Pharmacokinetics and Bioavailability of Aerosolized Tobramycin in Cystic Fibrosis*

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**Study objectives:** To describe the pharmacokinetics and bioavailability of inhaled tobramycin (TOBI; Chiron Corporation; Seattle, WA), 300-mg dose, delivered by a nebulizer (PARI LC Plus; Pari Respiratory; Richmond, VA) and a compressor (Pulmo-Aide, model 5650D; DeVilbiss Health Care; Somerset, PA) in cystic fibrosis (CF) patients during the pivotal phase III trials.

**Design:** Data from two identical, 24-week, randomized, double-blind, placebo-controlled, parallel-group studies.

**Setting:** US sites randomized 258 patients with CF to receive tobramycin, 300 mg twice daily, in three 28-day on/28-day off treatment cycles.

**Measurement:** Tobramycin sputum concentrations were assessed 10 min after the first and last doses were administered in the 20-week study. Serum tobramycin concentrations were assessed before and 1 h after the first and last doses had been administered. The population estimate of the apparent clearance was used to estimate the bioavailability fraction.

**Results:** The mean peak sputum concentration was 1,237 μg/g. About 95% of patients achieved sputum concentrations > 25 times the minimum inhibitory concentration of the *Pseudomonas aeruginosa* isolates. One hour after the dose, the mean serum concentration was 0.95 μg/mL. Tobramycin did not accumulate in the sputum or serum over the course of the study. Pharmacokinetic data were best represented by a two-compartment model with biexponential decay and slope estimates comparable to those following parenteral administration. The estimated systemic bioavailability after aerosol administration was 11.7% of the nominal dose.

**Conclusions:** The administration of tobramycin, 300 mg bid, in a 28-day off/28-day on regimen produced low serum tobramycin concentrations, reducing the potential for systemic toxicity. High sputum concentrations ensure efficacious antibiotic levels at the site of the infection. Inhaled tobramycin significantly improved the therapeutic ratio over that of parenteral aminoglycosides.

**Key words:** bioavailability; cystic fibrosis; inhaled antibiotics; pharmacokinetics; *Pseudomonas aeruginosa*; tobramycin

**Abbreviations:** CF = cystic fibrosis; CL = systemic clearance of tobramycin; CL/F = apparent clearance; F = fraction of tobramycin dose absorbed systemically; LOQ = limit of quantitation; MIC = minimum inhibitory concentration; V/F = apparent volume of distribution

Cystic fibrosis (CF) patients suffer from chronic endobronchial infections most commonly caused by *Pseudomonas* species. Cystic fibrosis patients eventually become colonized with *Pseudomonas aeruginosa*, and 90% of all CF patients die due to progressive pulmonary disease. The standard therapy for *P aeruginosa* endobronchial infections in CF patients usually involves the administration of two parenteral antipseudomonal antibiotics, including an aminoglycoside agent. Parenteral aminoglycosides are highly polar and penetrate poorly into the endobronchial space. The mean peak sputum concentration after parenteral administration is only 12 to 20% of the peak serum concentration. Local endobronchial concentrations that are 10-fold to 25-fold above the minimum
inhibitory concentration (MIC) are required to overcome the effect of sputum binding on aminoglycoside availability to bacterial targets. Although adequate drug concentrations may be achieved at the endobronchial site of infection with parenteral administration, serum levels approaching those associated with nephrotoxicity, vestibulotoxicity, and ototoxicity also may be reached.11,12

The administration of topical aminoglycosides by inhalation offers an attractive alternative, delivering high concentrations of antibiotic directly to the site of infection while minimizing systemic bioavailability.13–15 Therapy with aerosolized tobramycin in CF patients has been studied extensively, and its safety and efficacy in older patients is the most thoroughly documented of all the inhaled antibiotics.16–19 Results and outcomes varied in the earlier clinical trials of inhaled tobramycin. Some (but not all) studies showed patient improvements in one or more of the following: lung function; pulmonary exacerbation rate; P aeruginosa colony count; or weight gain. The inconsistency among earlier studies is not surprising, considering the small numbers of patients in those studies and the differences in entry criteria, length of treatment, nominal dose of tobramycin, and aerosol delivery devices used. Most early studies of inhaled tobramycin used IV preparations that contained preservatives such as phenol and metabisulfites, which may cause bronchoconstriction and thus can influence pharmacodynamic behavior.30

