

# Efficiency of Pulmonary Administration of Tobramycin Solution for Inhalation in Cystic Fibrosis Using an Improved Drug Delivery System\*

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**Study objectives:** To determine whether tobramycin solution for inhalation (TSI) can be administered safely and more efficiently with a new-generation aerosol device, the AeroDose 5.5 RP inhaler (Aerogen; Mountain View, CA) than with the approved PARI LC PLUS nebulizer (PARI Respiratory Equipment; Monterey, CA) with Pulmo-Aide compressor (DeVilbiss Corp; Somerset, PA). Second, we wanted to ascertain which AeroDose-delivered tobramycin dose is equivalent to the standard 300-mg dose administered with the PARI LC PLUS.

**Design:** Open-label, randomized, multicenter, single-dose, three-period, four-treatment, active-control, crossover trial.

**Setting:** Nine US cystic fibrosis (CF) centers.

**Patients:** Fifty-three patients  $\geq 12$  years of age with a confirmed diagnosis of CF, the ability to expectorate sputum, and FEV<sub>1</sub> of  $\geq 40\%$  of predicted.

**Methods:** Subjects inhaled three single doses of TSI at 1-week intervals, as follows: conventional control treatment, 300 mg via the PARI LC PLUS; and two of three experimental treatments, 30, 60, or 90 mg via the AeroDose. FEV<sub>1</sub> was measured before and after dosing. After each dose, sputum and serum samples were collected at various intervals for 8 h, and urine was collected for 24 h to estimate lung and systemic tobramycin delivery.

**Results:** There were no significant differences between treatments in the change in FEV<sub>1</sub> 30 min after dosing or in the frequency of adverse events. Sputum and serum levels of tobramycin produced by the AeroDose 90-mg dose treatment approximated those achieved with the PARI LC PLUS 300-mg dose treatment. Nebulization times using the AeroDose inhaler were  $< 50\%$  those of the PARI LC PLUS.

**Conclusions:** Compared with the standard nebulizer, the AeroDose safely achieved an approximately threefold greater efficiency in the delivery of TSI to the lungs in less than half the time.

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**Key words:** antibiotics; cystic fibrosis; drug delivery systems; inhalation administration; nebulizers; pharmacokinetics; *Pseudomonas aeruginosa*; tobramycin

**Abbreviations:** AUC<sub>(0–8)</sub> = area under the concentration-time curve through 8 h postdose; CF = cystic fibrosis; C<sub>max</sub> = maximum tobramycin concentration; LOQ = lower limit of quantitation; T<sub>max</sub> = time at which maximum tobramycin concentration was observed; TSI = tobramycin solution for inhalation

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Cystic fibrosis (CF) patients with endobronchial infections caused by *Pseudomonas aeruginosa* are customarily treated with two parenteral antipseudomonal antibiotics, one of which is typically an

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aminoglycoside. IV administered aminoglycosides penetrate poorly into the endobronchial space, reaching mean peak sputum concentrations that are

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only 12 to 20% of the peak serum concentrations.<sup>1-3</sup> However, because components of CF sputum bind aminoglycosides, sputum concentrations must exceed 10-fold to 25-fold the minimum inhibitory concentration to be bactericidal.<sup>4,5</sup> Thus, to achieve adequate drug concentrations at the site of infection, it is necessary to use large IV doses, which may produce serum levels associated with renal toxicity, vestibular toxicity, and ototoxicity.<sup>6,7</sup>

These problems can be overcome with the use of aerosolized aminoglycosides, which can deliver high concentrations of drug topically to the lungs while minimizing systemic exposure.<sup>8,9</sup> Inhaled tobramycin has been shown to be safe, well-tolerated, and effective in improving lung function and in decreasing the density of *P aeruginosa* in sputum.<sup>10</sup>

Nebulizer systems for administering inhaled tobramycin have improved in efficiency over the past decade. Weber et al<sup>11</sup> showed that the UltraNeb 100 ultrasonic nebulizer (DeVilbiss Corp; Somerset, PA) was an effective delivery system for tobramycin and that its use resulted in high sputum concentrations. The UltraNeb 100 was used in an open-label study<sup>12</sup> and later in a placebo-controlled, randomized trial of inhaled tobramycin, 600 mg three times daily.<sup>13</sup> Despite the positive study results, therapy with high-dose tobramycin via the ultrasonic system was

not used widely, because of the high medication cost, patient inconvenience, and problems with nebulizer maintenance. Breath-enhanced jet nebulizers offered a simpler, more efficient system for tobramycin delivery, which, with half the nominal dose of drug, achieved sputum concentrations rivaling those of the ultrasonic nebulizer.<sup>14,15</sup> The PARI LC PLUS jet nebulizer (PARI Respiratory Equipment; Monterey, CA) powered by the Pulmo-Aide compressor (DeVilbiss Corp) was successfully used in the two large pivotal trials of a tobramycin solution for inhalation (TSI) [TOBI; Chiron Corp; Emeryville, CA].<sup>16</sup> Yet, the administration of 300 mg TSI with the PARI LC PLUS system still takes > 15 min twice daily. This imposes a significant time burden on patients with CF, who are commonly treated with multiple inhaled medications. Thus, further improvement in aerosol delivery systems with greater efficiency and portability, and shorter nebulization times could improve patient quality of life and compliance.

