Safety of Extended Interval Tobramycin in Cystic Fibrosis Patients Less Than 6 Years Old

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OBJECTIVES The primary objective of this study was to assess the nephrotoxicity and ototoxicity risks of extended interval tobramycin in cystic fibrosis (CF) patients who are <6 years old. A secondary objective included analyzing pharmacokinetic parameters in this age group.

METHODS A retrospective chart review was conducted of patients with CF who were <6 years old, admitted for an acute pulmonary exacerbation from January 1, 2003, to January 1, 2014, and treated with intravenous tobramycin.

RESULTS The median baseline serum creatinine (SCr) was 0.26 mg/dL among the 31 patients included in the study. Of the 20 patients who experienced increases in SCr, the absolute median increase was 0.065 mg/dL (0.033–0.1 mg/dL). Abnormal audiograms seen in 4 patients are attributable to middle ear effusion present on exam. The median dose of tobramycin was 11.7 mg/kg (11.3–12 mg/kg), the elimination constant was 0.4 hr^{-1} (0.32–0.47 hr^{-1}), half-life was 1.7 hr (1.5–2.1 hr), volume of distribution was 0.37 L/kg (0.31–0.47 L/kg), and median peaks and troughs fell within ranges of 20 to 30 mg/L (20.9–32.7 mg/L) and <0.01 mg/L, respectively.

CONCLUSIONS Extended interval dosing tobramycin is safe in CF patients who are <6 years old. There was no drug-related ototoxicity, and some nephrotoxicity was observed. When dosed at 12 mg/kg, similar pharmacokinetics were seen among all age groups, and concentrations were within the desired range.

ABBREVIATIONS ARF, acute renal failure; CF, cystic fibrosis; Cp_{PEAK} , serum peak concentration; Cp_{TR} , serum trough concentration; CrCL, creatinine clearance; eCCL, estimated creatinine clearance; EID, extended interval dosing; ke, elimination constant; MIC, minimum inhibitory concentrations; PK, pharmacokinetics; SCr, serum creatinine; $T_{1/2}$, half-life, Vd, volume of distribution

KEYWORDS cystic fibrosis; extended interval aminoglycosides; extended interval tobramycin; safety

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Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease that primarily affects the lungs and digestive system. Approximately 30,000 people in the United States have been diagnosed with CF, and there are around 1000 new patients diagnosed every year.¹ In patients with CF, a defective gene and its protein product (CF transmembrane conductance regulator, *CFTR*) cause the body to produce a thick, sticky mucous that builds up within the lungs, leading to infections, and it also affects other organ systems throughout the body.² The lungs of patients with CF will eventually become colonized and infected by bacteria, leading to acute pulmonary exacerbations. One of the pathogens commonly responsible for these acute episodes is *Pseudomonas aeruginosa*. The prevalence of *P aeruginosa* among CF patients increases with age. Approximately 20% of patients <6 years of age are infected, compared to 75% of those who are 35 to 44 years of age.³ Double coverage with 2 antipseudomonal drugs (i.e.,

aminoglycosides and beta-lactams) is recommended to enhance bactericidal activity and minimize resistance among all age groups.²

Aminoglycosides are widely used for treating pulmonary exacerbations in patients with CF.⁴ Patients will have extended courses of aminoglycosides, often from a very young age, which makes them especially vulnerable to the adverse effects of these drugs, specifically nephrotoxicity and ototoxicity. In the kidney, these drugs can cause proximal tubular damage, while toxic concentrations can cause acute tubular necrosis. In the inner ear, these drugs can damage cochlear hair cells and lead to impairment and even deafness.⁵ In the past, aminoglycosides have been traditionally dosed 3 times daily in patients with normal renal function; however, in 2008 the CF Foundation recommended the use of extended interval dosing (EID) when treating an exacerbation.² This change is due to the results of the TOPIC Trial, which compared EID to 3 times-daily dosing of tobramycin in CF patients.⁶ Within the adult CF patient population, serum creatinine (SCr) increased by 2% in

the extended interval group and decreased by 1.1% in the traditionally dosed group; however, these changes were not statistically significant ($p = 0.14$). In contrast, children aged 6 to 17 years had a decrease in SCr of 4.5% in the EID group and an increase of 3.7% in traditionally dosed patients ($p = 0.04$). The potential toxicity risks for nephrotoxicity and ototoxicity have yet to be studied in children who are less than 6 years of age.