One multicenter study20 evaluated high-dose, preservative-free tobramycin (600 mg thrice daily) delivered by an ultrasonic nebulizer. Although this regimen proved efficacious in improving pulmonary function and decreasing the sputum density of P aeruginosa, the high cost of therapy and the cumbersome, inefficient delivery system prevented its acceptance by patients and caregivers. Eisenberg et al.17 subsequently demonstrated that a jet nebulizer (PARI LC; Pari Respiratory; Richmond, VA) could achieve high sputum levels of tobramycin in most CF patients with only a 300-mg nominal dose, although the sputum levels of the drug were still about half those achieved with a dose of 600 mg via the ultrasonic nebulizer.

To avoid bronchoconstriction and unwanted effects from additives, a preservative-free formulation of tobramycin for inhalation (TOBI; Chiron Corporation; Seattle, WA) was developed and tested. Ramsey et al.29 reported the results of the pivotal phase III, multicenter studies that were conducted to determine the safety and efficacy of tobramycin for inhalation in CF patients with P aeruginosa infections. A jet nebulizer (PARI LC PLUS; Pari Respiratory) powered by a compressor (Pulmo-Aide, model 5650D; DeVilbiss Health Care; Somerset, PA) was chosen as the delivery system. This system has significantly improved efficiency vs that of the previous model tested (PARI LC; Pari Respiratory) by Eisenberg et al.17 The addition of one-way valves to the nebulizer directs inspiratory flow through the medication bowl, which increases aerosol delivery during inhalation. This breath-enhanced nebulizer was predicted to deliver double the dose of drug to the patient vs that of an unvented nebulizer,31 thus we expected that sputum levels may have approached those of the ultrasonic nebulizer and higher nominal doses used in earlier studies.17,23

The parallel studies by Ramsey et al.29 were the largest studies of therapy with inhaled antibiotics in CF patients performed to date. Safety, efficacy, and microbiology results from the multicenter studies have been reported previously.29 The purpose of this report is to describe tobramycin pharmacokinetic and bioavailability results obtained from the large database of the pivotal phase III studies. Sputum and serum tobramycin concentrations were determined to characterize endobronchial and systemic exposure to tobramycin in these patients. A population pharmacokinetic analysis was performed, and the population estimate of the apparent clearance was used to estimate the absorbed fraction of the inhaled dose. Analyses also were performed to correlate the sputum and serum tobramycin levels with demographic and pulmonary function variables of the CF population in the studies.

Materials and Methods

Patient Enrollment

Five hundred twenty patients from 69 CF centers in the United States participated in the randomized, placebo-controlled studies. Two identical studies were performed in parallel to satisfy regulatory requirements, and the results were pooled for analysis. Patients were eligible to participate if they were at least 6 years of age, had a documented diagnosis of moderate-to-severe CF, a respiratory tract culture yielding P aeruginosa,32 and an FEV1 that was at least 25% of the predicted value but not >75%. Two hundred fifty-eight patients received tobramycin for inhalation via the stratified randomization process, and 257 patients had at least one measurable sputum and serum concentration of tobramycin collected at specified times during the study.

Tobramycin for Inhalation Treatment Regimen

Tobramycin for inhalation, 300 mg, was administered twice daily during a 28-day treatment period (ie, “on cycle”) followed by a 28-day no-treatment period (ie, “off cycle”). A total of three 28-day-on/28-day-off cycles were completed during the 24-week studies. Patient compliance with the treatment regimen was assessed based on the number of unused medication ampules that were returned at the end of each study cycle.

The active drug is a sterile, pH-adjusted solution of 300 mg preservative-free tobramycin in 5 mL of 0.25 normal saline
solution, 60 mg/mL. Treatment was delivered by the aforementioned reusable jet nebulizer. Compressed air was delivered using the aforementioned compressor.

All doses were self-administered by patients, who were instructed to wear nose clips and to perform normal tidal breathing. Aerosol treatments were to occur each day approximately 12 h apart, but not < 6 h apart. Patients were allowed to use their routine medications for the management of CF during the study. However, inhaled antibiotic medications other than the study drug were prohibited, and patients using dornase alfa and/or a pneumatic vest for chest physiotherapy were required to begin using them at least 4 weeks before week 0 of the study and to maintain the same regimen throughout the study.