The AeroDose 5.5 RP (Aerogen; Mountain View, CA) is a new, hand-held, battery-powered, breath-actuated aerosol delivery system (Fig 1). The AeroDose nebulizes fluid by a novel method that minimizes the amount of residual drug that is present at the end of a treatment and aerosolizes at a faster rate than typical jet nebulizers. Due to the technology that the AeroDose employs, it has the potential to decrease the nebulization time of TSI by at least half using a smaller nominal dose than the PARI LC PLUS. The goals of the current study were to investigate whether the AeroDose inhaler can de-

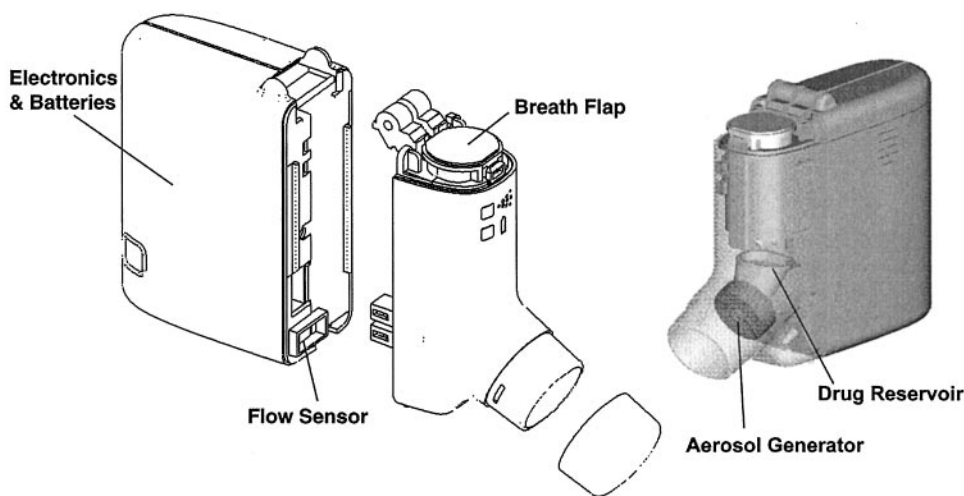


FIGURE 1. The AeroDose 5.5 RP inhaler has a compartment containing the batteries and electronics to coordinate breath actuation and a separate compartment that contains the refillable drug reservoir and the aerosol generator. The aerosol generator is a porous dome surrounded by a piezoelectric element, which oscillates the dome at a high frequency and pumps the medication through the pores to form an aerosol.

liver equivalent amounts of TSI to the respiratory tract in less time than the PARI LC PLUS nebulizer, to determine which AeroDose-administered dose of TSI is equivalent to the standard 300-mg dose administered with the PARI LC PLUS device, and to compare the safety and tolerability of the two delivery systems.

## MATERIALS AND METHODS

### Subjects

Inclusion criteria included a documented diagnosis of CF,<sup>17</sup> age of  $\geq 12$  years, ability to expectorate  $\geq 2$  g sputum in 24 h, and an FEV<sub>1</sub>  $\geq 40\%$  of the predicted value.<sup>18</sup> Exclusion criteria included receiving therapy with inhaled or IV aminoglycosides within 7 days prior to the initial study drug administration; receiving any investigational drug within 2 weeks of study initiation; receiving loop diuretics; positive results for a serum pregnancy test; hemoptysis of  $> 60$  mL within 30 days prior to study initiation; serum creatinine level of  $> 2$  mg/dL; BUN level of  $\geq 40$  mg/dL or urinalysis results with  $\geq 2+$  proteinuria; and known hypersensitivity to aminoglycosides. All patients or their guardians provided written informed consent, and the study was approved by the institutional review board at each participating center.

### Aerosol Delivery Devices

The approved, conventional nebulizer system for TSI is the PARI LC PLUS jet nebulizer powered by the Pulmo-Aide compressor. The aerosol is produced by the shearing forces of a jet of compressed air on a thin film of liquid, causing it to form small droplets. This breath-enhanced nebulizer improves lung delivery compared to conventional jet nebulizers by entraining inspired air through a one-way valve into the nebulizer cup, which increases nebulizer output to the patient during inhalation. The PARI LC PLUS/Pulmo-Aide system requires a power outlet, produces a TSI aerosol with a mass median diameter of 4.8  $\mu\text{m}$ , and has an output rate of 3.6  $\mu\text{L}/\text{sec}$ .

The AeroDose is a new-generation aerosol device that is slightly larger than a metered-dose inhaler (Fig 1). The aerosol is produced by a piezoelectric ring, which oscillates a porous dome over the TSI at ultrasonic frequencies, causing a "pumping" action to occur. The device is battery-operated and generates an aerosol of TSI with a mass median diameter of 4.0  $\mu\text{m}$  at a rate of 8.0  $\mu\text{L}/\text{s}$ . Drug waste is minimal because almost all of the nominal dose is nebulized, and an airflow sensor and microprocessor limit aerosol generation to inhalation only.

### Study Design

This open-label, randomized, multicenter, three-period, cross-over trial compared the safety, efficiency, and pharmacokinetics of TSI delivered by the AeroDose 5.5 RP (called the *experimental treatment*) with those delivered by the PARI LC PLUS jet nebulizer with Pulmo-Aide compressor (called the *conventional treatment*).

