

Distribution and elimination of tobramycin administered in single or multiple daily doses in adult patients with cystic fibrosis

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Aminoglycosides are often prescribed as part of the treatment regimen for acute pulmonary exacerbations due to their potent activity and low potential for development of resistance. Preliminary evidence from randomized controlled trials in patients with cystic fibrosis (CF) suggests that once-daily administration of aminoglycosides results in similar efficacy and a low risk for toxicity compared with traditional dosing. The pharmacokinetics of aminoglycosides administered once daily in CF patients are currently not well described. In this study we compare the distribution and elimination patterns of traditional dosing (3.3 mg/kg q8h) versus once-daily dosing (10 mg/kg q24h) of tobramycin in six adult patients with CF. The pharmacokinetics of tobramycin administered either once daily or every 8 h were best described by a two-compartment model. No statistically significant differences in any of the pharmacokinetic parameter values between regimens were noted. The distribution phase half-lives of 32 and 24 min following the q8h and q24h regimens were longer than expected. The use of a one-compartment model requires clinical peak levels to be drawn 2 h after initiation of either a 30 min infusion for multiple daily dosing or a 60 min infusion with once-daily dosing, to ensure completion of the distribution phase. Our data indicate that a dose of 10 mg/kg/day provides post-distributional phase peak concentrations that achieve the desired goal for susceptible organisms (>20 mg/L) and AUC₂₄ values at the upper end of the desired range (70–100 mg·h/L).

Introduction

Acute pulmonary exacerbations requiring intravenous antibiotics are a frequent complication in patients with cystic fibrosis (CF). Aminoglycosides are often prescribed as part of the treatment regimen due to their potent activity and low potential for development of resistance. Traditionally, aminoglycosides have been dosed multiple times a day. Over the past decade, investigations into the pharmacodynamic properties of aminoglycosides have yielded data that favour extended interval administration. Demonstration of concentration-dependent bactericidal activity and the presence of a post-antibiotic effect (PAE) suggests that less frequent administration of larger doses may maximize bactericidal activity. In addition, saturable uptake mechanisms within the

renal cortex and inner ear indicate that extended interval dosing may also minimize the likelihood of developing nephrotoxicity and ototoxicity.¹⁻³ Experience from randomized controlled trials suggests that once-daily administration of aminoglycosides results in similar efficacy and perhaps a decreased risk of developing toxicity compared with traditional dosing.^{4,5} Clinical data in CF patients, although limited, support this concept.⁶⁻¹¹

The pharmacokinetics of aminoglycosides administered once daily in CF patients are currently not well described. Several investigators have compared the pharmacokinetics of once-daily with multiple daily dosing of tobramycin in small numbers of patients with CF.^{6-9,12,13} However, these investigations have utilized model-independent analysis and thus have not characterized the distribution phase. Preliminary

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evidence suggests that the pharmacokinetics may be dose dependent.^{8,14}

This study evaluated the pharmacokinetics of once-daily tobramycin administration in adult CF patients admitted for the treatment of an acute pulmonary exacerbation. The specific aim of this project was to compare the distribution and elimination patterns of traditional dosing (3.3 mg/kg q8h) with once-daily dosing (10 mg/kg q24h).

Materials and methods

Study design

The pharmacokinetics of once-daily tobramycin in CF patients admitted for an acute pulmonary exacerbation was examined in this prospective, crossover trial. This study was approved by the Institutional Review Board at the University of Southern California. All patients gave written informed consent. Six adult patients were recruited to receive either 3.3 mg/kg every 8 h or a single 10 mg/kg dose of intravenous tobramycin in 100 mL of 5% dextrose in water on the first day. On the second day, the patients were crossed over to receive the alternative dose. The 3.3 mg/kg dose was infused over 30 min and administered every 8 h for 1 day, while the 10 mg/kg dose was administered as a single 60 min infusion. Inclusion criteria for this study were: age >18 years, most recent sputum culture positive for *Pseudomonas aeruginosa* and admission for treatment of an acute pulmonary exacerbation. Patients were excluded if they were pregnant, attempting to conceive or nursing an infant, had a history of hypersensitivity to an aminoglycoside, or did not have intravenous access at the time of recruitment.

