ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1999, p. 1445–1448 Vol. 43, No. 6
0066-4804/99/$04.00+0

Comparison of the Toxicity of Amphotericin B in 5% Dextrose with That of Amphotericin B in Fat Emulsion in a Randomized Trial with Cancer Patients

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Received 2 December 1998/Returned for modification 3 February 1999/Accepted 6 April 1999

A multicentric randomized trial was undertaken to compare the toxicity of amphotericin B in 5% dextrose with that of amphotericin B in a fat emulsion (Intralipid) in cancer patients. Group 1 ($n = 33$) received amphotericin B diluted in 5% dextrose with premedication consisting of promethazine plus an antipyretic. Group 2 ($n = 28$) received amphotericin B diluted in 20% Intralipid without premedication. Amphotericin B was infused daily at a dose of 1 mg/kg of body weight over a 1-h period to members of both groups for empirical antifungal therapy (in neutropenic patients) or for the treatment of documented fungal infections. The majority of patients (80%) received empirical amphotericin B treatment. The two groups were comparable with regard to age, gender, underlying disease, and the following baseline characteristics: use of other nephrotoxic drugs and serum levels of potassium and creatinine. The median cumulative doses of amphotericin B were 240 mg in group 1 and 245 mg in group 2 ($P = 0.73$). Acute adverse events occurred in 88% of patients in group 1 and in 71% of those in group 2 ($P = 0.11$). Forty percent of the infusions in group 1 were associated with fever, compared to 23% in group 2 ($P < 0.0001$). In addition, patients in group 2 required less meperidine for the control of acute adverse events ($P = 0.008$), and fewer members of this group presented with hypokalemia ($P = 0.004$) or rigors ($P < 0.0001$). There was no difference in the proportions of patients with nephrotoxicity ($P = 0.44$). The success rates of empirical antifungal treatment were similar in the two groups ($P = 0.9$). Amphotericin B diluted in a lipid emulsion seems to be associated with a smaller number of acute adverse events and fewer cases of hypokalemia than amphotericin B diluted in 5% dextrose.

Amphotericin B is considered the drug of choice for the treatment of systemic fungal infections. However, the use of this drug is associated with frequent and potentially severe side effects, including infusion-related events such as fever, rigors, and hypotension, as well as metabolic derangements such as hypokalemia and nephrotoxicity (4). The frequency of occurrence of such events may be as high as 80% (7). Over the last decade, many efforts have been made to develop less-toxic formulations of amphotericin B, and currently there are three commercially available preparations: amphotericin B in liposomes (AmBisome), in a colloidal dispersion (Amphocil), and in a lipidic complex (Abelcet). Clinical experience with these preparations showed that adverse reactions and nephrotoxicity were significantly reduced and, in the case of amphotericin B in liposomes, infusion-related toxicity was also reduced (6). The major limitation of these preparations is their high cost.

Another type of amphotericin B preparation can be made by mixing amphotericin B deoxycholate with a fat emulsion usually employed for parenteral nutrition (Intralipid). The toxicity of this preparation has been evaluated in a few randomized studies of patients with AIDS (2, 8), neutropenic cancer patients (1, 12, 13, 15), and critically ill patients (17), with conflicting results. In this study, we compared the toxicity of amphotericin B in 5% dextrose plus premedication with that of amphotericin B in Intralipid without premedication as empirical antifungal therapy and in the treatment or secondary prophylaxis of systemic fungal infections in neutropenic patients.

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MATERIALS AND METHODS

Study population. This was a multicenter nonblinded randomized trial conducted at the University Hospitals of Universidade Federal do Rio de Janeiro and Universidade do Estado do Rio de Janeiro and at the Hospital do Câncer, National Cancer Institute, Rio de Janeiro, Brazil. The following persons were eligible: febrile neutropenic patients requiring empirical antifungal therapy (i.e., those exhibiting persistent fever despite the use of empirical antibiotic therapy) and cancer patients needing antifungal therapy for documented fungal infections or for secondary prophylaxis. The exclusion criteria were as follows: a previous history of serious reaction to amphotericin B; a serum creatinine level of ≥2.0 mg/dl; a serum potassium level of <2.5 mEq/liter; pregnancy or postnatal nursing; hyperlipidemia, pancreatitis, or a history of malignant ventricular arrhythmia; and a high probability of death in the first 48 to 72 h after enrollment. In addition, patients whose antifungal medication was discontinued in less than 4 days were excluded from the analysis. The study was approved by the scientific committees of all participating institutions.