**Specimen Collection**

Sputum samples for the determination of endobronchial tobramycin concentrations were obtained twice during the study, at 10 min after the initial dose was administered (week 0) and at 10 min after the last dose was administered at the end of the third 28-day on period (week 20). Following the completion of inhalation during study treatments, patients gargled three times with 30 mL normal saline solution for 10 s and expectorated the solution to avoid contamination of the specimen by drug deposited in the oropharynx. The purpose was to document the sputum tobramycin levels achieved and their variability during the studies.

Sputum samples were stored and shipped on ice to a central laboratory (at Children’s Hospital and Regional Medical Center, Seattle, WA) where culturing and susceptibility testing of each morphologically distinct *P. aeruginosa* isolate were performed. The MIC of tobramycin for the *P. aeruginosa* isolates cultured from each patient at week 0 and week 24 were documented. The proportion of patients with sputum tobramycin levels exceeding 10-fold and 25-fold the MIC was calculated.

Serum samples for the determination of tobramycin concentrations were collected predose and 1 h after the first dose (week 0) and the last dose (week 20) were administered. Additional serum samples for the determination of tobramycin concentrations were collected from 1 to 12 h after dosing at weeks 4, 8, 12, and 16.

**Tobramycin Assays**

Two separate assays were employed to determine tobramycin concentrations in sputum and serum. The limit of quantitation (LOQ) for each of these assays represents the lowest concentration at which tobramycin could be positively identified and accurately quantitated using that method. Sputum tobramycin concentrations were determined by reverse-phase high-performance liquid chromatography method (LOQ, 20 µg/g), a procedure that was modified from that of one previously published. Sputum was solubilized in 0.2 N NaOH, diluted in Tris buffer (pH 10), and derivatized with 2,4-dinitrofluorobenzene. Absorbance of derivatized tobramycin was measured by ultraviolet detection at 360 nm.

Tobramycin concentrations in serum were determined by fluorescent polarization immunoassay using the standardized testing procedure (TDxFxLx system; Abbott Laboratories; Abbott Park, IL) [LOQ, 0.18 µg/mL]. The system was calibrated with serum calibrators, and assay performance was checked by quality control samples.

**Pharmacokinetic Analysis**

The pharmacokinetic data from the 258 patients who received tobramycin for inhalation was analyzed (MDS Pharma Services, Lincoln, NE) using computer software (NONMEM; NONMEM Project Group, University of California, San Francisco; San Francisco, CA). The pharmacokinetic models for one and two compartments with first-order elimination were obtained using the subroutines of the program. The input fraction for both models was treated as an IV bolus with the exception of the bioavailability fraction (F). The one-compartment model was characterized by apparent clearance (CL/F) and apparent volume of distribution (V/F). The two-compartment model was characterized by the CL/F of the parameter, the V/F of the central compartment, the clearance from the central to the peripheral compartment (Q [also called the intercompartmental clearance]), and the apparent V/F in the steady state.

**Pulmonary Function**

At each visit, spirometry tests (FEV₁ and FVC) were performed according to American Thoracic Society standards. Pulmonary function was expressed as a percentage of the value predicted based on age, gender, and height according to the methods of Knudson et al. In order to assess potential airway reactivity to tobramycin for inhalation administration, FEV₁ was measured 10 min prior to dosing and 30 min after dosing at weeks 0 and 20.

**Statistical Analysis**

In order to investigate the potential effects of pulmonary function on tobramycin for inhalation pharmacokinetics, an analysis of variance (ANOVA) was performed. This analysis was performed at weeks 0 and 20, and it evaluated pulmonary function (i.e., FEV₁ percent predicted, FVC percent predicted, and FEV₁/FVC ratio) in relation to tobramycin concentrations in sputum (10 min postdose) and serum (60 min postdose). The analysis was performed using both baseline predose and 30-min postdose pulmonary function values.

**Results**

**Patient Characteristics**

Demographic and baseline characteristics of the patients in the two parallel phase III studies were similar. Pharmacokinetic and bioavailability data from the tobramycin-for-inhalation groups in the two studies therefore were pooled for analysis. There were 149 male and 109 female patients in the tobramycin-for-inhalation treatment group. The mean age of the 258 tobramycin for inhalation patients was 21 years (range, 6 to 48 years).