Blood samples

Blood samples (5 mL) were obtained from an indwelling venous catheter prior to administration, at the end of infusion, then at 10, 20, 30, 45, 60, 90, 120, 240 and 450 min post-dose. An additional sample at 720 min was obtained following the administration of the 10 mg/kg dose. The catheter was flushed with 5–10 mL of 0.9% sodium chloride before and after each blood sample was collected. The first 3 mL of each blood sample was discarded. Each blood sample was immediately placed on ice and allowed to clot. The sample was then centrifuged and the serum harvested. Serum (1–2 mL) was transferred from each sample and frozen at -70°C until assayed.

Analytical determination of tobramycin concentrations

Serum tobramycin concentrations were determined using a validated fluorescence polarization immunoassay (TDx; Abbott Laboratories, Irving, TX, USA). The lower limit of detection for the assay is 0.1 mg/L. The assay precision was determined by measuring four replicates of six concentrations

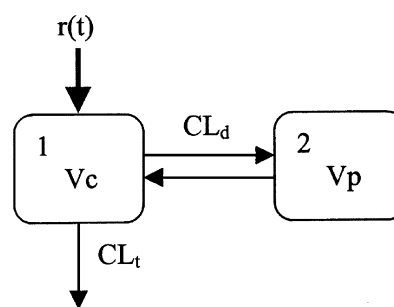


Figure 1. Two-compartment pharmacokinetic model. r , rate of infusion; t , time; V_c , volume of central compartment; V_p , volume of peripheral compartment; CL_d , distribution clearance; CL_t , total clearance.

representing the observed range of concentrations in all patients. The coefficient of variation for concentrations of tobramycin equal to 0.25, 4, 11, 21, 29 and 35 mg/L was 3.5, 3.7, 1.3, 1.2, 1.5 and 3.4%, respectively.

Pharmacokinetic analysis

Standard two-stage pharmacokinetic analysis was performed using ADAPT II (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA, USA).¹⁵ Serum concentrations were fitted to one- and two-compartment models (Figure 1) using maximum likelihood analysis. Model discrimination was based on Akaike information criteria. The primary pharmacokinetic parameters obtained from the analysis were the volume of central compartment and peripheral compartments (V_c , V_p), the clearance (CL) and distribution clearance (CL_d). The distribution (α) and elimination (β) rate constants, and distribution ($t_{1/2}^{\alpha}$) and elimination ($t_{1/2}^{\beta}$) half-lives were also derived using standard equations.

Statistical analysis

Descriptive statistics were calculated for each subject's height, weight, age, body surface area, body mass index, predicted creatinine clearance and dose. Differences in pharmacokinetic parameters between the two dosing regimens were assessed by the Mann–Whitney U -test. A P value <0.05 was considered statistically significant. Correlation analyses were performed to assess the relationship between pharmacokinetic parameters and individual patient covariates.

Results

Patient demographics are summarized in Table 1. The patients were all adults with ages ranging from 23 to 34 years old. Renal function, normalized for body surface area, was normal in all patients. Six patients received both the 3.3 mg/kg q8h and the 10 mg/kg q24h doses of tobramycin. Mean doses were 186.7 mg (140–240 mg) for the q8h regimen and 543.3 mg (440–740 mg) for the q24h regimen.

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Table 1. Patient demographics and clinical parameters

Parameter	Mean \pm S.D.	Range
Males/females	4/2	–
Age (years)	29.0 \pm 4.6	23–34
Height (inches)	65.5 \pm 1.3	64–68
TBW (kg)	55.3 \pm 13.8	45–75
BSA (m ²)	1.6 \pm 0.2	1.47–1.87
BMI (kg/m ²)	19.7 \pm 3.2	16.5–25.9
CL _{CR} (mL/min/1.73 m ²)	127.0 \pm 5.8	120.6–132.9

TBW, total body weight; BSA, body surface area; BMI, body mass index; CL_{CR}, creatinine clearance.