Antifungal therapy. After signing an informed consent acknowledgment, each patient was randomly assigned to one of the following regimens: amphotericin B in 5% dextrose with premedication (group 1) and amphotericin B in Intralipid without premedication (group 2). Amphotericin B in 5% dextrose was prepared by diluting the amount of amphotericin B deoxycholate needed for each treatment in 5% glucose to attain a final concentration of 0.25 mg of amphotericin B/ml. Amphotericin B in fat emulsion was initially prepared by dissolving the amount of amphotericin B required in 10 ml of distilled water. This solution was then added to Intralipid at a proportion of 2 ml of 20% Intralipid per milligram of amphotericin B or 4 ml of 10% Intralipid per milligram of amphotericin B. The final solution was shaken and administered within 15 min of preparation. Regardless of the preparation type, amphotericin B was given daily as a 1-h infusion of 1 mg/kg of body weight, without filtration. For patients with documented fungal infections, the dose of amphotericin B could be increased to 1.5 mg/kg. Amphotericin B was infused into either a central or a peripheral vein. The premedication given to the patients assigned to group 1 consisted of acetaminophen (750 mg orally [p.o.], or 15 mg/kg for patients weighing ≤40 kg) or

TABLE 1. Baseline characteristics of patients

Characteristic	Value for:		*P*
	Group 1 ($n = 33$)	Group 2 ($n = 28$)	
Age, median (range)	19 (2–62)	17 (1–67)	0.85
Gender, male/female	23/10	15/13	0.19
Underlying disease			0.70
Acute leukemia	25	20	
Lymphoma	3	3	
Other	5	5	
Bone marrow transplant recipient	2	4	0.39
Use of amikacin	29	22	0.50
Cumulative dose of amikacin (g), median	8.1	8.3	0.84
Use of vancomycin	15	14	0.72
Cumulative dose of vancomycin (g), median	10	11	0.79
Use of oxacillin	12	6	0.17
Use of a diuretic	6	5	0.97
Use of amphotericin B			
Empirically	25	24	0.51
As therapy for fungal infection	8[a]	4[b]	
Baseline serum creatinine level (mg/dl), median (range)	0.7 (0.3–1.8)	0.7 (0.4–1.4)	0.55
Baseline serum potassium level (mEq/liter), median (range)	4.1 (2.6–5.2)	3.9 (2.7–5.3)	0.42
No. of doses of amphotericin B, median (range)	9 (4–20)	7.5 (4–32)	0.39
Cumulative dose of amphotericin B (mg), median (range)	240 (20–1,360)	245 (90–960)	0.73

[a] Candidemia (six), disseminated candidiasis, and *Aspergillus fumigatus* sinusitis.
[b] Candidemia (three) and *Rhodotorulla rubra* fungemia.

dipirone (500 mg p.o., or 15 mg/kg for those weighing 40 kg or less) plus promethazine (25 mg p.o. or intravenously (i.v.), or 0.5 mg/kg p.o. or i.v. for patients weighing ≤40 kg) or diphenidramine (1.5 mg/kg p.o.). No premedication was given to the patients in the Intralipid group. The infusion was interrupted in patients in both groups who presented with rigors and fever during the infusion, and if these manifestations did not resolve after 5 min, the patients were given meperidine (50 mg i.v., or 1 mg/kg for patients weighing ≤40 kg). The infusion was restarted as soon as the symptoms resolved. No potassium supplementation was given routinely.

Evaluation. Patients were hospitalized during therapy. A clinical evaluation of each patient was performed daily by one of the physicians responsible for the study, and any adverse event was recorded. Standard biochemical tests, including determination of levels of potassium, magnesium, creatinine, alanine and aspartate aminotransferases, alkaline phosphatase, amylase, and hemoglobin in serum, were performed at least twice per week. Creatinine clearance was determined before and after treatment. Patients were monitored for the occurrence of infusion-related side effects during each infusion and for 6 h afterward. The minimum period of evaluation was 4 days for infusion-related toxicity and 7 days for nephrotoxicity. The maximum period of evaluation was 14 days. The final evaluation was performed 1 week after the patient went off treatment.