Tobramycin is the preferred aminoglycoside in CF patients with an acute CF exacerbation. A case-control study by Smyth et al⁷ evaluated 24 patients who previously developed acute renal failure while on aminoglycosides and matched them to control subjects to determine if aminoglycosides increased the risk of acute renal failure (ARF) and to see if gentamicin was more nephrotoxic compared to other aminoglycosides. Of the initial 24 cases who developed ARF, 21 had recently received an aminoglycoside. When patients were matched to controls, it was clear that gentamicin was more nephrotoxic than was tobramycin. Seventy-nine percent of patients who received gentamicin developed ARF, compared to only 38% in those who received tobramycin. As a result of this and previous studies, gentamicin is no longer recommended for CF exacerbations.

The objective of this study was to assess the incidence rates of nephrotoxicity and ototoxicity among CF patients who were <6 years old and who received EID tobramycin. Secondary objectives included evaluating the weight-based dosing and serum drug concentrations required to meet desired pharmacokinetic parameters in this age group.

Materials and Methods

Patients and Setting. This institutional review board–approved retrospective study was conducted at a large academic pediatric hospital with a CF Foundation–accredited CF center. Cystic fibrosis patients who were less than 6 years of age who were admitted to the hospital for an acute pulmonary exacerbation during the time period from January 1, 2003, through January 1, 2014, were included in the study. Patients were excluded if they did not receive tobramycin, had preexisting hearing impairment (i.e., history of abnormal audiometry), preexisting renal impairment (i.e., history of renal disease or injury, as noted in the past medical history), had received nebulized antibiotics during the hospitalization (e.g., inhaled tobramycin), had received thrice-daily dosing of tobramycin, or had undergone previous intravenous aminoglycoside treatment within the past 6 years. The study population was limited to the first intravenous aminoglycoside exposure to control the variable of multiple courses of aminoglycosides relative to the incidence of nephrotoxicity.

Data Collection. Retrospectively collected data included the patient's demographic characteristics, duration of aminoglycoside therapy, SCr values drawn

during the course of intravenous antibiotic administration, hydration status, urine output, minimum inhibitory concentrations (MICs), audiometry results from 2003 through 2014, tobramycin dose, duration of treatment, drug serum concentrations, calculated pharmacokinetic parameters, concurrent nephrotoxic or ototoxic medications, and time to next exacerbation. Efficacy was not evaluated as a result of the inability of patients <6 years of age to properly perform lung function testing.

Definitions and Pharmacokinetic Equations. Nephrotoxicity was defined as an increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ (from admission SCr value) over the course of 48 hours. This is categorized as “stage 1 acute kidney injury” by the Acute Kidney Injury Network.⁸ Serum creatinine levels are drawn at the discretion of the rounding physicians and based on pharmacy recommendations. The lower end of detection for SCr reported by the lab is <0.2 mg/dL, and results are reported out in the hundredths. Patients were then classified using the pRIFLE criteria into the categories of risk (estimated creatinine clearance, eCCL, decrease by 25% or urine output of <0.5 mL/kg/hr for 8 hours), injury (i.e., eCCL decrease by 50% or urine output of <0.5 mL/kg/hr for 16 hours), failure (i.e., eCCL decrease by 75% or urine output of <0.3 mL/kg/hr for 24 hours or anuric for 12 hours), loss (i.e., persistent failure for >4 weeks), and end stage (i.e., persistent failure for >3 months).⁹ Creatinine clearance (CrCL) was calculated using the revised Schwartz formula ($\text{CrCL} = 0.413 \times \text{height/SCr}$).¹⁰ Urine output was calculated in mL/kg/hr over the course of a 24-hour period. Hydration status was determined by evaluating if the patient took in his daily fluid goal based on weight (4 mL/kg/hr for the first 10 kg + 2 mL/kg/hr for the next 10 kg + 1 mL/kg/hr for every kg >20 kg). Strict intake and output documentation is ordered on all CF patients. Documentation is completed by nursing staff. Ototoxicity was defined as any loss of hearing determined by audiometry. For pharmacokinetic (PK) parameters, doses required to meet PK goals were evaluated (i.e., peak tobramycin concentration 20–30 mg/L, non-detectable trough tobramycin concentration of <0.6 mg/L), along with average PK parameters for this age group. The equations outlined in Table 1 are the standard pharmacokinetic equations used within the institution to calculate the elimination constant (k_e), half-life ($T_{1/2}$), peak serum concentrations ($C_{p, \text{PEAK}}$), trough serum concentrations ($C_{p, \text{TR}}$), and volume of distribution (V_d) of tobramycin. The PK data were further broken down into smaller age groups of <1 year of age, 1 to <3 years of age, and ≥ 3 through <6 years of age. The patient's weight on admission was used for the PK calculations. Obtaining 2- and 6-hour serum concentrations after the first or second dose is standard in the study center. Random 18-hour serum tobramycin concentrations are drawn after 3 to 5 days of therapy to assess clearance. All serum concentrations and calculations are analyzed and completed by

