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Treatment of Neonatal Candidiasis with Liposomal Amphotericin B

I read with interest the recent paper(1) on the treatment of neonatal candidiasis with a novel liposomal formulation of amphotericin B. Though a cheap and effective antifungal has been the dream of every clinician, I would like to draw attention to some salient features of the study.

1. It is interesting to note that this formulation is delivered in a normal saline infusion. All Amphotericin B formulations, including the conventional deoxycholate and all currently available lipid formulations carry explicit precautions regarding incompatibility of Amphotericin B and saline solutions. How does this current preparation get around this incompatibility?
2. It should also be noted that LD 50 for Ambisome® is 175 mg/kg, a more accurate value than the <17.5 mg/kg cited in the article. This is a ten-fold greater value than that of the current liposomal preparation being described.
3. To claim a 100% response rate in the assessable cases fails to consider the fact that the patients who died or were otherwise non-evaluable could have had persisting fungal infections and in fact, may have been treatment failures. This is the rationale behind an intent-to-treat analysis, where all patients who receive atleast one dose of study drug treatment must be included in the efficacy analysis. Viewed in this way according to the results presented in *Table I* of the article, 13 of 23 patients treated had favourable outcomes, a response rate of 56.5%.
4. It should also be noted that all patients in this report had infections with Candida albicans. The other reports referenced included cases of non-albicans species of Candida as well, which are known to be more difficult to treat and many require longer courses of treatment. Thus, the response rate of treatment as well as the total doses of Amphotericin B needed to treat in this paper are not appropriately comparable to those reported in the references cited.
5. Too many patients in this study have required significant amount of blood transfusion. Authors do not mention whether that was due to ongoing sepsis or an adverse effect of the drug itself.
6. Step up doses (or inability to use an optimal dose) right from the begining may be deterimental to the outcome of

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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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