Each patient received three single doses of TSI at 1-week intervals, as follows: the conventional treatment (TSI, 300 mg, via the PARI LC PLUS/Pulmo-Aide compressor); and two of three experimental treatments (TSI, 30, 60, or 90 mg, via the AeroDose 5.5 RP). TSI was formulated as a 60 mg/mL preservative-free

tobramycin in one quarter normal saline solution adjusted to a mean ( $\pm$  SD) pH of  $6.0 \pm 0.5$ . It was supplied as a single 5-mL ampule for the active control treatment and as 0.5-mL unit dose syringes for the experimental treatment. The experimental treatment doses were chosen to deliver levels of tobramycin to the lower respiratory tract that were comparable to those produced by the conventional treatment, based on the increased efficiency of the AeroDose nebulizer. Subjects were randomly assigned to one of 12 treatment sequences consisting of one active control treatment and two experimental treatments. The conventional treatment was administered in either the first or the second treatment period. This approach maximized the number of patients who were available for comparisons of control treatment vs experimental treatment in the event that early patient withdrawals were frequent.

Subjects inhaled the study drug while in the seated position, wearing noseclips and using normal tidal breathing. They were instructed to continue inhaling the study drug until no further mist was produced by the nebulizer. A bronchodilator was administered 15 to 60 min before the study treatment in patients who routinely used bronchodilators. Since the AeroDose holds one 0.5-mL syringe at a time (containing 30 mg TSI), the refilling of the device was required for the 60-mg and 90-mg doses. Immediately after treatment, patients rinsed and gargled with saline solution. Sputum and serum were collected for the assay of tobramycin concentrations before study drug administration and 10 min, 1 h, 2 h, 4 h, and 8 h after the completion of study drug aerosol inhalation. Urine was collected for the assay of tobramycin concentrations at 12 h before dosing and at 0 to 8 h and 8 to 24 h after dosing. The total volume was recorded, and a 10-mL aliquot from each time period was retained for analysis. Spirometry was performed according to American Thoracic Society standards<sup>19</sup> before and 30 min after dosing. Serum was collected for the measurement of BUN and creatinine levels at the initial screening and at the third treatment visit.

### Measurement of Tobramycin Concentrations

Sputum and serum samples were frozen immediately after collection. Urine was refrigerated. Tobramycin concentrations in sputum were measured by high-performance liquid chromatography at Chiron Corporation (lower limit of quantitation [LOQ], 20.0  $\mu\text{g}/\text{g}$  sputum).<sup>20</sup> Tobramycin concentrations in serum and urine were measured by immunoassay (TDx/FLx fluorescence polarographic immunoassay; Abbott Laboratories; Irving, TX) at a core laboratory (Covance Laboratories, Inc; Vienna, VA) [serum LOQ, 0.18  $\mu\text{g}/\text{mL}$ ; urine LOQ, 1.0  $\mu\text{g}/\text{mL}$ ].<sup>21</sup>

### Safety Analysis

The intention-to-treat population, consisting of all randomized patients who received at least one dose of study medication, was included in safety analyses. The primary outcome measure was the change in FEV<sub>1</sub> between the predosing value and that obtained 30 min after dosing. The frequency of predose to postdose declines in FEV<sub>1</sub> by  $\geq 10\%$  and  $\geq 20\%$  of the absolute value in each treatment group was compared using the McNemar test for paired comparisons. Pairwise *t* tests also were used to compare the mean relative changes in FEV<sub>1</sub> percent predicted from predose to postdose between each experimental treatment group and the control treatment group. The incidences of treatment-emergent adverse events and abnormal and/or clinically significant changes in physical examination and laboratory values were evaluated descriptively.

### Pharmacokinetic Analyses

Patients who had received one control treatment and at least one of the experimental treatments were evaluable for pharma-

cokinetic analyses. The maximum tobramycin concentration (C<sub>max</sub>) in sputum and serum and the time at which C<sub>max</sub> was observed (T<sub>max</sub>) were identified for each patient for each treatment period. The areas under the concentration-time curve through 8 h postdose (AUC<sub>0-8</sub>) were calculated from sputum and serum tobramycin concentrations using the linear trapezoidal method. Relative systemic bioavailability was calculated as the experimental group serum AUC<sub>0-8</sub> divided by the control group serum AUC<sub>0-8</sub>, then multiplied by 100. The natural logarithms of AUC<sub>0-8</sub> and C<sub>max</sub> based on sputum and serum tobramycin concentrations were analyzed using a mixed-effect, repeated-measure, analysis-of-variance model containing treatment, period, and carryover (*ie*, treatment by period interaction) as fixed effects and containing patient as a random effect. Because exploratory evaluations of age, gender, and body weight demonstrated no important effects on pharmacokinetic results, these characteristics were not included in the models. A correlation analysis between baseline FEV<sub>1</sub> and dose-corrected sputum and serum C<sub>max</sub> was performed.

#### Nebulization Times

The duration of nebulization was defined as the time from the patient's first tidal breath after the device was in place until no more solution could be aerosolized by the device. Nebulization time did not include any interruptions or the time needed for repeat filling of the AeroDose 5.5 RP. It was assumed that if the AeroDose were commercialized for use with TSI, a single ampule would be used that would not require refilling. Descriptive statistics for nebulization time were reported for each treatment group.

All analyses were conducted using computer software (SAS, version 8.1; SAS Institute, Cary, NC). A two-tailed *p* value of < 0.05 was considered to be significant. The program (SAS) code for noncompartmental pharmacokinetic analyses was validated against the output from another program (WinNonlin; Pharsight Corp; Mountain View, CA).