Definitions of response and toxicity. Successful empirical antifungal therapy was defined as defervescence for at least four consecutive days after the start of amphotericin B treatment. Clinical resolution of the fungal infection was defined as no clinical or mycological evidence of active infection plus complete resolution of the symptoms attributed to the infection. Improvement was defined as a favorable evolution of the clinical signs and symptoms of infection without fulfillment of all criteria for clinical resolution. Toxicities attributed to amphotericin B were fever, rigors, hypokalemia, nephrotoxicity, and arrhythmia. The occurrence of dyspnea was also recorded. Fever related to the infusion of amphotericin B was defined as an axillary temperature above 38°C up to 6 h after the end of the infusion. Rigors were defined as chills with shaking during amphotericin B infusion, as documented by a physician or nurse. Nephrotoxicity was defined as a 50% or more decrease in creatinine clearance or at least a 0.5-mg/dl increase in serum creatinine from baseline levels. Hepatotoxicity was defined as at least a 1.5-fold increase in the aminotransferase levels above the baselines. Hypokalemia was defined as a >1-mEq/liter decrease in serum potassium from the baseline level without potassium supplementation (>0.5 mEq/liter with supplementation).

Statistics and sample size calculation. On the basis of previous studies (2, 3), we assumed that an absolute reduction in the frequency of adverse events of 40% was likely and would be clinically significant. Each group would have to comprise 28 patients for such a difference to be detected, with an alpha error of 0.05 and a beta error of 0.20. In comparing dichotomous variables, the *P* value (two tailed) was calculated by using Fisher's exact test or the chi-square test. In addition, the 95% confidence intervals (95% CIs) for the differences between proportions were calculated. For continuous variables, the *P* value was calculated by using the Wilcoxon method or Student's *t* test as deemed appropriate.

RESULTS

Clinical characteristics. Between February 1994 and November 1995, 72 patients were enrolled in the study. Eleven patients were excluded (seven patients in group 1 and four in group 2) for the following reasons: protocol violation (six patients) or <4-day duration of antifungal therapy (five patients). There were 61 evaluable patients, 33 in group 1 and 28 in group 2. There were 38 males and 28 females, with a median age of 17 years (range, 1 to 67). Amphotericin B was used for empirical antifungal therapy in 50 neutropenic patients (82%), in the treatment of documented systemic fungal infections in 10 patients, and as secondary prophylaxis in 1 patient. The fungal infections treated in group 1 were candidemia (six patients), disseminated candidiasis (one patient), and sinusitis due to *Aspergillus* sp. (one patient), whereas in group 2 the fungal infections were candidemia (three patients) and fungemia due to *Rhodotorulla rubra* (one patient). One patient in group 1 received amphotericin B as secondary prophylaxis for pulmonary aspergillosis. As shown in Table 1, there were no differences in the baseline characteristics of the two groups with regard to age, gender, underlying disease, reasons for the use of amphotericin B, use of concomitant nephrotoxic drugs, baseline serum potassium and creatinine levels, number of doses of amphotericin B, and cumulative dose of amphotericin B and other drugs that have the potential to be nephrotoxic (e.g., amikacin and vancomycin) or induce hypokalema (e.g., oxacillin and diuretics).

Toxicity. Table 2 shows a comparison of the toxicities for the two groups. Overall, acute adverse events (fever or rigors) occurred in 80% of the patients in the study, and the percentages for the two groups did not differ significantly (88% in group 1 and 71% in group 2; $P = 0.11$ and 95% CI = −4 to 37). Infusion-related fever occurred in 28 patients (85%) in group 1 and 19 (68%) in group 2 ($P = 0.11$; 95% CI, −4 to 38). Forty percent of the 310 infusions of amphotericin B in group 1 were associated with fever, compared to 23% of the 252 infusions in group 2 ($P < 0.0001$; 95% CI, 9 to 24). The median duration of

TABLE 2. Infusion-related events in patients receiving amphotericin B in 5% dextrose (group 1) or in Intralipid (group 2)