**Sputum Concentrations of Tobramycin**

Ninety-five percent of patients had sputum concentrations ≥ 25 times their MIC, and 97.5% had sputum concentrations ≥ 10 times their MIC (data on file). Sputum tobramycin concentrations exhibited substantial interpatient variability, as the coefficient of variation (i.e., the SD divided by the mean times 100) was approximately 100%. Individual patient results ranged from values that were below the LOQ (i.e., < 20 µg/g) to > 8,000 µg/g. The mean and
median sputum tobramycin concentrations measured 10 min after administration of the first dose of tobramycin for inhalation were 1,237 and 959 μg/g, respectively (Table 1). Sputum tobramycin concentrations were not significantly different after the final dose of tobramycin for inhalation was administered.

Subgroup analyses of stratification factors showed that sputum tobramycin concentrations were not significantly influenced by age, gender, or baseline disease severity, as measured by pulmonary function (Table 2).

Exploratory regression analyses showed no association between sputum tobramycin concentrations and pulmonary function (i.e., FEV₁, FVC, or FEV₁/FVC ratio) either at week 0 or week 20. Thus, endobronchial deposition measured by sputum levels of tobramycin appeared to not be significantly affected by pulmonary function (in the range of 25 to 75% of predicted FEV₁) for > 20 weeks.

**Serum Concentrations of Tobramycin**

Mean serum tobramycin concentrations at 1 h after the administration of aerosolized tobramycin for inhalation were approximately 1 μg/mL after the first dose (week 0) and the last dose (week 20) [Table 3]. Individual serum tobramycin results did not exceed 3.6 μg/mL at 1 h after dosing. The random serum tobramycin measurements obtained at interim visits, when the sampling was not fixed at 1 h after the aerosol administration, were mostly below the LOQ for the assay (0.18 μg/mL).

The ratios of the serum concentrations at week 0 and week 20 for individual patients (Table 3) were highly variable due to the frequency of samples near the LOQ. There was no apparent accumulation of tobramycin from the first to the last dosing period, as evidenced by similar mean week 20 and week 0 serum tobramycin levels. Nonadherence with therapy did not appear to be responsible for the lack of tobramycin accumulation in the serum, since 88% of the patients had used at least 75% of the ampules dispensed.²⁹

Subgroup analyses showed that age, gender, and disease severity (as measured by baseline FEV₁) did not significantly influence serum concentrations of tobramycin (Table 4).

Exploratory regression analyses of the effects of pulmonary function on serum tobramycin concentrations showed that 60-min post-treatment serum concentrations were significantly associated with FEV₁ and FVC percent predicted at week 0 (p < 0.01), but not at week 20 (p > 0.5). On average, CF patients with better pulmonary function achieved higher serum tobramycin concentrations from the first inhaled tobramycin dose, but the correlation was not found with the last dose. The FEV₁/FVC ratio, a measure of airway obstruction, was not significantly associated with serum tobramycin levels either at week 0 or week 20.

**Ratio of Serum to Sputum Tobramycin Concentration**

The studies showed that high sputum and low serum concentrations of tobramycin were achieved (Table 5). The median ratio of serum to sputum tobramycin concentrations was 0.010. The mean ratio (0.191) was substantially higher than the median due to a small number of extreme values for the serum/sputum ratio.

**Population Pharmacokinetic Analysis**

The pharmacokinetic analysis indicated that the data were best fit by a two-compartment model. The population estimate of the systemic CL/F was 49.6 L/h, and this value was used to estimate the systemic exposure (i.e., F) of the inhaled dose. Three previous studies³⁷–³⁹ of tobramycin pharmacokinetics showed mean estimates of systemic CL of tobramycin following parenteral doses were 7.05 L/h (estimated using mean weight), 5.04 L/h (estimated using mean surface area), and 5.28 L/h, respectively. Dividing the average of these three values (5.79 L/h as an estimate of clearance) by the CL/F estimate of 49.6 L/h results in an estimate for F of 0.117 (11.7%). This estimate of bioavailability is consistent

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sputum Tobramycin Concentrations at 10 Min After Dosing, μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
</tr>
<tr>
<td>Mean</td>
<td>1,237</td>
</tr>
<tr>
<td>SD</td>
<td>1,090</td>
</tr>
<tr>
<td>Median</td>
<td>959</td>
</tr>
<tr>
<td>Range</td>
<td>35–7,417 BQL–8,085 BQL</td>
</tr>
<tr>
<td>Patients with available specimens, No. (%)</td>
<td>240/258 (93)</td>
</tr>
</tbody>
</table>

*BQL = below quantifiable limits.