## RESULTS

Of 56 patients screened for the study, 53 met the eligibility criteria and were randomized. Fifty-two of these randomized subjects received at least one dose of study medication and were included in the intention-to-treat analysis, and one patient dropped out before the start of treatment because of a pulmonary exacerbation requiring hospitalization. Forty-nine patients completed the study and were included in the pharmacokinetic analysis. The demographic and clinical characteristics of these patients are summarized in Table 1. Two patients discontinued the study during the period

of treatment with TSI, 300 mg, one because of a pulmonary exacerbation 4 days after dosing and one because of urticaria, petechial rash, and nausea 48 h after dosing. A third subject withdrew from the study after experiencing hemoptysis 6 days after receiving TSI, 90 mg, by the AeroDose inhaler.

#### Bronchospasm

Bronchospasm, defined as a decline of  $\geq 10\%$  in FEV<sub>1</sub> 30 min after dosing relative to the predosing value, occurred in a total of 24 instances in 15 patients. Only two of these instances were marked by a fall in FEV<sub>1</sub> of  $\geq 20\%$ . One episode occurred after conventional treatment with TSI, 300 mg, delivered by the PARI LC PLUS, and the other occurred after treatment with TSI, 60 mg, by the AeroDose inhaler. There were no significant differences in either the magnitude of the relative change in FEV<sub>1</sub> or the overall incidence of bronchospasm between the control treatment and any of the three experimental treatments (Table 2).

#### Adverse Events

In general, the control and experimental treatments were well-tolerated. Drug-related adverse events were documented in 15.7% of patients after the control treatment, in 14.7% of patients after treatment with 30 mg TSI, in 6.3% of patients after treatment with 60 mg TSI, and in 15.2% after treatment with 90 mg TSI by the AeroDose. The most common treatment-related adverse events were decreased FEV<sub>1</sub> (five patients), mild increase in coughing (four patients), wheezing (two patients), and chest tightness (four patients). None of the posttreatment adverse events increased in frequency with increases in the TSI dose, and no correlation was seen between the frequency of adverse events and the drug delivery system used. The only serious adverse event regarded as possibly related to the study drug was the development of urticaria and petechiae in a 22-year-old man after the control treatment, without an identified secondary exposure. He was treated in the emergency department with subcutaneous epinephrine and IM diphenhydramine, with relief of symptoms.

**Table 1—Demographic and Clinical Characteristics of Patients Who Completed the Study (n = 49)\***

Parameter	Male Patients (n = 19)	Female Patients (n = 30)
Age, yr	23.9 (15–36)	24.3 (12–50)
Weight, kg	64.1 (7.0)	53.3 (12.0)
Height, cm	173.1 (8.0)	160.0 (9.0)
FEV <sub>1</sub> , % predicted		67.4 (40–116)†

\*Values given as mean (range) or mean (SD).

†Values are the mean (range) for both groups.

**Table 2—Incidence of Acute Bronchospasm\***

Measure of Bronchospasm	Control Group (n = 51)	Experimental Groups		
		TSI 30 mg (n = 34)	TSI 60 mg (n = 32)	TSI 90 mg (n = 33)
FEV <sub>1</sub> decrease ≥10%	9 (17.6)	5 (14.7)†	6 (18.8)†	4 (12.1)†
FEV <sub>1</sub> decrease ≥20%	1 (2.0)	0 (0.0)	1 (3.1)†	0 (0.0)

\*Values given as No. of patients (%). Patients may be counted in more than one treatment-group column.

†Not significant vs control group.

### Pharmacokinetics

Sputum tobramycin concentrations peaked rapidly after drug administration, reaching the measured C<sub>max</sub> within 10 min of dosing (Fig 2). The median half-life of tobramycin in sputum was approximately 2 h in all four treatment regimens. Interpatient variability of sputum tobramycin levels was very high in all treatment groups, with the coefficient of variation approaching 100% of the mean values. When TSI was delivered by the AeroDose, the C<sub>max</sub> and sputum AUC<sub>0–8</sub> increased linearly with dose increases, suggesting linear pharmacokinetics (Table 3). The sputum tobramycin concentrations achieved with the 90-mg dose administered by the AeroDose inhaler were similar throughout the 8-h postdosing measurement period to those obtained with the 300-mg dose delivered by the PARI LC PLUS nebulizer. When adjusted for the nominal dose of

TSI, the sputum C<sub>max</sub> was three times greater with the 90-mg dose of tobramycin administered by the AeroDose inhaler than with the 300 mg dose of tobramycin administered by the PARI LC PLUS nebulizer (10.64 and 3.29 μg/g/mg TSI, respectively), indicating greater efficiency of delivery with the new device.

Serum tobramycin concentrations peaked at approximately 60 min after dosing (Table 3 and Fig 3). The serum C<sub>max</sub> and AUC<sub>0–8</sub> after AeroDose inhaler delivery increased with increases in the dose at each measurement time point during the 8-h post-treatment period, suggesting that the serum pharmacokinetics, like the sputum pharmacokinetics, were linear. Serum C<sub>max</sub> and AUC<sub>0–8</sub> were slightly lower after the administration of 90 mg TSI via the AeroDose inhaler than after the administration of 300 mg TSI delivered with the PARI LC PLUS nebulizer.