The pharmacokinetics of tobramycin administered either once daily or every 8 h were best described by a two-compartment model, as shown by the lower AIC and higher r^2 values (Figures 2 and 3; Table 2). The pharmacokinetic parameter values and fitted maximum (C_{max}) and minimum (C_{min}) serum concentrations are summarized in Table 3. The distribution phase half-lives of 32 and 24 min following the

q8h and q24h regimens were relatively long. The elimination half-lives of 3.1 and 2.7 h following the q8h and q24h regimens are relatively short and reflect the excellent renal function exhibited by these adult patients with CF. No statistically significant differences in any of the pharmacokinetic parameter values between doses were noted. A significant negative correlation was noted between body surface area and $t_{1/2}^{\alpha}$ with the q24h regimen ($r = -0.89$, $P = 0.03$); however, no similar correlation was seen with the q8h regimen. No other significant relationship was seen between the other pharmacokinetic parameters and any specific patient covariates (e.g. weight, age).

Discussion

The objective of this study was to compare the pharmacokinetics of once-daily tobramycin dosing with the more traditional multiple daily dosing regimen in patients with CF. While there are a few studies evaluating the pharmacokinetics of once-daily aminoglycoside administration in this population (Table 4), none to our knowledge has used the com-

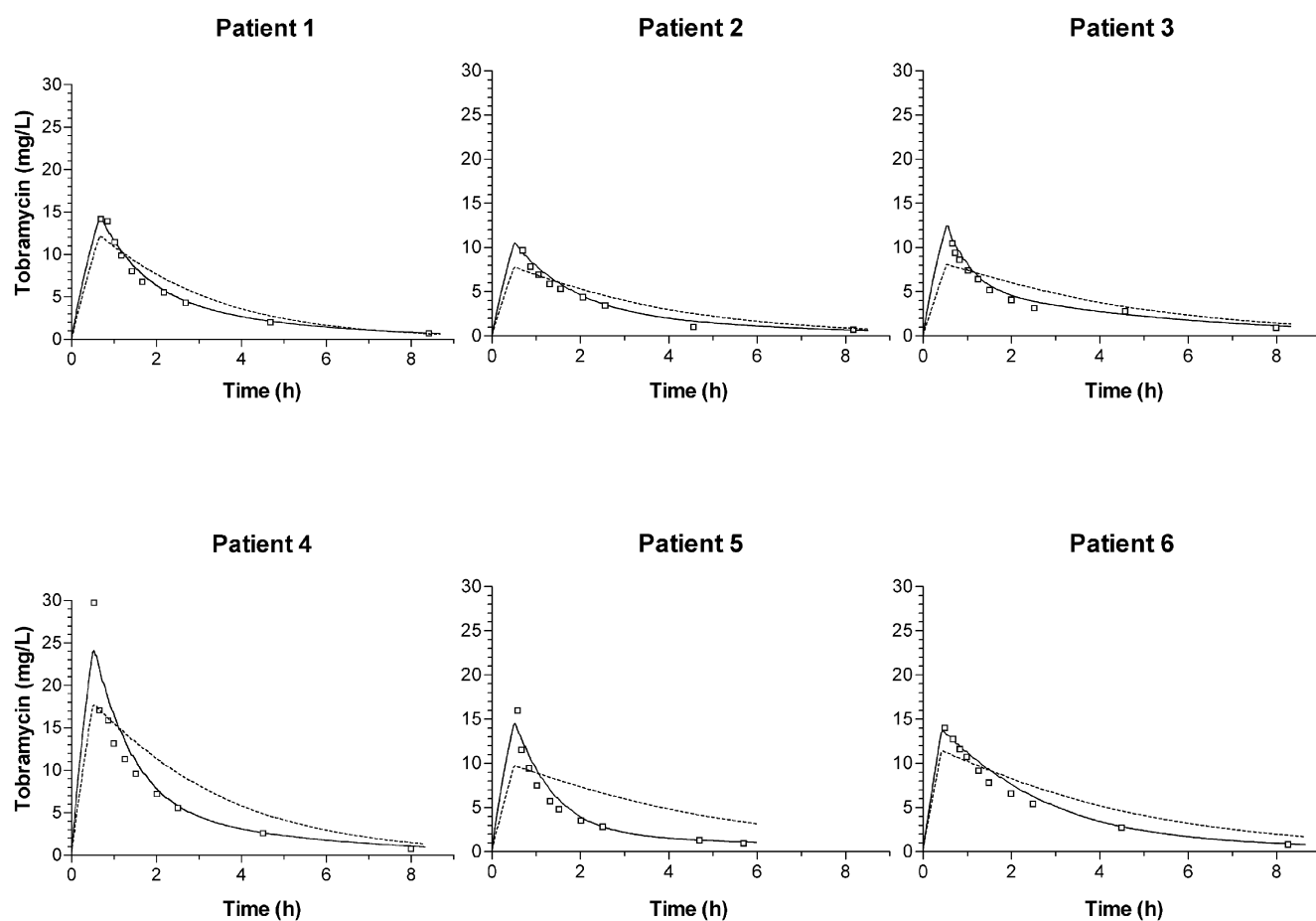


Figure 2. Individual serum concentration versus time curves (q8h regimen). Dashed line, one-compartment model; solid line, two-compartment model; squares, measured serum concentration data.