Table 1. Pharmacokinetic Equations

Value	Equation
Ke	$Ke = \ln(Cp_1/Cp_2)/\Delta \text{ time}$
$T_{1/2}$	$T_{1/2} = 0.693/Ke$
Cp_{PEAK}	$Cp_{PEAK} = Cp_1/e^{(-Ke \times t)}$
Cp_{TR}	$Cp_{PEAK} \times e^{(Ke \times \Delta \text{ time})}$
Vd	$Vd = \frac{\text{Dose}}{Ke \times Cp_{PEAK} \times tinf} \times \frac{(1 - e^{(-Ke \times tinf)})}{(1 - e^{(-Ke \times tau)})}$

Cp_1 , concentration #1; Cp_2 , concentration #2; Δ time, change in time (hr) from Cp_1 to Cp_2 ; t , time from end of infusion to when Cp_1 drawn (hr); tau, dosing interval (hr); t_{inf} , infusion time (hr).

clinical pharmacists. Medication administration records were reviewed to see if the patients received any nephrotoxic or ototoxic medications. The nephrotoxic and ototoxic medication lists were compiled from previous publications (Table 2).

Data Analysis. Descriptive statistics were used to evaluate data. Median and IQR were used for non-normally distributed data, and mean and SD were used for normally distributed data. Paired *t*-test analysis was completed using Minitab 17 Statistical Software (2010; Minitab, State College PA).

Results

Thirty-one unique patients were included in the study (Figure). A majority were male (54.5%), the median age was 2.1 years (0.1–5.9 years), and the median weight was 9.8 kg (5.9–16.1 kg). The median initial starting tobramycin dose was 11.8 mg/kg (11.2–12 mg/kg), and mean baseline SCr was 0.29 ± 0.11 mg/dL. The MICs of patient's *P aeruginosa* were all ≤ 1 , except for one patient who had an MIC = 6. The median length of stay was 10 days (6–13.3 days), and length of therapy was 10 days (6–12.3 days). The median time to next exacerbation was 416 days (213–662 days).

Of the 31 patients who met inclusion criteria, only 29 had more than one SCr level during their hospitalization, as 2 patients were discharged home on intravenous antibiotic therapy. These 29 patients were included in the nephrotoxicity analysis. The absolute median change in SCr from baseline among all patients was 0.04 mg/dL (0–0.09 mg/dL; percentage increase on average 19.6%). The absolute median change in SCr among the 20 patients who experienced an increase in SCr was 0.065 mg/dL (0.033–0.1 mg/dL; percentage increase on average 31.5%). No patients had an increase in SCr of ≥ 0.3 mg/dL. Two patients had a SCr increase of ≥ 0.2 mg/dL from baseline (i.e., +0.2 mg/dL, and +0.21 mg/dL), and 2 patients had an increase in SCr of $\geq 50\%$ from baseline (i.e., +0.09 mg/dL and +0.2 mg/dL). When classified into pRIFLE CrCl criteria, 12 patients fell within the risk category, 8 within the injury category, and none within the failure category (Table 3). Nine patients did not have an increase in CrCl. Two patients did not meet the daily urine output goal of ≥ 1 mL/kg/hr over 24 hours for 1 and 3 days, respectively; however, neither patient fell below 0.5 mg/kg/hr for ≥ 8 hours. Among the pRIFLE categories, 2 patients in the risk group and 3 patients in the injury group received concurrent nephrotoxic medications. Of the 29 patients who were monitored in the hospital for their full duration of antibiotics, 17 (59%) did not meet their calculated daily fluid requirement on one or more days. Seven patients received concurrent nephrotoxic medications of either vancomycin or ibuprofen.