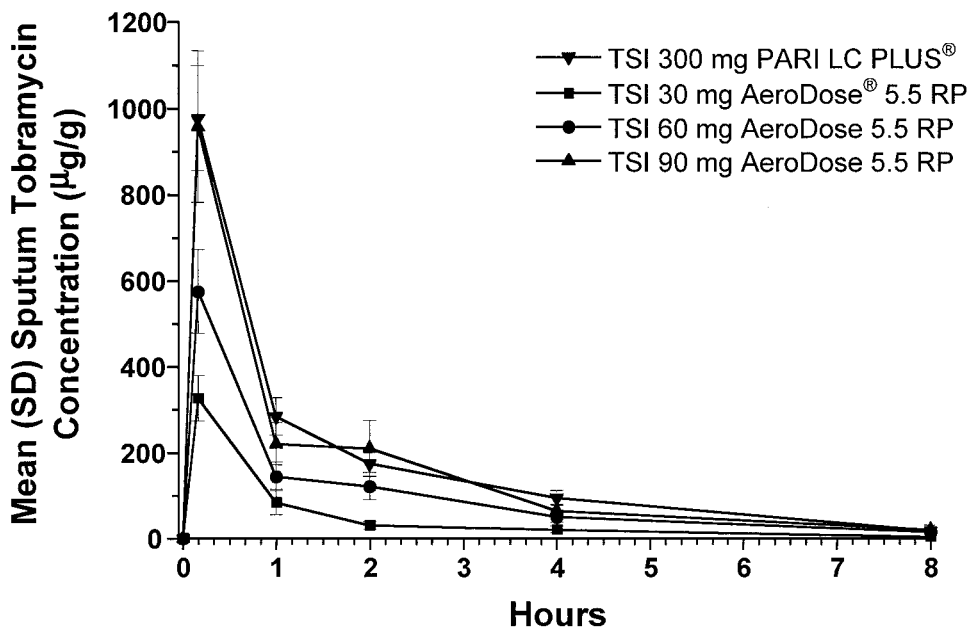


FIGURE 2. After dosing with TSI, the mean sputum tobramycin concentrations increased rapidly, reaching C<sub>max</sub> within 10 min (T<sub>max</sub>), and declined thereafter, with a median half-life of approximately 2 h. Sputum tobramycin concentrations were highly variable among patients, as coefficients of variation (SD divided by the mean, times 100%) approached or exceeded 100% for each treatment at all time points.

**Table 3—Pharmacokinetic Parameters and Nebulization Times\***

Pharmacokinetic Parameter or Nebulization Time	Control Group (n = 51)	Experimental Groups		
		TSI 30 mg (n = 34)	TSI 60 mg (n = 32)	TSI 90 mg (n = 33)
Sputum Tmax, h	0.26 (0.38)	0.24 (0.24)	0.38 (0.76)	0.33 (0.41)
Sputum Cmax, µg/g	985.65 (839.34)	329.05 (311.30)	577.83 (538.42)	958.00 (952.30)
Dose-normalized sputum Cmax, µg/g/mg	3.29 (2.80)	10.97 (10.38)	9.63 (8.97)	10.64 (10.58)
Sputum AUC <sub>(0-8)</sub> , µg/h/g	1,471.16 (1278.22)	360.79 (422.23)	804.78 (722.83)	1,275.23 (1358.52)
Serum Tmax, h	1.05 (0.38)	1.14 (0.42)	0.98 (0.28)	1.14 (0.64)
Serum Cmax, µg/mL	1.12 (0.44)	0.38 (0.17)	0.69 (0.34)	0.96 (0.40)
Serum AUC <sub>(0-8)</sub> , µg/h/mL	4.96 (2.24)	1.43 (1.43)	2.98 (1.92)	3.94 (1.52)
Dose-normalized serum AUC <sub>(0-8)</sub> , µg/h/mL/mg	0.0166 (0.0075)	0.0478 (0.0477)	0.0496 (0.0319)	0.0438 (0.0169)
Recovery in urine (0–24 h), mg	18.1 (8.3)	5.6 (3.0)	9.8 (3.8)	14.6 (6.0)
Relative bioavailability, %	100	29	60	79
Nebulization time, min	17.7 (4.7)	2.8 (1.0)	5.4 (2.1)	8.0 (2.5)

\*Values given are mean (SD).

The dose-normalized serum Cmax and AUC<sub>0-8</sub> were approximately three times higher after all three AeroDose-delivered TSI doses, indicating greater efficiency with the AeroDose inhaler than with the PARI LC PLUS nebulizer (Table 3). The median serum half-life ranged from 2.73 to 4.27 h with the AeroDose dose levels, compared with 3.14 h for the 300-mg dose of TSI using the PARI LC PLUS nebulizer. The half-life results using the AeroDose inhaler appeared to decrease with increases in the TSI dose, but it is likely that this is an artifact related

to the greater frequency of undetectable serum levels at lower dose levels. No cases of untoward elevations in serum tobramycin levels (*ie*, ≥ 4 µg/mL) were documented.