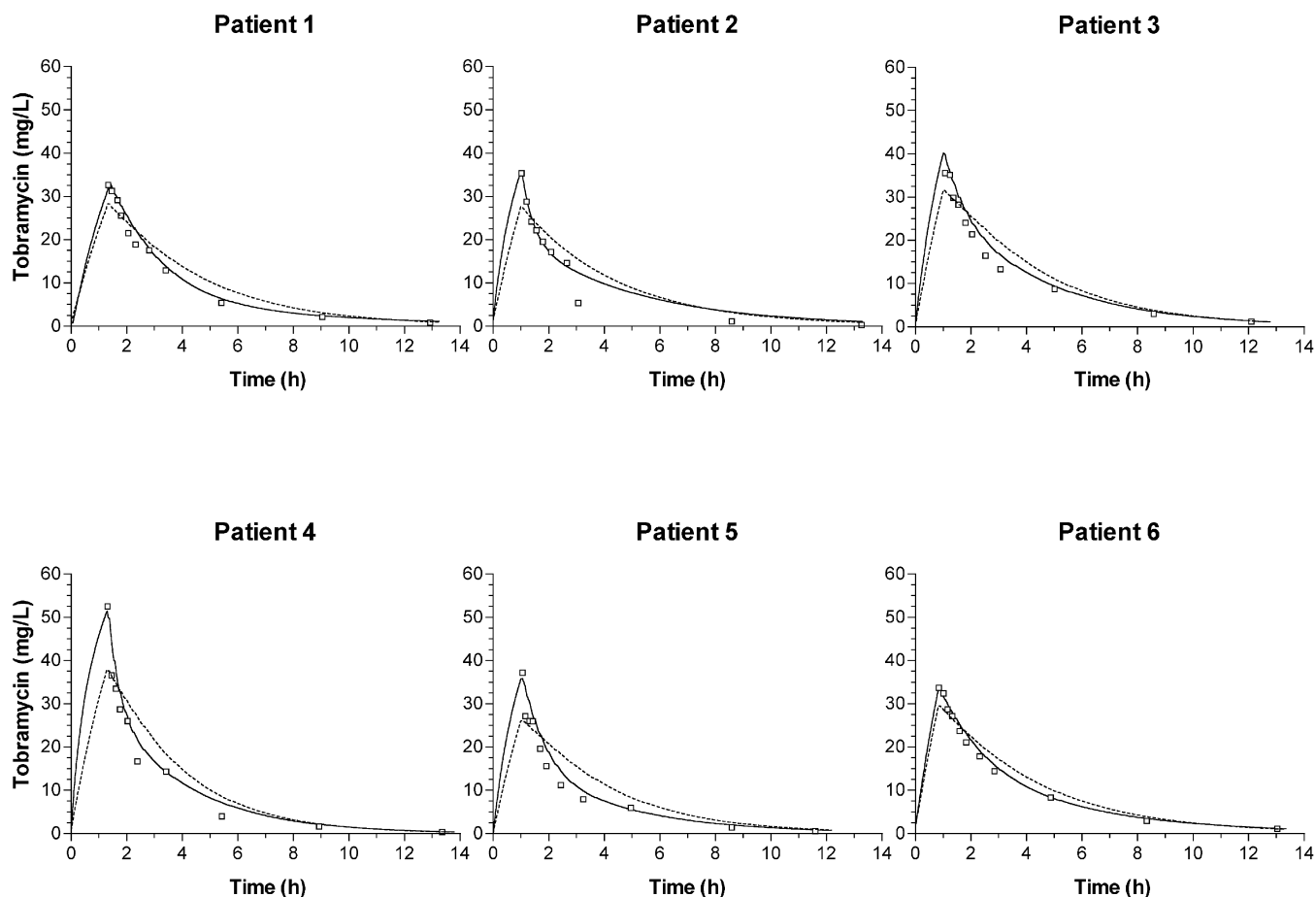


Figure 3. Individual serum concentration versus time curves (q24h regimen). Dashed line, one-compartment model; solid line, two-compartment model; squares, measured serum concentration data.

Table 2. Model discrimination when using a one- or two-compartment model to describe the individual serum time curves

Patient	q8h				q24h			
	one-compartment		two-compartment		one-compartment		two-compartment	
	r^2	AIC	r^2	AIC	r^2	AIC	r^2	AIC
1	0.94	44.70	0.98	20.36	0.97	69.75	1.00	47.10
2	0.93	49.89	0.99	18.73	0.88	194.92	0.97	179.45
3	0.86	60.60	0.99	15.39	0.96	42.32	1.00	31.12
4	0.79	136.93	0.94	36.03	0.90	85.98	0.99	59.48
5	0.67	235.33	0.97	15.71	0.90	100.74	0.98	40.56
6	0.93	73.68	0.99	14.67	0.98	45.17	1.00	35.31

AIC, Akaike information criteria.

partmental analysis necessary to characterize both the distribution and elimination phases.^{6-9,12,13} Considering the larger doses of aminoglycosides administered to patients with CF, the possibility for dose-dependent changes in pharmaco-

kinetics is potentially greater than that observed in healthy volunteers or other patient populations.

The pharmacokinetics of once-daily aminoglycoside administration has been well described in healthy volunteers.