Event	Value for:		*P*	95% CI
	Group 1	Group 2		
Infusion-related fever				
No. of patients affected (%)	28/33 (85)	19/28 (68)	0.11	−4–38
No. of associated administrations of amphotericin B (%)	124/310 (40)	58/252 (23)	<0.0001	9–24
Median duration, days (range)	2 (0–14)	2 (0–7)	0.07	
Infusion-related rigors				
No. of associated administrations of amphotericin B (%)	102/310 (33)	15/252 (6)	<0.0001	21–33
Median duration, days (range)	2 (0–9)	0 (0–3)	0.004	
Administration of meperidine				
No. of patients receiving (%)	18/33 (54)	6/28 (21)	0.008	10–56
No. of administrations of amphotericin B requiring drug (%)	45/310 (14)	8/252 (3)	<0.0001	7–16
Hypotension, no. affected (%)	3/33 (9)	1/28 (4)	0.62	−6–17
Hypokalemia, no. affected (%)	19/33 (58)	6/28 (21)	0.004	13–59
Nephrotoxicity, no. affected (%)	7/22 (32)	4/19 (21)	0.44	−16–37
Difference between baseline and final concentrations of creatinine (mg/dl), mean	0.36	0.26	0.5	

fever for patients in group 1 was 2 days (range, 0 to 14 days); in group 2, the median duration of fever was also 2 days (range, 0 to 7 days) ($P = 0.07$). The presence of a central venous catheter did not influence the frequency of febrile events ($P = 0.35$). Rigors occurred during 33 and 6% of amphotericin B infusions in groups 1 and group 2, respectively ($P < 0.0001$; 95% CI, 21 to 33). The median duration of rigors was 2 days in group 1 (range, 0 to 9) and 0 days in group 2 (range, 0 to 3) ($P = 0.004$). As shown in Table 3, fever and rigors tended to resolve more quickly in group 2: at day 3, the proportion of patients in group 1 with fever was 45%, compared to 18% in group 2 ($P = 0.02$; 95% CI, 5 to 50), whereas the proportions of patients with rigors at day 3 were 39 and 7%, respectively ($P = 0.003$; 95% CI, 13 to 51).

Eighteen patients (54%) in group 1 needed meperidine to control infusion-related toxicity, compared to six patients (21%) in group 2 ($P = 0.008$; 95% CI, 10 to 56). The numbers of courses of amphotericin B that required the administration of meperidine were 45 (14%) in group 1 and 8 (3%) in group 2 ($P < 0.0001$; 95% CI, 7 to 16). Four patients developed hypotension during the infusion of amphotericin B, three in group 1 and one in group 2 ($P = 0.62$; 95% CI, −6 to 17). One patient in group 2 had an episode of arrhythmia during infusion. No patient developed any sign of respiratory distress during the infusion of amphotericin B, and in no case was drug administration discontinued because of an adverse event.

Hypokalemia also occurred less frequently in group 2 (Table 2). It occurred in 19 (58%) patients assigned to group 1 and in 6 (21%) patients in group 2 ($P = 0.004$; 95% CI, 13 to 59). A total of 22 patients in group 1 and 19 in group 2 received amphotericin B for at least 7 days and were available for analysis of renal toxicity. Nephrotoxicity was observed in seven (32%) patients in group 1 and in four (21%) patients in group 2 ($P = 0.44$; 95% CI, −16 to 37). The difference between baseline and final serum creatinine levels was 0.36 mg/dl in group 1 and 0.26 mg/dl in group 2 ($P = 0.5$). Hepatotoxicity did not occur in any of the patients.

Efficacy. The success rates of empirical antifungal therapy were similar in the two groups: 69% (18 of 26 patients) in group 1 and 71% (17 of 24 patients) in group 2 ($P = 0.9$; 95% CI, −27 to 24). Clinical resolution or improvement was observed in five of six patients with systemic fungal infections in group 1 and in three of four patients in group 2. The only patient who received amphotericin B as secondary prophylaxis (group 1) did not develop a recurrence of the pulmonary aspergillosis during the period of neutropenia.

