Pharmacokinetics and Pharmacodynamics of Once-Daily Administration of Intravenous Tobramycin in Adult Patients with Cystic Fibrosis Hospitalized for an Acute Pulmonary Exacerbation

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The serum pharmacokinetic profile of intravenous (i.v.) tobramycin administration was characterized for a sample of nine adult patients with cystic fibrosis (CF) who were hospitalized for an acute pulmonary exacerbation. Current recommended i.v. tobramycin dosing protocols are predicted through modeling and simulation to be suboptimal. Empirical tobramycin regimens of ≥15 mg/kg of body weight administered i.v. once daily should be evaluated for adult patients with CF to optimize outcomes.

Morbitidity and mortality in adult patients with cystic fibrosis (CF) are most often attributed to acute pulmonary exacerbations (APE) due to Pseudomonas aeruginosa (1–4). Empirical therapy for management of this exacerbation consists of the combination of an antipseudomonal beta-lactam and an aminoglycoside such as tobramycin. Higher weight-based doses of tobramycin are recommended for patients with CF (10 mg/kg of body weight/day) than for patients without CF (5 to 7 mg/kg/day) (1, 5–7). Although more-intensive weight-based doses in patients with CF have been implemented by several institutions (8), there are still concerns that these tobramycin exposures may not optimize the pharmacodynamic (PD) profile of this agent (9, 10). To address these concerns, we characterized the pharmacokinetic (PK) and PD profile of once-daily intravenous (i.v.) tobramycin administration in adult patients with CF hospitalized for an APE.

The study protocol was approved by the institutional review board of Albany Medical Center Hospital (Albany, NY), and written informed consent was obtained from each patient. Adult patients (≥18 years of age) with CF who were receiving tobramycin for an APE requiring hospitalization were eligible for this study. Patients were excluded if any of the following criteria were met: (i) inability to tolerate venipuncture and multiple blood collections, (ii) female subject who was known to be pregnant, (iii) admission to the intensive care unit, (iv) estimated creatinine clearance (CL) of <50 ml/min (Cockcroft-Gault equation), and (v) any known hypersensitivity to tobramycin.

The patient’s demographic information, past medical history, history of present illness, and clinical laboratory data were reviewed and documented. Blood samples were collected at the following time points: end of infusion, 3 h postinfusion, 4.25 h postinfusion, 6.75 h postinfusion, and 8.25 h postinfusion. Serum samples were analyzed at Albany Medical Center Hospital (Albany, NY) by use of the AxSym immunoassay system (Abbott Laboratories, Abbott Park, IL). The mean accuracy (percent bias) and precision (percent coefficient of variation [CV]) levels for the serum quality control samples were ≤3.77% and ≤4.84%, respectively.

All data were analyzed using the nonparametric adaptive grid (NPAG) program within Pmetrics based on the R statistical environment (11). The PK model was parameterized as a 1- or 2-compartment model with zero-order infusion and first-order intercompartmental transfer (K12, K21) and elimination. Upon attainment of convergence, Bayesian estimates for each patient were obtained using the “population of one” utility. After the Bayesian step, goodness of fit and predictive performance were assessed as previously described (12). Embedded with the final PK model, 5,000-subject Monte Carlo simulations (MCS) were performed for administration of tobramycin at 7, 10, 15, and 20 mg/kg once daily (1-h i.v. infusion) as a single dose by use of ADAPT 5 (13). The population simulation without the “process noise” option was utilized, and log-normal distributions of PK parameter values were selected for all simulations. Since the aminoglycoside exposure targets for efficacy and toxicity have not been described for patients with CF, we relied on targets derived from non–CF patients. For efficacy, we modeled the probability of tobramycin effect based on a previously described logistic function developed to optimize aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria (14, 15). For toxicity, we modeled the amount of time that the drug concentration remained below the limit of detection of 0.3 mg/liter (T<sub>total</sub>). The goal of this dosing strategy was to achieve an undetectable concentration at the end of the dosing interval. We also evaluated the probability of achieving daily areas under the concentration-time curve (AUCs) associated with nephrotoxicity with once-daily administration of aminoglycosides for each regimen (14).