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Table 3. Pharmacokinetic parameters determined after once-daily and conventional administration of tobramycin

Parameter	q8h [median (interquartile range)]	q24h [median (interquartile range)]	P value
$t_{1/2}^{\alpha}$ (h)	0.54 (0.40–1.05)	0.40 (0.26–1.02)	0.39
$t_{1/2}^{\beta}$ (h)	3.07 (2.67–5.83)	2.72 (2.22–3.70)	0.18
V_c (L/kg)	0.20 (0.14–0.25)	0.16 (0.11–0.24)	0.39
V_{ss} (L/kg)	0.38 (0.26–0.46)	0.31 (0.22–0.33)	0.06
CL_t (mL/min/kg)	2.02 (1.37–2.46)	1.68 (1.30–2.04)	0.39
CL_d (mL/min/kg)	1.17 (0.49–2.44)	1.61 (0.53–2.14)	0.59
AUC_{24} (mg·h/L)	97.34 (77.58–122.5)	107.7 (95.74–123.1)	0.85
C_{max} (mg/L)	14.0 (11.5–19.3)	35.9 (33.2–45.8)	–
C_{min} (mg/L)	0.9 (0.8–1.2)	–	–
C_{12}	–	1.4 (0.8–1.5)	–

$t_{1/2}^{\alpha}$, distribution half-life; $t_{1/2}^{\beta}$, elimination half-life; V_c , volume of central compartment; V_{ss} , steady-state volume; CL_t , total clearance; CL_d , distribution clearance; AUC_{24} , area under the curve in 24 h; C_{max} , maximum serum concentration; C_{min} , minimum serum concentration; C_{12} , concentration 12 h after start of infusion.

