Does Lipid Emulsion Reduce Amphotericin B Nephrotoxicity? A Systematic Review and Meta-analysis

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This meta-analysis of 13 studies revealed that amphotericin B delivered as a locally prepared lipid emulsion or in liposomes reduced nephrotoxicity to a similar degree, by 18.4% (relative risk [RR], 0.40 [99% confidence interval, .25–.64]; n = 459) and 18.1% (RR, 0.48 [99% CI, .36–.64]); n = 1233), respectively.

Amphotericin B (AmB) is a polyenic antibiotic that was isolated in 1953 from Streptomyces nodosus and entered clinical use in the early 1960s [1]. AmB is still highly active in vitro and in vivo against many fungal species and most protozoa from the Leishmania genus [2]. Today, AmB is the drug of choice for treatment of patients with leishmaniasis who do not respond to antimonials [3]. Although its cellular toxicity is selective, use of AmB is associated with frequent and potentially serious adverse effects including infusion-related events (fever, chills, hypotension), metabolic disorders, cardiotoxicity and nephrotoxicity, and death [4]. The high rate of nephrotoxicity (30%–80%) has led to the development of AmB formulations in 3 different lipid bases: lipid complex, colloidal dispersion, and liposomal [5]. Although lower rates of nephrotoxicity are observed with each of these formulations than with conventional AmB, the cost of these agents is substantial, and access is limited in resource-limited settings. As a lower cost alternative to these formulations, AmB deoxycholate has been prepared in-house as an extemporaneous lipid emulsion (AmB-LE) for a number of years in many countries [6]. Although a number of clinical trials have compared the nephrotoxicity of AmB-LE to that of conventional AmB, most published trials have a small sample size and use different methods. This has generated conflicting results regarding the gain in safety achieved with use of these in house lipid emulsion preparations [4]. In this meta-analysis, we compared the rates of nephrotoxicity among patients who received AmB-LE versus rates among those who received liposomal AmB (AmB-LIP).

METHODS

This was a systematic review and meta-analysis of published randomized controlled clinical trials that compared conventional AmB in 5% dextrose (AmB-Dx) to either AmB-LE or AmB-LIP in the treatment of leishmaniasis or fungal infections. We performed 2 reviews: comparison I evaluated AmB-Dx versus AmB-LE, and comparison II evaluated AmB-Dx versus AmB-LIP.

Search Strategy

The search strategy was developed between June and July 2009 and performed in June 2011; there was no restriction on date or language. We searched LILACS, MEDLINE, SciSearch, SCOPUS, the Cochrane Central Register of Controlled Clinical Trials (issue 5, 2009), the Cochrane Infectious Diseases Group Specialized Register (June 2009), reference lists from published randomized clinical trials, and personal communication with authors. The search was divided into 2 parts. The first corresponded to the optimal search strategy for randomized clinical trials, and the second corresponded to the strategy to find studies related to specific clinical situations, using the following text words and medical subject headings: “amphotericin,” “lipid,” “intralipid,” “emulsion,” “fat,” “vesicular,” and “liposomal.” The syntax was adapted for each database consulted.

Inclusion Criteria and Quality Assessment

The studies were evaluated using Cochrane scale criteria for allocation concealment and external validity (defined by the characteristics of the participants, intervention, and outcomes) and then were assigned an “A,” “B,” “C,” or “D”. Clinical trials with scores of “A” or “B” (indicating that they were explicitly stated to be randomized) were included in the meta-analysis. The primary outcome was collected following the intention-to-treat analysis. The Jadad scale for quality was then applied to included studies [7].

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Statistical Analysis and Stratifications
Analysis was performed using the Metaview module of the software Review Manager from the Cochrane Collaboration [4, 8]. Risk ratios and 99% confidence intervals were calculated for dichotomous variables (fixed-effect or random-effects models were used, as appropriate), by Mantel-Haenszel analysis. For outcomes with a statistical difference, the absolute risk reduction (ARR) was calculated.

A funnel plot was generated to evaluate publication bias in comparisons with >5 trials. Heterogeneity was evaluated by visual inspection of the graphs and by the χ² test for homogeneity (significance level, 10%). Heterogeneity was explained by exploring the differences between doses or time of use for assessment of primary outcome, as well as by exploring the baseline serum creatinine levels. For data association, we used the fixed-effects model. In cases where the χ² statistic showed significant heterogeneity, we used the random-effects model.

To perform indirect comparison of AmB-EL and AmB-LIP, we compared the estimated ARR in nephrotoxicity revealed by the 2 meta-analyses.

Studies involving children were included because there was no evidence that the potential for nephrotoxicity among the formulations studied was different in children, compared with adults.

RESULTS

Eleven studies with 589 patients were included in comparison I. AmB-Dx was used in 287 patients, and 302 received AmB-LE. Nine clinical trials presented nephrotoxicity as a dichotomous variable.

