Safety, Tolerance, and Pharmacokinetics of a Small Unilamellar Liposomal Formulation of Amphotericin B (AmBisome) in Neutropenic Patients

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The safety, tolerance, and pharmacokinetics of a small unilamellar liposomal formulation of amphotericin B (AmBisome) administered for empirical antifungal therapy were evaluated for 36 persistently febrile neutropenic adults receiving cancer chemotherapy and bone marrow transplantation. The protocol was an open-label, sequential-dose-escalation, multidose pharmacokinetic study which enrolled a total of 8 to 12 patients in each of the four dosage cohorts. Each cohort received daily doses of either 1.0, 2.5, 5.0, or 7.5 mg of amphotericin B in the form of AmBisome/kg of body weight. The study population consisted of patients between the ages of 13 and 80 years with neutropenia (absolute neutrophil count, <500/mm3) who were eligible to receive empirical antifungal therapy. Patients were monitored for safety and tolerance by frequent laboratory examinations and the monitoring of infusion-related reactions. Efficacy was assessed by monitoring for the development of invasive fungal infection. The pharmacokinetic parameters of AmBisome were measured as those of amphotericin B by high-performance liquid chromatography. Noncompartmental methods were used to calculate pharmacokinetic parameters. AmBisome administered as a 1-h infusion in this population was well tolerated and seldom associated with infusion-related toxicity. Infusion-related side effects occurred in 15 (5%) of all 331 infusions, and only two patients (5%) required premedication. Serum creatinine, potassium, and magnesium levels were not significantly changed from baseline in any of the dosage cohorts, and there was no net increase in serum transaminase levels. AmBisome followed a nonlinear dosage relationship that was consistent with reticuloendothelial uptake and redistribution. There were no breakthrough fungal infections during empirical therapy with AmBisome. AmBisome administered to febrile neutropenic patients in this study was well tolerated, was seldom associated with infusion-related toxicity, was characterized by nonlinear saturation kinetics, and was effective in preventing breakthrough fungal infections.

Invasive fungal infections are important causes of morbidity and mortality in neutropenic patients (20, 22, 29). The use of conventional amphotericin B in neutropenic patients may be compromised by dose-limiting toxicity and infusion-related acute toxicity (8). Recently, advances have been made in the development of lipid formulations of amphotericin B which permit delivery of higher doses while sparing toxicity (11). AmBisome (manufactured by Nexstar, Inc., San Dimas, Calif. and provided by Fujisawa USA, Inc., Chicago, Ill.) is a small unilamellar formulation of amphotericin B which differs from several other lipid formulations of amphotericin B in that it forms true liposomes with uniform, stable, spherical single-membrane vesicles of <0.1 μm in diameter. AmBisome remains unchanged in the circulation and distributes as intact liposomes to tissues (1). Preclinical studies have demonstrated that AmBisome is as effective or more effective, but less nephrotoxic, than conventional amphotericin in the treatment of experimental disseminated candidiasis and invasive pulmonary aspergillosis in immunocompromised rodents and rabbits (7, 9, 26, 27). Consistent with these findings are the results of open-label clinical trials which also demonstrated antifungal efficacy in neutropenic patients (17–19, 24). No single study, however, has prospectively studied the safety, tolerance, and pharmacokinetics of AmBisome at multiple dosages in neutropenic patients. We therefore studied the safety, tolerance, and pharmacokinetics of AmBisome in a sequential-dose-escalation, multidose pharmacokinetic study administered as empirical antifungal therapy in persistently febrile neutropenic patients. This study establishes the foundation for randomized trials designed to investigate the efficacy of AmBisome in persistently febrile neutropenic hosts.