TABLE 3. Frequency of fever on different days of infusion of amphotericin B in 5% dextrose (group 1) or in Intralipid (group 2)

Day of administration	% with fever in:		*P*	95% CI
	Group 1	Group 2		
1	51	36	0.21	−9–40
3	39	7	0.003	13–51
6	35		0.003	16–53
10	31		0.056	6–56

DISCUSSION

In the present study, the overall numbers of group 1 and group 2 patients who did not exhibit infusion-related events did not differ significantly. However, the administration of amphotericin B in a fat emulsion (group 2) reduced the number of days with fever and rigors as well as hypokalemia compared to that occurring with the standard mode of administration, in 5% dextrose (group 1). Regarding the infusion-related events, these results are strengthened by the fact that patients in group 2 did not receive any premedication whereas patients in group 1 received premedication consisting of an antihistamine and an antipyretic, a combination associated with a reduction in the frequency of infusion-related side effects (9). The proportion of patients developing fever decreased from 85% in group 1 to 65% in group 2, but the difference was not statistically significant, possibly due to the small number of patients in the study. However, the total numbers of episodes of fever were significantly different: 40% of those in group 1 and 23% of persons in group 2 developed fever ($P < 0.0001$). Analysis by the number of administrations rather than by the number of patients may better reflect the differences between the regimens, since it is known that the frequency of occurrence of fever and chills in an individual patient tends to decrease over time (5). Indeed, the proportion of patients with fever or rigors decreased over time in both groups (Table 3). However, the occurrence of infusion-related events decreased faster in group 2 than in group 1. The number of courses that required the administration of meperidine was smaller in the group receiving amphotericin B in Intralipid. Since meperidine was given to patients with more-severe acute reactions, this result reflects the lower degree of severity of the acute adverse events in this

group. In addition, no patient required drug discontinuation because of adverse events.

Among the seven randomized studies reported so far, the number of acute adverse events was reduced by the administration of amphotericin B in Intralipid in five (1, 2, 8, 12, 17). Of the two studies in which no difference was found (13, 15), one had a very small sample size (13). Hypokalemia also occurred less frequently in patients receiving amphotericin B in Intralipid. These data are in agreement with those of a study of systemic murine candidiasis (10). In that study, amphotericin B toxicity was tested in mammalian erythrocytes in vitro, and it was shown that these cells lost 80% of their intracellular potassium when treated with amphotericin B deoxycholate but only 20% when treated with amphotericin B in Intralipid. Among the seven randomized studies published so far, data on variations in the potassium serum levels were reported for four, and in only one was a significant difference observed (15). However, in that study, patients receiving Intralipid received less diuretic. In the present study, the proportions of patients taking diuretics in the two groups were not significantly different. The discrepancies between these studies may be due to differences in the criteria used to define hypokalemia.

Renal impairment is a limiting factor for prolonged treatment with amphotericin B, with a decrease in the daily dosage being required when this condition occurs. Nephrotoxicity was reduced by the administration of amphotericin B in Intralipid in five of the seven randomized studies published to date. In one other study there was no difference (15), whereas in the remaining study (8) the toxicity was higher in the group receiving amphotericin B in Intralipid. In the present study, nephrotoxicity could be assessed in 41 of the 56 patients, and no difference was observed. Again, differences in sample size and definition of nephrotoxicity might explain these discrepancies.

There are some characteristics in the present study that must be kept in mind when interpreting the results: this was a nonblinded study that enrolled a young population of patients with cancer who received relatively low cumulative doses of amphotericin B, since in the majority of cases it was used empirically. Another limitation of the study is that we cannot draw conclusions on the efficacy of amphotericin B in Intralipid, since the sample size, calculated to detect differences in toxicity, was too small to detect differences in efficacy.

The stability of amphotericin B in lipid emulsions has been a concern. It has been demonstrated that precipitation of amphotericin B in Intralipid can occur, which could theoretically cause a massive administration of amphotericin B and a change in the granulometry of the solution, with a risk of pulmonary embolism (11, 14, 16). Nevertheless, pulmonary embolisms related to the administration of amphotericin B in lipid emulsions have not been reported in the literature so far. In the present study, in over 250 infusions, no patient developed manifestations of pulmonary toxicity. It has been recently published that the amount and size of undissolved particles are substantially increased in this preparation compared to those of amphotericin B in 5% dextrose (14). Although the particles can be removed by an in-line filter, this might reduce the antifungal efficacy. Another concern is related to the preparation of the mixture; methods for preparing this solution have not been standardized.

From the data already published, it is not clear that mixing amphotericin B with Intralipid results in a substantial improvement in the therapeutic index. Nevertheless, the use of amphotericin B in Intralipid seems warranted in patients presenting with severe acute reactions. Further studies should evaluate whether this preparation allows the administration of higher doses of amphotericin B without compromising its efficacy.

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