Urinary pharmacokinetics, like serum pharmacokinetics, showed that the amount of tobramycin recovered in the urine was higher during the 24 h after the administration of 300 mg TSI with the PARI LC PLUS nebulizer than after the delivery of 90 mg TSI via the AeroDose inhaler (18.1 and 14.6 mg, respectively). The mean 24-h amount of

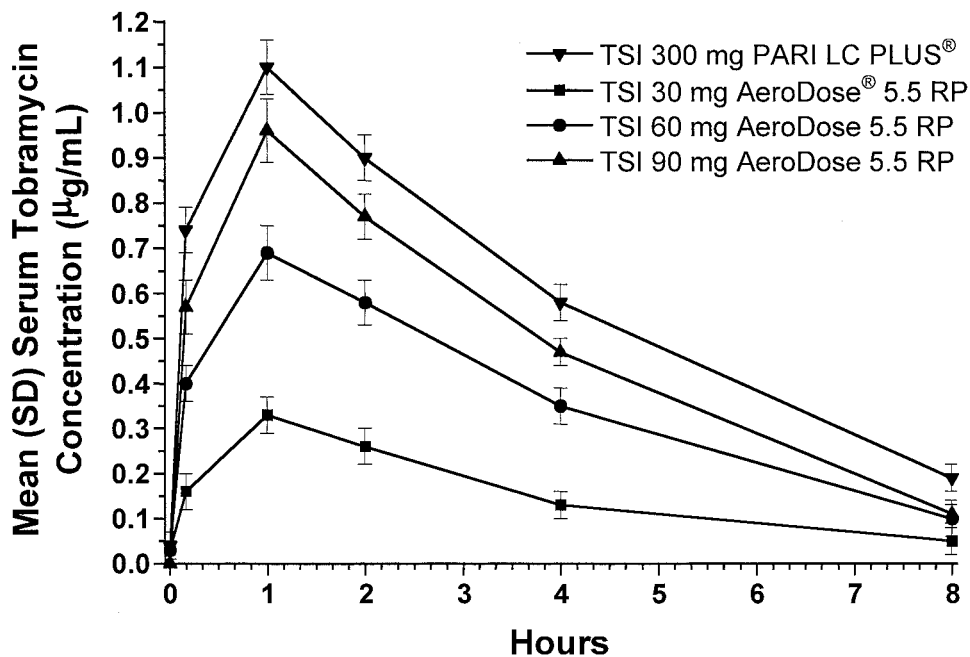


FIGURE 3. After dosing with TSI, the serum tobramycin concentrations gradually increased, reaching Cmax 1 h after dosing (Tmax), and declined thereafter, with median half-lives ranging from 2.73 to 4.27 h.

urinary tobramycin excretion after treatment with the AeroDose device increased with increases in the drug dose, which is consistent with linear pharmacokinetics. The proportion of the nominal dose of tobramycin that was recovered in the urine after AeroDose dosing was approximately three times greater than that recovered after PARI LC PLUS dosing (16.2% to 18.8% and 6.0%, respectively) [Table 3].

Analysis of the equivalent dose for the AeroDose device was performed using a mixed-effects, repeated-measures, analysis-of-variance model containing treatment, period, and carryover as fixed effects and patient as a random effect. The results showed that the equivalent dose for the AeroDose inhaler is between 99 mg, using the sputum C<sub>max</sub> data, and 111 mg, using the serum AUC<sub>0-8</sub> data.

Regression analysis demonstrated an inverse correlation between baseline FEV<sub>1</sub> and sputum tobramycin C<sub>max</sub>. That is, patients with a greater degree of airway obstruction had slightly higher sputum concentrations. The correlation coefficient was -0.321 for the PARI LC PLUS dose ( $p = 0.02$ ) and -0.204 for the AeroDose treatments ( $p = 0.04$ ). No correlation was found between serum pharmacokinetics and FEV<sub>1</sub> percent predicted at baseline.

#### *Nebulization Times*

The mean nebulization times with the AeroDose device were 2.8 min for the 30-mg TSI dose, 5.4 min for the 60-mg TSI dose, and 8.0 min for the 90-mg TSI dose (Table 3). It should be noted, however, that since the AeroDose drug reservoir used in this study holds only 30 mg TSI, two and three refills were needed for the 60-mg and 90-mg doses, respectively. The amount of time needed to refill the AeroDose was not measured. The nebulization time for the administration of 300 mg TSI via the PARI LC PLUS nebulizer averaged nearly 18 min.

Ten subjects experienced a malfunction of the AeroDose inhaler. In three instances, the malfunction was caused by the accumulation of dried tobramycin solution on the circuit board and on the leads to the aerosol generator during the refilling of the inhaler. After the discovery of this problem early in the study, all subsequent doses were administered with a fresh AeroDose unit. Three patients reported that the AeroDose device was difficult to actuate during normal tidal breathing but found that consistent device performance was produced by deep breathing. Three other patients reported slow or intermittent actuation of the inhalers, and a fourth patient found that the exhalation valve did not work. No malfunctions were reported with the PARI LC PLUS nebulizer.

## DISCUSSION

Our study shows that the delivery of TSI by the AeroDose 5.5 RP device is safe and well-tolerated by CF patients with mild-to-moderate lung disease. The AeroDose was three times more efficient at the delivery of TSI than the PARI LC PLUS. A dose of 90 mg TSI delivered by the AeroDose produced similar sputum levels and slightly lower serum and urine bioavailability of tobramycin than did those achieved by the 300-mg TSI dose delivered by the PARI LC PLUS/Pulmo-Aide compressor. The nebulization time for the AeroDose was less than half that of the PARI LC PLUS.

The AeroDose inhaler is an example of a new generation of aerosol delivery devices that are designed to be less wasteful, more efficient, and more portable. A key feature of the AeroDose is that it is breath-actuated, so that the drug is not nebulized to the atmosphere during exhalation. Since at least half of the respiratory cycle is exhalation, the breath-actuation feature should result in at least a doubling of the amount of the drug that is available to the lung. The AeroDose also nebulizes almost the entire drug dose that is placed in the unit. All current ultrasonic and jet nebulizers, including the PARI LC PLUS, leave a significant amount of drug in the bottom of the device or leave adherent to its walls or baffles after nebulization.<sup>22</sup> Since the AeroDose does not waste drug during exhalation and reduces residual losses in the nebulizer, it requires only one third of the nominal dose of TSI to achieve sputum levels that are similar to those of the PARI LC PLUS.