*Table 1—Tobramycin Concentrations in Sputum 10 Min After Tobramycin Treatment*
with previous results (9.1% reported by Cooney et al\textsuperscript{37} and 11.1% reported by Town et al\textsuperscript{39}) following aerosol administration of tobramycin in CF patients.

Steady-state serum tobramycin concentrations were simulated for a 300-mg bid dosage regimen using the parameter estimates from the analysis. A steady state was achieved rapidly. The predicted steady-state peak concentration value was 2.6 \( \mu g/mL \), and the predicted steady-state trough concentration value was 0.2 \( \mu g/mL \). The simulations graphically illustrate that there is an absorption phase during the first 2 h, which is very similar to an oral absorption model, with peak concentrations observed 1 to 2 h after dosing. The model was able to accurately predict the mean steady-state serum concentration 1 h after the aerosol administration of tobramycin, 1.13 \( \mu g/mL \), which is consistent with the observed mean concentration of approximately 1 \( \mu g/mL \) in these studies.

**DISCUSSION**

The sputum concentrations obtained from patients using the jet nebulizer in the current investigations were about twice as high (mean, 1,237 \( \mu g/g \); median, 959 \( \mu g/g \)) as those achieved with the earlier version of the nebulizer.\textsuperscript{17} The higher sputum levels approximated those achieved with the tobramycin nominal dose (600 mg) delivered by an ultrasonic nebulizer,\textsuperscript{17} and reflected the improved delivery efficiency of the new nebulizer by the addition of one-way valves.

We observed sputum concentrations as high as 8 \( \mu g/g \) sputum in the current study, and achieved the goal of reaching 10 times the MIC for a bacteriostatic effect and 25 times the MIC for a bactericidal effect in most patients.\textsuperscript{5} The concentration of drug in the sputum relative to the MIC of *P. aeruginosa*, as well as the exceedingly low serum/sputum concentration ratio, reflects the therapeutic advantage of the aerosolized administration of tobramycin over parenteral administration. The ototoxicity and nephrotoxicity related to high serum concentrations of tobramycin (ie, > 10 \( \mu g/mL \)) have not been reported in the literature following the aerosol administration of tobramycin, and they have not been observed in current\textsuperscript{29} or other\textsuperscript{17} tobramycin clinical trials.

This study and others\textsuperscript{16–18,40} have noted wide variability in sputum aminoglycoside levels following drug inhalation. There is a complex relationship between delivery device variables and patient-
related variables that have effects on sputum drug levels. Aerosol delivery devices can differ in efficiency, particle size distributions, and nebulization times.41 However, we observed 3-log exponential differences of sputum levels in a population using a single nebulizer/compressor combination. Although the nebulizer performance plays an important role, extreme variation in tobramycin delivery to the lower airways appears to be more to patient-specific variables than to particle size or other nebulizer variables.16 Due to the wide variations in lung morphology, disease state, and the quantity and distribution of sputum in the lung, peak sputum tobramycin levels alone may not be a good index of drug penetration into the lung.

Although there is some evidence in the literature that the pharmacokinetics of tobramycin administered parenterally may be influenced by age, there was no significant effect of age on the pharmacokinetics of tobramycin when delivered by inhalation in the current study or other studies.17 Coates et al42 used a model of aerosol deposition in CF patients and predicted that, on a weight-adjusted basis, smaller children would receive four times the inhaled drug dose than that of taller children using an unvented nebulizer. One would then expect that younger children would have higher serum levels of tobramycin if the nominal dose were held constant. However, there was no association of age with serum levels in this study (Table 4). Furthermore, a study of children who were < 6 years of age using the same nebulizer (PARI LC PLUS) and tobramycin for inhalation dose (300 mg)43 showed a mean serum level of only 0.6 μg/mL, which is lower than the current study, a finding that is not consistent with the model of Coates et al.42 There are two possible explanations for the discrepancy between the model and in vivo studies. First, the model used an unvented nebulizer, which allows greater dilution of the aerosol with ambient air with larger tidal volumes. With the breath-enhanced nebulizer (PARI LC PLUS), there is no dilution of aerosol with ambient air; rather there is an increase in aerosol output with larger tidal breaths. Thus, with this nebulizer, small children would inhale less total drug than larger patients. Second, the impaction of aerosol in the upper airway is several-fold higher in small children than in adults.44 This filtering effect of the upper airway size “auto-adjusts” the amount of drug that can reach the lung, a variable that was not