Comparison II included 5 clinical trials with 1335 patients; 749 were in the AmB-LIP group, and 586 were in the AmB-Dx group. Five studies presented nephrotoxicity as a dichotomous variable. Entry criteria for each of the studies included in the meta-analysis included normal renal function at baseline. Thus, baseline renal function was homogeneous among the studies included.

Figure 1 presents the results of the 2 meta-analyses. The tables include only studies in which nephrotoxicity was described as dichotomous variable. Overall results of each comparison reveal that both lipid formulations exhibited a similar degree of reduction in the risk of nephrotoxicity.

DISCUSSION

This meta-analysis revealed that AmB-LIP and AmB-LE yielded similarly reduced risks of nephrotoxicity, compared with the risk associated with AmB-Dx. However, this result must be observed with caution. First, our conclusion is based on 2 separate comparisons that used AmB-Dx as the comparator; thus, our conclusion is based on indirect comparisons in the absence of any published studies that directly compared AmB-EL and AmB-LIP. Second, we studied an adverse effect that is highly dose dependent, and the doses of AmB-LIP used were 2–5-fold higher than those of AmB-EL. Additionally, the methodological quality of the studies included in comparison II (AmB-LIP vs AmB-Dx) was significantly better than that observed in comparison I (AmB-LE vs AmB-Dx), as assessed by Jadad scores (Figure 1). We were also challenged by the fact that the studies did not use the same definition of nephrotoxicity.

Another important limitation of this study was an inability to compare the efficacy of AmB-LIP to that of AmB-EL. Although we focused on nephrotoxicity, in each individual trial included in the meta-analysis, neither lipid formulation demonstrated significantly less treatment efficacy, compared with AmB-Dx. Similar or better treatment response rates were previously demonstrated by Johansen et al [4] in their meta-analysis of AmB preparations.

The risk of nephrotoxicity from conventional AmB-Dx and the reduction in this risk with lipid formulations of the compound are well-defined [9]. This meta-analysis suggests that administration of AmB in locally prepared lipid deliveries also offers reduction in nephrotoxicity of a magnitude that is similar to that observed with AmB-LIP. In view of the cost advantage of locally prepared AmB-LE preparations over those prepared commercially, this approach may be of benefit in locations where healthcare resources are limited. Although cost alone is not a valid argument against the use of a better drug formulation with less toxicity, if toxicities can be reduced and activity can be preserved at lower cost, the savings achieved can be applied to other medical needs in settings where healthcare resources are constrained.

Local formulation of the AmB-LE preparations studied in this meta-analysis requires only the conventional AmB drug-infusion preparation that is modified by admixture with a lipid emulsion. One drawback of this approach is that a consensus about a standard preparation protocol that ensures the proper admixture interaction and stability has not yet emerged. Although some have advocated preparing the emulsion simply by shaking the ingredients together by hand, this approach is difficult to standardize. Egito et al have proposed that a lack of standardization in formulation procedures contributes to the divergence in results observed in clinical trials of lipid emulsion preparations. They demonstrated that agitation of the mixture with a mechanical shaker (Vortex Genie 2, model G-560; Scientific Industries, Inc., Bohemia, NY) led to the incorporation of AmB into lipid micelles of lipid emulsion [10]. Indeed, the Barquist study (Figure 1), which had the most favorable results of from AmB-LE, used a Vortex shaker to prepare the lipid emulsion. In India, where leishmaniasis is highly endemic and AmB is routinely used, AmB-LE is already manufactured by a local company with low cost [3]. Indeed, on the basis of this meta-analysis, further head-to-head comparisons of standardized
Figure 1. Jadad quality assessment and meta-analysis of included studies with a dichotomous variable for nephrotoxicity. In the Jadad scale, levels 1–5 represent the quality level of the study, with level 5 indicating highest quality. Abbreviations: ARR, absolute risk reduction; CI, confidence interval; RR, relative risk. aTotal number of patients in the study. bNumber of patients with nephrotoxicity/no. of patients in the group.
Vortex-based preparations of AmB-LE with AmB-LIP would seem to be warranted.

Finally, another promising way to reduce the nephrotoxicity of conventional AmB that involves heating the product prior to use has been experimentally studied. This approach changes the molecular aggregation state of this formulation and has reduced toxicity in human cells [11] and nephrotoxicity in a rat model [12]. AmB remains a critically important drug for the treatment of serious fungal infections. Further efforts to extend its availability, particularly the availability of lower toxicity preparations in resource-limited settings, should remain an important research priority. In conclusion, with regard to nephrotoxicity, AmB-Dx incorporated into locally prepared lipid emulsion showed a safety profile similar to that obtained with commercial liposomal formulations.

Notes

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