Of the 31 patients included, 17 had audiometry testing. Impairment was reported in 4 (24%) of the 17 tests; all of these patients had middle ear effusion/pathology on exam. Two of the 4 patients had received a concurrent ototoxic medication (vancomycin) during their admission. Thirteen audiograms reflected normal results, and 2 of those patients had also been on a concurrent ototoxic medication (vancomycin). The PK parameters among individual age groups (<1-year-old, 1 to <3 years

Table 2. Nephrotoxic and Ototoxic Medications

Adverse Effect	Medication
Nephrotoxicity ¹³	ACE inhibitors
	Acyclovir
	Amphotericin B
	Diuretics
	Lithium
	Nonsteroidal anti-inflammatory agents
	Radiocontrast media
	Tacrolimus
	Vasodilators (e.g., hydralazine, calcium-channel blockers, minoxidil, diazoxide)
	Vancomycin
Ototoxicity ^{14,15}	Anti-malarial medications (e.g., Chloroquine, mefloquine, Quinine)
	Cisplatin
	Loop diuretics
	Macrolide antibiotics
	Vancomycin

Figure. Patient selection criteria.

old, 3 to <6 years old) were similar to the overall patient averages (Table 4).

Discussion

In the past, aminoglycosides have traditionally been dosed 3 times daily in patients with normal renal function; however, in 2008 the CF Foundation recommended the use of extended interval dosing when treating a CF exacerbation.² Following this recommendation, a survey conducted by Prescott⁴ demonstrated that CF centers were routinely using EID for CF exacerbations and preferred this dosing regimen in patients older than 1 year of age.

Extended interval dosing of tobramycin has been studied in the adult CF population as well as in pediatric patients over 6 years of age; however, until now, there has been a gap in knowledge regarding the safety of this regimen in the younger population. The use of once-daily or extended interval dosing of tobramycin allows for enhanced bactericidal activity by maximizing the pharmacokinetic parameters and minimizes toxicities by providing an increased window of clearance.² The results of this study showed minimal nephrotoxicity and no ototoxicity attributable to tobramycin with the use of EID in patients <6 years old despite a majority of patients not hitting a daily fluid goal. While there were 20 patients who had an increase in SCr, the actual median increase of these patients was very minimal (0.065 mg/dL) and did not meet the predetermined definition of nephrotoxicity by the Acute Kidney Injury Network.

When evaluating patients individually, 2 patients had an increase of ≥ 0.2 mg/dL (0.2 and 0.21 mg/dL). The first patient (4.9 years old) had a baseline SCr of 0.2 mg/dL and a peak of 0.41 mg/dL. Tobramycin serum concentrations obtained during the patient's admission showed appropriate clearance. The second patient (5.2 years old) had a baseline SCr of 0.49 mg/dL and a peak of 0.7 mg/dL. Levels were also drawn on this patient, and no dose adjustments were made. While a SCr increase of ≥ 0.2 mg/dL is clinically significant, it did not alter dosing of tobramycin in either case. Two patients had an increase in SCr of $\geq 50\%$ from baseline SCr (i.e., +0.09 mg/dL and +0.2 mg/dL). The first patient had a baseline SCr of 0.14 mg/dL, which increased to 0.23 mg/dL. An 18-hour tobramycin concentration was detectable, and his interval was extended to every 36 hours. The second patient was previously mentioned above.

As previously mentioned, there is no literature demonstrating safety of EID tobramycin in patients less than 6 years of age; however, there are data available in pediatrics aged 6 to 16 years. The absence of nephrotoxicity based on absolute SCr change seen in this study was similar to the findings observed in the older pediatric age group. The TOPIC Study⁶ assessed the safety and efficacy of once-daily versus 3 times-daily tobramycin in both adult (>16 years old) and pediatric (6–16 years old) CF patients. Within the pediatric group, SCr concentrations decreased by 5% in the once-daily treatment group and increased by 4% in the three times-daily group, which was a significant difference in the per-protocol analysis. While our study did not com-

Table 3. Changes in CrCL Classified by pRIFLE Criteria

Category	n (%) N = 29	Patients Receiving Concurrent Nephrotoxic Drugs, n (%)
No change in CrCL	9 (29)	2 (22.2)
Increase in CrCL	20 (69)	5 (25)
Risk	12 (35)	2 (16.7)
Injury	8 (23)	3 (37.5)
Failure	0 (0)	N/A

CrCL, creatinine clearance; N/A, not applicable; pRIFLE, Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease

pare EID to traditional dosing regimens, there was no significant increase in SCr within either EID study group.