MATERIALS AND METHODS

Study design. The objective of the study was to evaluate the safety, tolerance, and plasma pharmacokinetics of intravenous AmBisome at four dosage levels in a population of adult cancer and bone marrow transplant patients requiring empirical antifungal therapy. Doses of AmBisome were calculated and expressed as the amount of amphotericin B administered. For example, a dose of 50 mg of AmBisome is the administration of an amount of AmBisome that contains 50 mg of amphotericin B. Patients were eligible for the study if (i) they were between the ages of 13 and 80 years, undergoing bone marrow transplantation or receiving active chemotherapy for neoplastic disease, and (ii) they had persistent or recurrent fever (oral temperature, ≥38.0°C) and neutropenia (absolute neutro-
following AmBisome administration was determined by noncompartmental analytically. The unweighted correlation coefficient was 0.998 for both curves, with interday overlapping standard curves were used: 0.05 to 20

analytical methods. The terminal elimination half-life \((t_{1/2})\) was obtained from plasma data in the postdistribution phase. The elimination rate constant \(\beta\) was defined as 0.693/ \(t_{1/2}\). The area under the plasma concentration-time curve and the area under the moment curve from 0 to 24 h \((AUC_{0–24} \text{ and } AUMC_{0–24})\), respectively, were calculated by the linear trapezoidal method. The \(AUC_{0–24}\) was calculated as \(AUC_{0–24} = AUC_{24–} + AUC_{24–}\) with \(AUC_{24–}\) extrapolated from \(C_{\beta}\), where \(C_{\beta}\) was the last measured concentration. The \(AUMC_{0–24}\) was calculated similarly, with \(AUMC_{24–}\) extrapolated from \((C_{\beta} \times t)/\beta + (C_{\beta})^{2}\). Total body clearance (CL) was calculated as dose/\(AUC_{0–}\). The volume of distribution at steady state \((V_{ss})\) was calculated as \([\text{dose} \times AUMC_{0–24}]/(AUC_{0–24})^{2} – [\text{dose} \times \text{infusion time}] \times (2 \times AUC_{0–})\].

Monitoring of safety and tolerance. The following laboratory examinations were performed every other day and on the last day of dosing: hemoglobin, hematocrit, total-leukocyte count with differential, platelet count, prothrombin time, partial thromboplastin time, blood urea nitrogen, and serum creatinine, calcium, potassium, sodium, AST, ALT, lactate dehydrogenase, alkaline phosphatase, total bilirubin, magnesium, and lipase. A specimen for complete urinalysis and blood samples from two separate sites for culture were obtained daily if the patient remained febrile.

Tolerance of infusion-related toxicity was monitored prospectively for each infusion of the study drug. Patients were not premedicated with acetaminophen, diphenhydramine, nonsteroidal anti-inflammatory agents, glucocorticosteroids, or analgesics for the administration of the first dose of AmBisome, thus permitting evaluation of infusion-related toxicity. If infusion-related symptoms developed during that first infusion, one or more of these agents could be administered.

A bedside data extraction sheet was utilized by the nursing staff to record serial vital signs during and after infusion, as well as signs and symptoms of infusion-related toxicity. This data extraction sheet then became a source document for reporting infusion-related toxicity. Pulse and blood pressure were monitored immediately before the 1-h infusion, at 15 and 30 min, and at the end of infusion. Between doses, temperature and vital signs were obtained every 4 h during waking hours. Signs, symptoms, and reported side effects associated with study drug infusion or occurring at any time during the study period were recorded and assessed for relationship to the study drug. The relationship of the study drug to possible clinical infusion-related toxicity was assessed by each patient's primary physician.

All safety and tolerance data were carefully assessed by an investigator and a clinical monitor in order to ensure that safety criteria had been fulfilled before escalation to the next dosage cohort. Six of eight patients were required to complete therapy with no significant drug-related toxicity before escalation to the next-higher dosage level was permitted.