Demczar *et al.*¹⁴ compared the pharmacokinetics of once-daily versus multiple daily dosing of gentamicin in 11 adult, healthy volunteers in a randomized, crossover, single-dose study. Subjects were randomized to receive either a 2 or 7 mg/kg dose in phase I of the study, and then were crossed over in phase II. Data were fitted to single and multiple compartment models, and it was determined that a two-compartment model best fitted the data. This study showed statistically significant differences in the distribution half-lives between the multiple daily and once-daily dose groups (21.4 versus 41.6 min), suggesting a prolonged distribution phase in the higher dose group.¹⁴ In addition, there were statistically significant differences in total clearance values between the two dosing regimens, with the low-dose regimen showing a higher rate of gentamicin clearance. The authors noted no explanation for this difference.

The pharmacokinetic parameters found in the present study compare favourably with those from previous investigations (Table 4),^{8,9,12} with the exception of the study conducted by Vic *et al.*⁷ Vic and colleagues published two studies evaluating the pharmacokinetics of amikacin and one comparative trial of multiple versus once-daily dosing of tobramycin in patients with CF.^{6,7,13} In each of these studies the estimates of the volume of distribution and the interpatient variability are much higher than that previously reported. In addition, the reported tobramycin clearance values for both the q8h and once-daily regimens are much lower than the values found in our study and those reported by previous investigators. In their pharmacokinetic analysis, Vic and colleagues fitted the serum concentration data to a two-compartment model using non-linear least squares regression. One possible explanation for the apparent discrepancy in the pharmacokinetic parameters may be inappropriate weighting of the serum concentration data in the regression

analysis.¹⁶ One limitation to our study is the small sample size, which may have limited the determination of any statistical significance between the two groups.

Our study is the first to characterize the distribution phase following single daily dosing of an aminoglycoside in patients with CF. In contrast to the results reported by Demczar *et al.*¹⁴ in healthy volunteers, we did not find the distribution phase to be dose dependent. The importance of the distribution phase in the clinical setting pertains to the timing of concentrations necessary to determine the optimal dose. The current practice commonly employed in the clinical setting is to obtain a peak concentration 30 min after a 30 min infusion.^{8,11} Our data suggest that sampling 30 min after a 30 min infusion of the multiple daily regimen, or 30 min after the once-daily regimen, would give concentrations in the distribution phase. Considering the relatively long distribution half-life of ~30 min for both dosing regimens in our study, the distribution phase would be expected to be 94% complete by 2 h (four distribution half-lives). Therefore, use of a one-compartment model would require clinical peak levels to be drawn 2 h after initiation of either a 30 min infusion for multiple daily dosing or a 60 min infusion with once-daily dosing, to ensure completion of the distribution phase. If the peaks were drawn prior to completion of the distribution phase, the pharmacokinetic parameter estimates determined by a one-compartment model would be inaccurate and could lead to incorrect assumptions about the appropriateness of the dosing regimen. As our data show, a two-compartment model more accurately describes the disposition of tobramycin than a one-compartment model, and should ideally, therefore, be used in the therapeutic drug monitoring of these patients. D-optimal sampling design is a method that has been employed to determine the optimal number, and timing, of measurements to maximize the information about the pharmacokinetic para-

Table 4. Comparative pharmacokinetics of single and multiple daily dosing of tobramycin in patients with CF