The higher output rate and the greater efficiency of the AeroDose device compared to current nebulizers allow for a more rapid delivery time, which may lead to improved patient adherence to therapy. If the AeroDose were modified to accommodate a 90-mg dose of TSI without the need for refilling, the average patient would save 9 h of nebulization time during a 4-week treatment cycle. In addition, because the AeroDose device is compact and battery-operated, patients can administer a dose while traveling to school or work. However, to achieve the time savings with the AeroDose in the clinical setting, the device will require modification to eliminate the need for refilling the unit with TSI during a treatment. In addition, this proof-of-concept study was performed with a modification of a device that was not initially designed for the tidal-breathing technique. Manufacturing a reusable device that corrects the malfunctions encountered in this study has yet to be realized and would be necessary before performing larger clinical trials.

The delivery of TSI with the AeroDose 5.5 RP was safe and well-tolerated. The rate of adverse events

and the declines in FEV<sub>1</sub> were similar in all treatment groups. The incidence of bronchospasm (*ie*, < 10% decline in FEV<sub>1</sub>) was similar to that found in the study by Ramsey et al,<sup>16</sup> which also used the PARI LC PLUS system. Adverse events in this study occurred with the same frequency as those reported prior to dosing and were characteristic of the signs and symptoms of the underlying CF.

By assessing sputum antibiotic concentrations, we can compare device performance and can ensure that an adequate amount of tobramycin reaches the endobronchial site of infection.<sup>4,5</sup> Drug deposition and distribution in the lung depend on aerosol particle size, particle velocity, and patient factors, including breathing patterns, airway anatomy, and degree of airway obstruction. The complexity of aerosol drug delivery contributes to the high variability of sputum concentrations that were seen in this study and in others.<sup>14,15,23</sup> Variability was not reduced by the dosimetric characteristic of the AeroDose, which was disappointing. The extreme variability also makes it difficult to correlate sputum drug levels with patient demographic characteristics and to predict total lung deposition (*ie*, the number of milligrams of TSI reaching the lower airways).<sup>23</sup> Nuclear scintiscan studies in CF patients have shown that as airway disease worsens (*ie*, as FEV<sub>1</sub> decreases), total lung deposition increases and the distribution of aerosol deposition in the lung favors the central airways and becomes less homogeneous.<sup>23-26</sup> The current study demonstrated that patients with a greater degree of airway obstruction had slightly higher sputum levels, although the correlation was weak. It is unlikely that this finding has clinical significance, given the high nominal doses of TSI that were used. We also lack the evidence to link the clinical effectiveness of TSI with the pattern of distribution in the lung.

Imaging studies with gamma scintigraphy provide an alternative to sputum concentrations for measuring lung deposition. In a recent study<sup>27</sup> using radio-labeled TSI in healthy volunteers, the AeroDose delivered 35.4% of the dose to the lungs, compared with only 9.1% of the dose for the PARI LC PLUS. The increased efficiency of the AeroDose over the PARI LC PLUS was partly due to a decrease in the residual dose (15% vs 43.5% of the nominal dose, respectively) and a decrease in the amount of the dose wasted from or during exhalation (16.3% vs 28.3%, respectively). The efficiency ratio is similar to our 3:1 deposition ratio of the AeroDose vs PARI LC PLUS using sputum and serum concentrations. From sputum levels, we calculated that the equivalent dose of TSI would be 99 mg delivered with the AeroDose, compared with 300 mg delivered with the PARI LC PLUS.

In addition to achieving high antibiotic levels at

the site of infection, the inhalation of TSI minimizes systemic exposure.<sup>8,9</sup> Serum levels were measured to monitor safety of the dosing with the AeroDose as well as to compare the bioavailability and pharmacokinetics of tobramycin between doses and devices. The highest individual peak serum concentration (2.2 µg/mL) occurred after dosing with the PARI LC PLUS. As was the case for sputum levels, the mean serum levels increased with increasing TSI doses but were highly variable. In all subjects, the peak serum tobramycin levels were well below levels associated with toxicity.

Most of the aerosolized tobramycin found in serum is a result of lung absorption, with a small component from GI absorption.<sup>28</sup> The determinants of the systemic absorption of tobramycin from the lung include the complex variables that contribute to lung deposition and distribution, as well as the epithelial surface area and permeability. Healthier patients may be able to deposit the antibiotic more peripherally in the lung for easier absorption (larger surface area), but they also have a more intact epithelium, which acts as a barrier to hydrophilic drugs like tobramycin.<sup>29</sup> Therefore, predicting serum levels on the basis of pulmonary function or other patient demographic variables would be difficult. In our study, there were no correlations between serum peak or AUC<sub>0-8</sub> levels and age, gender, level of lung function, or sputum levels.

Serum and urine levels were correlated because both measure the systemic exposure to tobramycin. Also, the mean serum and urine levels increased with increasing doses of tobramycin delivered by the AeroDose device. The mean serum C<sub>max</sub> was slightly higher for the 300-mg dose of TSI administered by the PARI LC PLUS nebulizer than for the 90-mg dose of TSI administered with the AeroDose inhaler. Based on a systemic bioavailability comparison, one would need 111 mg of TSI delivered with the AeroDose inhaler to equal a 300-mg TSI dose administered via the PARI LC PLUS nebulizer.