### TABLE 2. Renal function in neutropenic patients receiving AmBisome

<table>
<thead>
<tr>
<th>Dosage cohort (mg/kg)</th>
<th>Creatinine (mg/dl)</th>
<th>Potassium (meq/liter)</th>
<th>Magnesium (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of therapy</td>
<td>Baseline</td>
</tr>
<tr>
<td>1.0</td>
<td>0.98 ± 0.08</td>
<td>0.83 ± 0.07</td>
<td>3.8 ± 0.19</td>
</tr>
<tr>
<td>2.5</td>
<td>0.93 ± 0.08</td>
<td>0.88 ± 0.07</td>
<td>4.2 ± 0.23</td>
</tr>
<tr>
<td>5.0</td>
<td>0.95 ± 0.07</td>
<td>1.00 ± 0.13</td>
<td>3.9 ± 0.12</td>
</tr>
<tr>
<td>7.5</td>
<td>1.01 ± 0.18</td>
<td>1.41 ± 0.23</td>
<td>4.2 ± 0.22</td>
</tr>
<tr>
<td>All patients (36)</td>
<td>0.95 ± 0.04</td>
<td>1.03 ± 0.08</td>
<td>4.0 ± 0.09</td>
</tr>
</tbody>
</table>
Monitoring of efficacy. Serial blood cultures, urine cultures, and chest radiographs were performed for all febrile neutropenic patients. Blood was cultured by lysis centrifugation (Wampole Laboratories, Cranbury, N.J.) and the BacT-Alert system (Organon Teknika Corporation, Durham, N.C.). Computerized tomographic scans and bronchoalveolar lavage were performed as appropriate in evaluating patients for possible invasive fungal infection.

Statistical analysis. Data are expressed as means ± standard deviations (SD). Comparisons of the mean pharmacokinetic values between the first and last doses and between different dosage levels of AmBisome were performed by using a two-tailed, unpaired Student’s t test. Differences in means of clinical laboratory values and indicators of tolerance to the study drug were analyzed by the Wilcoxon rank sum test. A P value of ≤0.05 was considered to indicate a significant difference.

RESULTS

Study patient population. A total of 36 patients were enrolled in the study and received at least three doses of AmBisome (Table 1). These patients (14 males and 22 females) had a mean age of 38.9 years. Underlying conditions included autologous bone marrow transplantation (n = 16), allogeneic bone marrow transplantation (n = 8), lymphoma (n = 8), acute leukemia (n = 3), and sarcoma (n = 1). The mean duration of administration of the study drug was 9.2 ± 0.8 days.

Safety. Serum creatinine, potassium, and magnesium levels were not significantly changed in any of the dosage cohorts (Table 2; Fig. 1). There also was no overall net increase in elevation of serum transaminase levels. There was, however, a trend of increased serum alkaline phosphatase and bilirubin levels in the overall population, as well as in individual dosage groups (Table 3). Serum alkaline phosphatase levels increased by approximately one-half above baseline (P ≤ 0.001), and serum bilirubin levels increased two- to fourfold above baseline (P ≤ 0.05). These changes in serum alkaline phosphatase and bilirubin levels were observed in all dosage groups and were not dose dependent. Serum lipase did not change from baseline in any of the dosage cohorts. One patient receiving concomitant L-asparaginase sustained increases in serum lipase and amylase levels in association with symptoms of pancreatitis while receiving AmBisome. However, as he continued to receive AmBisome, serum lipase and amylase levels returned to baseline. His symptoms resolved, while he continued on the study drug, in a pattern consistent with L-asparaginase-induced pancreatitis.

Tolerance. AmBisome was associated with minimal infusion-related toxicity (Table 4). All infusions of AmBisome were directly monitored; vital signs and symptoms were recorded in a data collection sheet at the patient’s bedside. Of the 331 infusions that were administered, 15 (5%) were associated with a temperature elevation of $\geq 1^\circ C$. Chills were present during 7

![FIG. 1. Changes in serum creatinine at baseline and end of therapy in neutropenic patients receiving AmBisome.](http://aac.asm.org/)