### Table 4—Subgroup Analyses of Serum Tobramycin Concentrations at 60 Min After Dosing

<table>
<thead>
<tr>
<th>Variables</th>
<th>Week 0</th>
<th>Week 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD), μg/mL</td>
<td>Median, μg/mL</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>1.12 (0.58)</td>
<td>1.01</td>
</tr>
<tr>
<td>13–17</td>
<td>0.99 (0.50)</td>
<td>0.86</td>
</tr>
<tr>
<td>≥ 18</td>
<td>0.95 (0.40)</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.07 (0.51)</td>
<td>0.97</td>
</tr>
<tr>
<td>Female</td>
<td>0.89 (0.38)</td>
<td>0.85</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 &lt; 50%</td>
<td>0.90 (0.36)</td>
<td>0.88</td>
</tr>
<tr>
<td>FEV1 ≥ 50%</td>
<td>1.08 (0.53)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### Table 5—Comparison of the Serum and Sputum Concentrations Using the Jet Nebulizer (PARI LC Plus)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>60-min Serum Level, μg/mL</th>
<th>10-min Sputum Level, μg/g</th>
<th>Serum/Sputum Ratio, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.0</td>
<td>1,199</td>
<td>0.191</td>
</tr>
<tr>
<td>Median</td>
<td>0.93</td>
<td>588</td>
<td>0.010</td>
</tr>
<tr>
<td>SD</td>
<td>0.58</td>
<td>1,116</td>
<td>0.342</td>
</tr>
<tr>
<td>Range</td>
<td>BQL–3.62</td>
<td>BQL–8085</td>
<td>0.002–5.05</td>
</tr>
<tr>
<td>Patients, No.</td>
<td>262</td>
<td>247</td>
<td>195</td>
</tr>
<tr>
<td>Samples, No.</td>
<td>479</td>
<td>441</td>
<td></td>
</tr>
</tbody>
</table>

*See legend of Table 1 for abbreviations not used in the text.
†The samples from week 0 and week 20 were combined.
included in the model. Therefore, the nominal dose of inhaled tobramycin does not need to be adjusted by age or size when using a breath-enhanced nebulizer like the one used in this study.

The data demonstrated no significant differences between men and women for either the sputum or serum concentrations. In the absence of any apparent gender effect, no adjustment in dose recommendations for gender should be required.

With data from a large population, we were able to average the effects of the many patient variables to calculate the pharmacokinetics and bioavailability of inhaled tobramycin. The systemic pharmacokinetics of tobramycin, when administered by inhalation, are comparable to those following parenteral administration both in terms of clearance and volume of distribution. Estimates of the terminal elimination half-life for tobramycin following aerosol administration are quite variable, ranging from 1.3 to 13 h.\(^37,39\) The systemic pharmacokinetics of tobramycin following aerosol administration are best described by a two-compartment model with biexponential decay from the serum with slope estimates that are comparable to that following parenteral administration.

The administration of drugs by inhalation with jet or ultrasonic nebulizers is recognized to be inefficient relative to oral or IV administration. Only a fraction of the nominal dose is deposited in the lung, with most of the dose either being adhered to the delivery apparatus, deposited in the oropharynx, or exhaled into the surrounding atmosphere.\(^14\) The numerous nebulizer and patient-specific factors that have been discussed have the net effect of a large interpatient variability in sputum tobramycin concentrations that necessitates large doses of nebulized tobramycin to sufficiently exceed the MICs of most \(P\) aeruginosa isolates in most of the patients. Fortunately, the low systemic bioavailability of aerosolized tobramycin (11.7% in this study) allows the safe administration of a relatively large dose. Further improvement in aerosol-generating devices may increase the delivery efficiency to the lung and improve the patient-device interface so that lower nominal doses can achieve high and consistent sputum levels of the drug.

The administration of tobramycin for inhalation, 300 mg bid, in a regimen of 28 days off/28 days on produces low serum tobramycin concentrations, reducing the potential for systemic toxicity and high sputum concentrations that ensure efficacious antibiotic levels at the site of infection. The studies reported here demonstrate that therapy with tobramycin for inhalation significantly improves the therapeutic ratio over that with parenteral aminoglycosides.

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