## CONCLUSION

The AeroDose 5.5 RP delivered TSI to the lung with three times the efficiency and in less than half the time of the US Food and Drug Administration-approved PARI LC PLUS nebulizer with PulmoAide compressor. The current study showed that the delivery of 90 mg TSI by the AeroDose 5.5 RP inhaler achieved similar sputum levels, systemic absorption, and urinary recovery of tobramycin as those achieved by the administration of 300 mg TSI by the PARI LC PLUS system. There was no increase in the risk of adverse events or of excessively

high serum tobramycin levels with the AeroDose device. The malfunction of a few AeroDose inhalers demonstrates some of the difficulties encountered when investigating new aerosol delivery technology. Despite those problems, this study has demonstrated a quantum improvement in tobramycin delivery by inhalation. The further development of new aerosol devices supported by clinical testing will allow CF patients to be the beneficiaries of an effective aerosol therapy that minimizes time constraints and may improve quality of life.

## APPENDIX

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## REFERENCES

- Klastersky J, Thys JP, Mombelli G. Comparative studies of intermittent and continuous administration of aminoglycosides in the treatment of bronchopulmonary infections due to gram-negative bacteria. *Rev Infect Dis* 1981; 3:74-83
- Alexander MR, Schoell J, Hicklin G, et al. Bronchial secretion concentrations of tobramycin. *Am Rev Respir Dis* 1982; 125:208-209
- Braude AC, Hornstein A, Klein M, et al. Pulmonary disposition of tobramycin. *Am Rev Respir Dis* 1983; 127:563-565
- Mendelman PM, Smith AL, Levy J, et al. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. *Am Rev Respir Dis* 1985; 132:761-765
- Levy J, Smith AL, Kenny MA, et al. Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum. *J Infect Dis* 1983; 148:1069-1076
- American Academy of Otolaryngology. Guide for the evaluation of hearing handicap. *JAMA* 1979; 241:2055-2059
- Brummett RE. Drug-induced ototoxicity. *Drugs* 1980; 19:412-428
- Touw DJ, Brimicombe RW, Hodson ME, et al. Inhalation of antibiotics in cystic fibrosis. *Eur Respir J* 1995; 8:1594-1604
- Rosenfeld M, Cohen M, Pharm B, et al. Aerosolized antibiotics for bacterial lower airway infections: principles, efficacy, and pitfalls. *Clin Pulm Med* 1997; 4:101-112
- Pai VB, Nahata MC. Efficacy and safety of aerosolized tobramycin in cystic fibrosis. *Pediatr Pulmonol* 2001; 32:314-327
- Weber A, Smith A, Williams-Warren J, et al. Nebulizer delivery of tobramycin to the lower respiratory tract. *Pediatr Pulmonol* 1994; 17:331-339
- Smith AL, Ramsey BW, Hedges DL, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr Pulmonol* 1989; 7:265-271
- Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993; 328:1740-1746
- Eisenberg J, Pepe M, Williams-Warren J, et al. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizer systems. *Chest* 1997; 111:955-962
- Geller DE, Pitlick WH, Nardella PA, et al. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. *Chest* 2002; 122:219-226
- Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999; 340:23-30
- Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement; Cystic Fibrosis Foundation Consensus Panel. *J Pediatr* 1998; 132:589-595
- Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127:725-734
- American Thoracic Society. Standardization of spirometry: 1987 update; statement of the American Thoracic Society. *Am Rev Respir Dis* 1987; 136:1285-1298
- Baran D, De Vuyst P, Ooms HA. Concentration of tobramycin given by aerosol in the fluid obtained by bronchoalveolar lavage. *Respir Med* 1990; 84:203-204
- Jolley ME, Stroupe SD, Wang CJ, et al. Fluorescence polarization immunoassay: I. Monitoring aminoglycoside antibiotics in serum and plasma. *Clin Chem* 1981; 27:1190-1197
- Geller DE. Choosing a nebulizer for cystic fibrosis applications. *Curr Opin Pulm Med* 1997; 3:414-419
- Ilowite JS, Gervoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. *Am Rev Respir Dis* 1987; 136:1445-1449
- Diot P, Palmer LB, Smaldone A, et al. RhDNase I aerosol deposition and related factors in cystic fibrosis. *Am J Respir Crit Care Med* 1997; 156:1662-1668
- Mukhopadhyay S, Staddon GE, Eastman C, et al. The quantitative distribution of nebulized antibiotic in the lung in cystic fibrosis. *Respir Med* 1994; 88:203-211
- Wilson D, Burniston M, Moya E, et al. Improvement of nebulised antibiotic delivery in cystic fibrosis. *Arch Dis Child* 1999; 80:348-352
- Newman SP, Flora M, Hirst PH, et al. Pharmacoscintigraphy of TOBI in the PARI LC PLUS, and the AeroDose inhaler [abstract]. *J Aerosol Med* 2001; 14:388
- Weber A, Williams-Warren J, Ramsey B, et al. Tobramycin serum concentrations after aerosol and oral administration in cystic fibrosis. *Am J Ther* 1995; 2:81-87
- Widdicombe J. Drug uptake in the trachea. *J Aerosol Med* 1996; 9:11-17