Nine adult patients with CF hospitalized for an APE were studied at a mean (standard deviation [SD]) of 4.1 (2.5) days following admission. The mean (SD) age was 33.0 (12.6) years, and most patients were female (n = 8) and white (100%). The mean (SD) weight and height were 53.6 (6.5) kg and 164 (6.0) cm, and the mean (SD) once-daily tobramycin dose received was 7.4 (1.4) mg/kg. The mean (SD) population parameter value estimates were as follows: V<sub>c</sub> (volume of central compartment), 5.06 (1.60) liters;
against isolates for which the MIC is 80%. The mean (SD) probability of effect is 71 (5.0)% with a 20-mg/kg once-daily tobramycin dose against isolates for which the MICs is 2 to 4 mg/liter, which is often the case in patients with CF. Tobramycin doses of 15 to 20 mg/kg/day should increase the probability of clinical response. This higher-dosing strategy should also reduce the probability for emergence of resistance at treatment initiation, when the lung bacterial burden is expected to be at its highest (19). Although the suggested consideration of 15- to 20-mg/kg/day dosages may be perceived to be high at first glance, it is important to recognize that all adult CF patients are likely to have undetectable trough concentrations, a marker of clinical safety, and the median $T_{\text{bld}}$ is 2.32 to 3.51 h over the 24-h dosing interval (Table 1). The best evidence to date also demonstrates that the daily AUCs with the simulated 20-mg/kg/day regimen are well below the daily AUCs associated with nephrotoxicity with once-daily administration of aminoglycosides (14). Finally and most importantly, there are data to suggest that administration of 15- to 20-mg/kg/day doses are safe and well tolerated (20, 21). Patients with CF receive repeated courses of tobramycin during their lifetime. The auditory, vestibular, and renal safety levels of these repeated doses, high doses, and cumulative doses (632 to 7,644 mg/kg) have been documented for this population (20, 21). Aminoglycoside-induced nephrotoxicity is reversible in >90% of the cases where the aminoglycoside is discontinued (20–22).

In conclusion, we sought to better quantify the PK and PD of tobramycin among adults with CF hospitalized for an APE. Overall, we found that higher weight-based once-daily doses of tobramycin are likely to be necessary in adult patients with CF for pathogens for which the MIC is 2 or 4 mg/liter. Given that tobramycin MICs for P. aeruginosa are frequently ≥2 mg/liter (23), our results suggest that a reevaluation of tobramycin treatment guidelines for this patient population is needed. Use of 15- to 20-mg/kg/day regimens for a shorter duration of 5 to 10 days could theoretically improve the probability of effect over toxicity. This suggestion for future study aligns with the recommendations of a

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**TABLE 1** Model-predicted AUC$_{24}$ values based on the final population pharmacokinetic model and administration of the dose as a 1-h infusion once daily

<table>
<thead>
<tr>
<th>Model-predicted dose (mg/kg/day) ($n = 5,000$)</th>
<th>AUC$_{24}$ (mg · h/liter)</th>
<th>$T_{\text{bld}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (5th %ile, 95th %ile)</td>
</tr>
<tr>
<td>7</td>
<td>96.2 (20.3)</td>
<td>94.7 (66.1, 132)</td>
</tr>
<tr>
<td>10</td>
<td>138 (29.0)</td>
<td>135 (94.3, 188)</td>
</tr>
<tr>
<td>15</td>
<td>206 (45.4)</td>
<td>203 (142, 282)</td>
</tr>
<tr>
<td>20</td>
<td>275 (57.9)</td>
<td>271 (189, 376)</td>
</tr>
</tbody>
</table>

**FIG 1** Model-predicted median serum concentration-time profile for tobramycin administered on a weight basis once daily in patients with cystic fibrosis, with a horizontal reference line at 2 mg/liter.

**FIG 2** Predicted probability of effect with once-daily weight-based tobramycin dosing in patients with cystic fibrosis by MIC.
systematic review to define optimal treatment duration in patients with CF and of thought leaders in the field of drug dose design (19, 24). As with all simulation studies, validation of our findings is critically important given that multidrug-resistant pathogens that can necessitate the use of tobramycin monotherapy are common in patients with CF. As part of the validations, studies should attempt to delineate the tobramycin targets for efficacy and toxicity since these targets have not been described for patients with CF.

REFERENCES