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BRIEF REPORT

Fixed Dosing of Liposomal Amphotericin B in Morbidly Obese Individuals

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In this prospective study, we examined the pharmacokinetics of 1 and 2 mg/kg liposomal amphotericin B in 16 morbidly obese individuals (104–177 kg). Body size had no effect on clearance. We recommend a fixed dose in patients ≥100 kg (ie, 300 or 500 mg rather than the current dose of 3 and 5 mg/kg, respectively).

Clinical Trials Registration. NCT02320604.

Keywords. fungal treatment; fungal infection; obese; population pharmacokinetics; optimal dosing.

Liposomal amphotericin B (L-AmB, AmBisome) is a broad-spectrum antifungal agent widely used for the treatment of invasive fungal disease. The typical dose for invasive aspergillosis is 3 mg/kg. Although L-AmB has been on the market for several decades, little is known about its pharmacokinetics in obese patients [1, 2]. This is highly relevant since the prevalence of obesity is increasing yearly and obesity is a risk factor for development of infections [3, 4]. We performed a pharmacokinetic study in morbidly obese individuals to quantify the impact of obesity on the clearance of L-AmB in order to guide dosing.

METHODS

Study Population and Procedures

We performed a pharmacokinetic study in 16 morbidly obese but otherwise healthy adults with a body mass index (BMI) >40 kg/m^2 the day before they underwent bariatric surgery. The study was approved by the Central Committee on Research Involving Human Subjects and conducted in accordance with the Declaration of Helsinki and good clinical practice regulations. Patients were randomly assigned to receive a single L-AmB intravenous infusion of 1 mg/kg in 0.75 hours or 2 mg/kg in 1.5 hours. Blood samples were collected 15 minutes after the end of infusion and at t = 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours. Samples were centrifuged at 1900 *g* for 5 minutes and immediately stored at −80°C. Total AmB concentrations were measured using ultraperformance liquid chromatography with photodiode array detection, validated according to European Medicines Agency guidelines. Lower and higher limits of quantification ranged from 0.50 to 50 mg/L, and the accuracy ranged from 97.6 to 112%.

Pharmacokinetic Analysis

Concentration–time data were analyzed using nonlinear mixed effects modeling (NONMEM; v7.3.0) with Perl-speaks-NONMEM (PsN; v4.7) [5]. We explored 1-, 2-, and 3-compartment models and used the first-order conditional estimation method with interaction for all model runs. Interindividual variability (IIV) was assumed to be log-normally distributed. Additive, proportional, and combined residual error models were evaluated. We investigated first-order and Michaelis-Menten elimination, and a previously reported time-dependent volume of distribution of the central compartment (V_c) was explored using an exponential-decay function. For the covariate analysis, the relationships between empirical Bayes estimates and the covariates total body weight (TBW), lean body weight [6], BMI, ideal body weight [7], body surface area [8], age, and sex were investigated in scatter plots. The performance of the final model was assessed using a prediction-corrected visual predictive check based on 1000 Monte Carlo simulations. Parameter precision and model robustness of the structural and covariate models were measured using the sampling importance resampling (SIR) procedure.

Simulations

The final model was used to simulate the area under the curve ($AUC_{0\text{-}24h}$) and maximum concentration (C_{max}) in steady-state conditions in 10.000 patients, with body weights uniformly distributed between 60 and 180 kg. Although normal-weight patients were not studied, we added them to the simulations to act as the comparison group with an established dose; this is justified since our model is in line with previous reports [9]. Each virtual patient received daily 3 mg/kg L-AmB infused in 1 hour; patients who weighed ≥100 kg received either 3 mg/kg or a fixed 300-mg dose. Simulating a 3-mg/kg dose is justified due to reported linear pharmacokinetics in the lower dose range

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[1]. Simulations were performed with parameter uncertainty through the stochastic simulation and estimation functionality in PsN using the SIR results as model input (n = 500 models).

RESULTS

We included 16 morbidly obese patients with median (range) BMI of 45.9 (40.2–52.1) kg/m^2 and TBW of 137 (104–177) kg. Other patient characteristics are summarized in Supplementary Table S1. Supplementary Figure S1 shows the observed mean plasma concentrations for each dose group.