### TABLE 3. Hepatic function in neutropenic patients receiving AmBisome

<table>
<thead>
<tr>
<th>Dosage cohort (n)</th>
<th>AST (IU/liter)</th>
<th>ALT (IU/liter)</th>
<th>Alkaline phosphatase (IU/liter)</th>
<th>Total bilirubin (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of therapy</td>
<td>Baseline</td>
<td>End of therapy</td>
</tr>
<tr>
<td>1.0 mg/kg (8)</td>
<td>27 ± 11.6</td>
<td>14 ± 1.3</td>
<td>27.0 ± 10.9</td>
<td>19.8 ± 6.0</td>
</tr>
<tr>
<td>2.5 mg/kg (8)</td>
<td>19.1 ± 4.6</td>
<td>28 ± 10.9</td>
<td>20.9 ± 5.0</td>
<td>43.6 ± 17.6*</td>
</tr>
<tr>
<td>5.0 mg/kg (12)</td>
<td>45.5 ± 10.8</td>
<td>44.4 ± 17.0</td>
<td>53.8 ± 13.7</td>
<td>47.0 ± 16.4*</td>
</tr>
<tr>
<td>7.5 mg/kg (8)</td>
<td>40.4 ± 9.4</td>
<td>40.3 ± 7.6</td>
<td>45.3 ± 8.1</td>
<td>45.9 ± 14.8</td>
</tr>
<tr>
<td>All patients (36)</td>
<td>34.4 ± 5.1</td>
<td>33.1 ± 6.5</td>
<td>38.6 ± 5.9</td>
<td>39.9 ± 7.5</td>
</tr>
</tbody>
</table>

*Expressed as mean ± SD. *, P ≤ 0.05; †, P ≤ 0.01; ‡, P ≤ 0.001.
Two (5.5%) of the 36 study patients required premedication for infusion-related side effects. One patient demonstrated dyspnea on infusion, which was associated with a generalized flushing reaction. This reaction occurred during the first two infusions which this particular patient received. Another patient experienced a transient localized facial urticaria during two infusions. Both patients were subsequently premedicated with diphenhydramine, and no further infusion-associated reactions were noted.

Two patients sustained infusion-related toxicity which did not require premedication for subsequent infusions. One patient experienced sharp flank pain within the first 5 min of infusion of 5.0 mg of AmBisome/kg. No interventions were made at the time, and the patient tolerated the remainder of the infusion and all subsequent infusions without incident or premedication. The other patient reported dyspnea 20 min after initiation of the infusion of 7.5 mg of AmBisome/kg. The infusion was temporarily withheld, and the dyspnea resolved. No further episodes of dyspnea ensued during subsequent infusions.

**Pharmacokinetics.** The plasma concentration-time curves of each dosage cohort on the 1st and last days are depicted in Fig. 2 and 3, respectively. The means ± SD of the AUC\(^{0–}\) values determined on the 1st day of infusion for the four dosage cohorts (1.0, 2.5, 5.0, and 7.5 mg/kg/day) were 32 ± 15, 71 ± 36, 294 ± 102, and 534 ± 429 mg·h/ml, respectively, reflecting a nonlinear dosage relationship (Table 5). The increase in AUC exceeding dose proportionality is consistent with reticuloendothelial saturation and the subsequent entry of AmBisome into the plasma compartment. Furthermore, the effect of reticuloendothelial saturation is evidenced by the in-

![Graph showing plasma concentration-time curve](http://aac.asm.org/)
crease in AUC₀₋₂₄/dose vis-à-vis the dose as the dosage increases (Fig. 4). As the AUC₀₋₂₄ increased with escalating dosage, CL tended to decrease with escalating dosage: from the highest to the lowest dosage, CL values were 39 ± 22, 51 ± 44, 21 ± 14, and 25 ± 22 µg · h⁻¹/ml (Table 5). Trough concentrations were relatively constant for a given patient and dosage, suggesting negligible plasma accumulation (data not shown).

Of note, the mean ± SD for the AUC₀₋₂₄ of the last dose at 7.5 mg/kg did not increase beyond the last-dose AUC₀₋₂₄ for the 5.0-mg/kg cohort, suggesting a change in the disposition process through elimination and/or metabolism.

The pharmacokinetic data of the last day were analyzed by using a model that included a short infusion with Michaelis-Menten elimination. As evidenced by a high coefficient of variation and wide confidence intervals, a Michaelis-Menten elimination model did not explain these data. High Kₘ values in that analysis indicated that pseudolinear elimination would be evident at all achievable plasma levels. Since there was clearly nonlinearity in the parameters describing AUC and CL, a much more complex model appears to be required to explain the plasma pharmacokinetic profile of AmBisome in this study.

