicated liposomes in cancer patients with fungal infections. Eur J Cancer Clin Oncol 1988; 24: 527-538.
6. Lopez-Berestein G, Boldey GP, Fanistein V, Keating M. Franker LS, Zeluff B, *et al*. Treatment of systemic fungal infections with liposomal amphotericin B. Arch Intern Med 1989; 149: 2533-2536.
7. Coker RJ, Viviani M, Gazard BG, Bertrand DP, Pohle D, Murphy SM, *et al*. Treatment of cryptococcosis with liposomal amphotericin B (AmBisome) in 23 patients with AIDS. AIDS 1993; 7: 829-835.
8. Bodhe PV, Kotwani RN, Kirodian BG, Kshirsagar NA, Pandya SK. Open label, randomized, comparative Phase III safety and efficacy study with conventional amphotericin B and liposomal amphotericin B in patients with systemic fungal infection. JAPI 2002; 50: 662-670.