A 2-compartment model in which no relationship could be identified between TBW and clearance was identified (Supplementary Figure S2A). A linear relationship was found between TBW and the central volume of distribution (V_c; $P < .01$ and there was a decrease in IIV on V_c from 17.6% to 13.8%; Supplementary Figure S2B. None of the remaining covariates further improved the model. In the final model, we found the following parameter (% IIV) estimates: clearance, 0.84 L/h (37.7%); inter-compartmental clearance, 0.61 L/h (115%); volume of distribution of the peripheral compartment, 7.3 $L \cdot {}^{TBW}/_{130}$ (13.8%); and V_p, 12 L (22.1%); Supplementary Tables S2. Supplementary Figure S3 and S4 show that the model describes the observed data correctly and has good predictive performance. Figure 1 shows how the $AUC_{0\text{-}24h}$ and C_{max} change with body weight (Monte Carlo simulations) when patients receive a daily 3-mg/kg L-AmB dose infused in 1 hour with and without a dose cap at 100 kg.

We identified a subgroup of 4 individuals (all received 2 mg/kg) with a significantly lower clearance and V_c and, as a consequence, a higher C_{max} and $AUC_{0\text{-}24h}$. No covariates (eg, size descriptors, liver or renal function tests, complete blood count, and electrolytes) could be identified that helped to explain the pharmacokinetic differences in this subgroup.

DISCUSSION

To our knowledge, this is the first study that specifically focused on the pharmacokinetics of L-AmB in morbidly obese patients. Strikingly, we found no evidence of any body size descriptor predicting differences in AmB clearance. Furthermore, we show that V_c increases linearly with TBW but is relatively small in obese patients, confirming earlier preclinical observations of a limited disposition in adipose tissue [10]. The consequence of these findings is that the $AUC_{0\text{-}24h}$ will increase when (obese) patients are dosed on a per-kilogram basis (Figure 1A). In parallel, C_{max} also increases with body weight when L-AmB is dosed on a per-kilogram basis (Figure 1B). This phenomenon is primarily driven by the absolute increase in the dose with a clearance that does not change with weight. When using a fixed dose, C_{max} decreases due to the increase in V_c with weight.

Although $AUC_{0\text{-}24h}$ [11] and C_{max} [11, 12] have been reported to be associated with efficacy, the $AUC_{0\text{-}24h}$ has been associated with an increased risk of toxicity [13, 14]. To lower the potential risk of toxicity in obese patients, it seems prudent to use a fixed dose. In addition, evidence to suggest that obese patients would benefit from a higher dose is lacking; therefore, we suggest a weight of 100 kg to cap the dose (ie, 300 mg for the 3-mg/kg dose). Our simulation shows that a dose cap on 100 kg would not result in a further increase in the $AUC_{0\text{-}24h}$ in obese patients who weigh ≥100 kg and would also result in a similar C_{max} (13% lower) in a patient who weighs 140 kg compared to 70 kg (Figure 1B).