### DISCUSSION

This study demonstrated that AmBisome was safe and well tolerated when administered as empirical antifungal therapy to persistently febrile neutropenic patients receiving cytotoxic chemotherapy. The frequency of infusion-related side effects was less than or equal to 5% of all infusions. Only two patients (5%) required premedication. Serum creatinine, potassium, and magnesium levels were not significantly changed from baseline, and there were no net increases in hepatic transami-

### TABLE 5. Pharmacokinetic variables in neutropenic patients receiving AmBisome

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Value (mean ± SD for dosage cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>AUC₀₋₂₄ (µg/ml · h)</td>
<td>27 ± 14</td>
</tr>
<tr>
<td>AUCᵦ₋₂₄ (µg/ml · h)</td>
<td>32 ± 15</td>
</tr>
<tr>
<td>t₁/₂ (h)</td>
<td>10.7 ± 6.4</td>
</tr>
<tr>
<td>V (liters/kg)</td>
<td>0.58 ± 0.40</td>
</tr>
<tr>
<td>Vᵦ (liters/kg)</td>
<td>0.44 ± 0.27</td>
</tr>
<tr>
<td>CL (ml/h/kg)</td>
<td>39 ± 22</td>
</tr>
</tbody>
</table>
with diphenhydramine and the remaining two patients received no premedication. Severe infusion-related dyspnea was reported previously for a patient receiving a multilamellar liposomal formulation of amphotericin B (14) and for two patients receiving AmBisome (4). The pathogenesis of the infusion-related reactions due to these two lipid formulations appears to differ. Infusion-related dyspnea due to the multilamellar formulation was associated with hypoxia, pulmonary hypertension, and systemic hypotension (14). By comparison, patients receiving AmBisome had no systemic hypotension, electrocardiographic changes, or hypoxia as measured by pulse oximetry.

There was no significant difference between baseline and end-of-therapy serum creatinine levels in patients receiving AmBisome. Nor was there any significant hypokalemia or hypomagnesemia. These combined findings suggest that AmBisome’s reduced nephrotoxicity is related to attenuation of both glomerular and tubular injury. By comparison, conventional amphotericin B compromises both glomerular and tubular function.

Several mechanisms may account for the reduced nephrotoxicity of lipid formulations of amphotericin B. The first mechanism relates to the observations by Mehta et al. (16), who described the liposome-mediated selective transfer of amphotericin B to fungal-cell membranes and away from mammalian-cell membranes, with preferential cytotoxicity for Candida albicans and reduced cytotoxicity for human erythrocytes. This contrasts with conventional amphotericin B, which had cytotoxic effects on both C. albicans and human erythrocytes. Another mechanism is the reduced concentrations of amphotericin B in the kidney relative to the high concentrations achieved in the RES (13, 23, 27). This mechanism alone, however, is not sufficient to explain reduced nephrotoxicity, as AmBisome may accumulate over time in the kidney. A third mechanism, proposed by Perkins et al. (21), is the selective degradation, by fungus-derived phospholipases and lipases, of the liposome, which then releases amphotericin B directly onto the fungal cells. Such lipases and phospholipases are not normally secreted by glomerular cells or renal tubular epithelial cells. A fourth possible mechanism, proposed by Wasan and colleagues, is the preferential binding of the liposome to high-density lipoproteins (HDL), in comparison to conventional amphotericin B, which is bound to low-density lipoproteins (LDL) (30). Renal endothelial cells tend to express high concentrations of LDL, while the hepatic endothelial cells express high concentrations of HDL. A greater-than-twofold increase in serum creatinine levels was observed in only 3 (8%) of the 36 patients treated in this study. Patients in this study often were receiving concomitant nephrotoxic agents, which included gentamicin, vancomycin, fosfomycin, and cyclosporine, which also may have contributed to the elevation of serum creatinine levels. A recently completed randomized, double-blind, multicenter trial of AmBisome versus conventional amphotericin B further demonstrated that the liposomal formulation was significantly less nephrotoxic than conventional therapy and that this safety profile was maintained even with concomitant nephrotoxic agents (28).