Ref. no.	Drug	Regimen	n	Age (years)	CL	V _{ss} (L/kg)	t _{1/2} ^α (h)	t _{1/2} ^β (h)
12	tobramycin	3.3 mg/kg q8h	5	NR	0.10	0.26 ± 0.06	NR	1.98 ± 0.30
		10 mg/kg single dose			0.10 (L/h/kg)	0.26 ± 0.06		1.96 ± 0.25
8	tobramycin	7–15 mg/kg divided q8h	18	25 ± 8	1.93 ± 0.30	0.27 ± 0.05	NR	NR
9	tobramycin	7–15 mg/kg qd	7	10–14	1.75 ± 0.44 (mL/min/kg)	0.27 ± 0.06	NR	2.37 ± 0.37
		8 mg/kg qd			3.67 ± 0.82	0.43 ± 0.09		2.32 ± 0.20
7	tobramycin	15 mg/kg qd	22	11 ± 3	3.74 ± 1.24 (L/h)	0.45 ± 0.07	NR	NR
		5 mg/kg q8h			3.73 ± 1.37	0.54 ± 0.88		
		15 mg/kg qd			4.73 ± 2.43 (mL/h/kg)	0.97 ± 0.44		
Present study	tobramycin	3.3 mg/kg q8h	6	29 ± 5	2.02 ^a	0.38 ^a	0.54 ^a	3.1 ^a
		10 mg/kg single dose			1.68 (mL/min/kg)	0.31	0.40	2.7
14	gentamicin	2 mg/kg q8h	11 ^b	38 ± 11	76.6 ± 6.6	0.23 ± 0.11	0.36	2.7
		7 mg/kg single dose			67.2 ± 4.2 ^c (mL/min/1.73 m ²)	0.19 ± 0.04	0.69 ^d	2.9

n, number of patients or subjects; t_{1/2}^α, distribution half life; t_{1/2}^β, elimination half life; V_{ss}, steady-state volume; CL_T, total clearance; qd, once daily; NR, not reported.

Where relevant, numbers given are mean ± S.D.

^aMedian.

^bHealthy volunteers.

^cP < 0.001.

eters to be estimated.^{15,17} A prospective study comparing the traditional method of monitoring (e.g. one-compartment model applied to a peak obtained 30 min after a 30 min infusion and trough) with the recommended method (e.g. two-compartment model applied to serum concentrations obtained at the D-optimal times) would enable determination of the most precise method of achieving the pharmacodynamic goals of therapy.

The larger aminoglycoside doses prescribed to patients with CF are based on the altered pharmacokinetics (higher clearance and larger volume of distribution) demonstrated in previous studies, allowing for larger total daily doses to achieve higher peak concentrations, followed by rapid elimination prior to the next dose. The reported advantage of once-daily aminoglycoside administration is that a significantly greater number of patients will achieve the pharmacodynamic target of a peak concentration exceeding 10 × MIC.¹⁸ Results of a large phase III study of aerosolized tobramycin in patients with CF demonstrated that the MIC₅₀ and MIC₉₀ against *P. aeruginosa* are 1 and 8 mg/L, respectively.¹⁹ Therefore, in order to maximize the pharmacodynamic activity of tobramycin in patients with CF, a peak concentration of 20 mg/L is required to provide the desired peak/MIC ratio of 10 against susceptible isolates (MIC ≤ 2 mg/L).²⁰ Our data indicate that a dose of 10 mg/kg/day provides post-distributional phase peak concentrations that achieve the desired goal for susceptible organisms (>20 mg/L) and AUC₂₄ values at the upper end of the desired range (70–100 mg·h/L).²¹

In conclusion, the pharmacokinetics of once-daily tobramycin in patients with CF was best described using a two-compartment model. Our data suggest that distribution is not complete 30 min after a conventional dose or once-daily dose. Thus, clinical analysis using ‘standard’ peak times may lead to erroneous conclusions about the revised pharmacokinetic parameters and clinical efficacy. Rather, it is recommended that clinicians utilize a two-compartment model with samples obtained immediately after the end of infusion and at trough times for a 3.3 mg/kg q8h dose, and immediately after the end of the infusion and 12 h after the start of the infusion for a 10 mg/kg q24h dose. Samples beyond 12 h will approach the limit of detection for the assay and may therefore preclude estimation of the pharmacokinetic parameters. Alternatively, if a one-compartment model is assumed, the ‘peak’ concentration should be obtained at least 2 h after initiation of either a 30 min infusion when receiving q8h dosing or a 60 min infusion for once-daily dosing to determine the appropriateness of the dose and facilitate revision of the regimen if necessary.

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