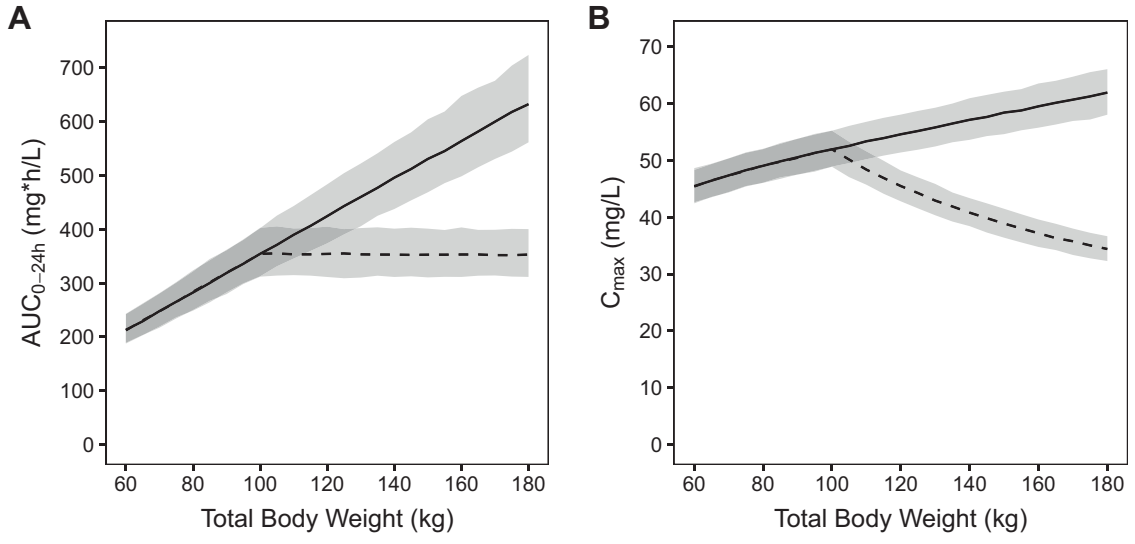

Figure 1. Monte-Carlo simulations based on the final model of the steady-state $AUC_{0\text{-}24h}$ and C_{max} after a daily 3-mg/kg (solid line) L-AmB dose infused in 1 hour. The dashed line represents the situation were the dose is capped on a 100-kg individual (300 mg AmBisome). The shaded areas represent the 90% confidence intervals of the prediction.

Abbreviations: $AUC_{0\text{-}24h}$, area under the curve; C_{max}, maximum concentration.

In our study, we found an $AUC_{0\text{-}24h}$ of 279 mg*h/L after a single dose of 2 mg/kg that was much higher than the previously reported 171 mg*h/L in normal-weight healthy volunteers (median weight of 77 kg) who received the same single dose. This substantiates our results for increased exposure after weight-based dosing [15]. The absence of body weight as a covariate on clearance is in line with the findings of Würthwein et al (2012) who reported no model improvement after inclusion of body size on pharmacokinetic parameters in patients with weights ranging from 44 to 105 kg [16].

In our analyses we identified a specific subpopulation with a relatively lower clearance in half of our patients given 2 mg/kg. Several other studies also identified a subgroup with altered pharmacokinetics within their population. The data from Hope et al (2012) illustrate an almost 2-fold difference between 2 subgroups of equal size [17]. In the study by Würthwein et al (2012), use of a 3 mg/kg-dose showed higher plasma concentrations in a third of their population due to decreased clearance [16]. A third study used a model with a time-dependent decrease of V_c to explain atypical pharmacokinetics in one-third of their pediatric population who received 2.5–10 mg/kg. Although we cannot explain the difference between these groups, we expect it to be unrelated to nonlinearity.

Our study has some limitations. First, we used a single low dose (1 and 2 mg/kg) of L-AmB instead of the licensed 3-mg/kg dose. While there is evidence of nonlinearity with high-dose L-AmB, linearity is reported at current dosages (3–5 mg/kg) used for treatment of *Aspergillus* infections [17]. Therefore, our results are expected to be applicable for currently used dose regimens but should be used with caution when extrapolating to high-dose L-AmB (>5 mg/kg). Second, our study lacked a control group of normal-weight individuals. Nevertheless, our results are in line with those from the study by Würthwein et al who reported no effect of weight on clearance in patients who weighed between 44 and 105 kg, which we extend to 177 kg in our study [16]. Furthermore, the parameter estimates (%IIV) we found for clearance of 0.84 L/h (37.7%) are similar to the 0.75 L/h (55%) found in a study in normal-weight healthy volunteers. Finally, we found a high IIV on clearance, which is mainly caused by the previously mentioned subgroup. We encourage future studies to investigate this phenomena.

Based on our results, we show that body weight–derived dosing might lead to an increased risk of toxicity in obese patients as clearance and therefore exposure to AmB is not affected by body weight. In obese patients specifically, we recommend using the licensed 3 or 5 mg/kg dose and cap the dose at a maximum weight of 100 kg, resulting in a 300- or 500-mg fixed dose, respectively.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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