Serum transaminase levels were not significantly elevated compared to baseline in any of the dosage cohorts, suggesting that AmBisome may have little if any direct toxic effect on hepatocytes. However, there was elevation of serum alkaline phosphatase and total-bilirubin levels across the dosage cohorts, suggesting an effect on biliary epithelium. Some of these changes may have been related to the effects of chemotherapy, preparative regimens for bone marrow transplantation, graft-versus-host disease, early veno-occlusive disease, and intercur-

![Graph](http://aac.asm.org/Downloaded/from http://aac.asm.org/)
rent septic events rather than to AmBisome. Alternatively, perhaps these concomitant conditions lower the threshold for AmBisome’s possible induction of hyperbilirubinemia and elevated alkaline phosphatase levels.

There have been few reports of the plasma pharmacokinetics of AmBisome in humans. Heinemann et al. (10) studied the pharmacokinetics of AmBisome at 3 mg/kg/day versus conventional amphotericin B at 1 mg/kg/day and amphotericin B mixed in a 20% lipid emulsion. Ten bone marrow transplant recipients received AmBisome, which resulted in maximum concentrations of the drug in serum (Cmax) and AUC values 8- and 12-fold greater, respectively, than those reached with conventional amphotericin B at 1 mg/kg/day. The higher Cmax values achieved with AmBisome were related to a V1/fourfold smaller than that obtained with conventional amphotericin B at 1 mg/kg/day.

The plasma pharmacokinetic profile of AmBisome in our study revealed a nonlinear dose-related pattern, consistent with reticuloendothelial uptake and redistribution. Plasma concentrations and AUC0-∞ values increased disproportionately to the infused dose for the overall dosage range, both at the initial dosage and in steady state. The CL values of AmBisome measured on day 1 declined as the dosage of AmBisome increased, which is consistent with its nonlinear pharmacokinetic profile. The decreased CL measured from day 1 through the last day is consistent with the nonlinear saturation-like kinetic profile of AmBisome. Continued administration of AmBisome may saturate the reticuloendothelial uptake mechanisms, resulting in more-sustained plasma levels and decreased CL. The CL values of AmBisome also declined from the 1st day to the last day by more than 50% at 1.0, 2.5, and 5.0 mg/kg/day. These data further suggest that at least one saturable pathway is involved in the elimination of AmBisome. Reflecting possible reticuloendothelial deposition with a slow release of drug into the circulation, plasma samples collected following the last day of dosing in the 5.0- and 7.5-mg/kg/day dosage groups demonstrated a prolonged measurable elimination of AmBisome as long as 4 weeks postdosage.

The plasma pharmacokinetics for the highest-dosage cohort studied, 7.5 mg/kg/day, demonstrated AUC values on day 1 which were consistently greater than the AUC values on the last day. By comparison, the AUC values on the last day for dosages of 1.0, 2.5, and 5.0 mg/kg/day were consistently greater than those on day 1. Such findings have not been described previously for AmBisome or any other lipid formulation of amphotericin B. These results suggest that an alternate mechanism of elimination may have been triggered at the highest dosage of AmBisome. Amphotericin B is eliminated from the circulation by the RES, biliary tract, and urinary tract (12, 27); in addition, elimination of AmBisome from the circulation also is dependent on the RES (1, 11, 13, 23, 26, 27). Higher concentrations of AmBisome may induce a concentration-driven elimination mechanism for amphotericin B, as observed for the renal elimination of carprofen (5) and reticuloendothelial elimination of hemoglobin (6).

As this study was designed to determine safety, tolerance, and pharmacokinetics, conclusions about efficacy in a noncomparative study must be approached with caution. Nevertheless, there were no breakthrough fungal infections in our patients, 24 of whom were autologous or allogeneic bone marrow transplant recipients and hence at risk for invasive fungal infections. Randomized trials will further elucidate the efficacy of AmBisome in the treatment of invasive fungal infections.

REFERENCES