When the pRIFLE criteria were used to categorize acute kidney injury in this patient population, some risk and injury were detected. This criterion was not used in the TOPIC Study. By pRIFLE, 12 patients fell into the risk category and 8 patients fell within the injury group, and 3 of these patients had their interval extended. The urine output for all 8 patients remained ≥ 1 mL/kg/hr throughout the entire admission. Of the 12 patients who fell into the risk category, 2 required interval adjustments, and all maintained adequate urine output throughout their admission. There was no correlation between concurrent nephrotoxic medications and pRIFLE classification.

Tobramycin doses and therapy durations in CF patients are greater by a factor of between 2 and 4 when compared to those of non-CF patients.¹¹ The median incidence of cochleotoxicity following a single course of therapy in non-CF patients is 7.5%; thus, it is hypothesized that CF patients should be at an increased risk for developing hearing impairment or even deafness. Ideally, audiometry testing would be performed at baseline and then yearly thereafter. Unfortunately, during the study period, audiometry was not routinely tested, and timing of these exams was variable.

In this study, impairment was reported in 4 of the 17 patients. These audiograms were not conducted at the same time of therapy. The first patient had an audiogram conducted at the time of admission. The second patient had audiograms conducted at 4 months and 1.4 years after the first aminoglycoside exposure and received an additional 3 courses of aminoglycosides in the interim. The third patient was tested at baseline, 1 year, and 2 years after first exposure, having only received one course of tobramycin. The fourth patient was evaluated at baseline and 1.8 years post-dose and also only received one course of tobramycin. While there was impairment seen on these audiograms, it is important to note that all 4 of these patients who had an abnormal audiogram also had middle-ear effusion/pathology present on exam. The first patient never had follow-up audiometry, and the second patient had middle-ear effusion noted on both evaluations, with no follow-up after the second infection. Neither of these patients received concurrent ototoxic medications.

While the final readings on the abnormal results of the 2 patients who received concurrent ototoxic medications were “normal hearing in at least one ear” and “mild loss at low frequencies,” these results can largely be attributed to infection, as both of these patients eventually required tympanostomy tubes because of recurrent infections. Additionally, ototoxicity due to aminoglycosides typically presents as loss of high-frequency hearing first, followed by progressive loss relative to lower frequencies, which is not consistent with the loss observed in our 2 patients.¹²

Ototoxicity results were similar to those seen in CF patients who initially participated in the TOPIC Study. The TOPIC Study showed no evidence of pure tone audiometry and high-frequency pure tone audiometry threshold elevation at day 14 or at the follow-up 6 to 8 weeks later.^{6,11} The authors concluded that these results may indicate either a more rapid clearance observed in CF patients or that CF may confer some protection against aminoglycoside toxicity.¹¹

It is standard practice within the study center to empirically dose tobramycin at 12 mg/kg in pediatric CF patients and to obtain 2- and 6-hour post-dose serum concentrations. Using the equations in Table 1, pharmacokinetic parameters were calculated. Repeat 2- and 6-hour tobramycin serum concentration are obtained anytime a dose was changed as a result of a sub- or supratherapeutic peak or trough. A random serum concentration drawn usually around 18 hours post-dose is obtained 3 to 5 days after the first set of concentrations to ensure proper clearance. When tobramycin was dosed at approximately 12 mg/kg (11.7 mg/kg median dose rounded), calculated peaks serum concentrations were within or near the goal range of 20 to 30 mg/L (19.8–32.8 mg/L), and trough serum concentrations were undetectable prior to the next dose. The 5 patients who did require subsequent dose adjustments had their doses changed from every 24 hours to every 36 hours as a result of a detectable random concentration. All patients achieved a drug-free interval based on their final dosing regimen. By ensuring a drug-free interval, there is more time for the medication to clear the proximal tubule and inner ear, decreasing the risk of accumulation and associated toxicities. These data will assist with dosing recommendations in this age group.

The PK data observed in this study were similar to

Table 4. Pharmacokinetic Parameters by Age*

Age Group, yr	Patients, n (%)	Serum Concentrations Drawn, n	Dose, mg/kg	Ke, hr ⁻¹	T _{1/2} , hr	Vd, L/kg	Peak Serum Concentration, mg/mL	Trough Serum Concentration, mg/L
<1	12 (13)	16	11.6 (10.2–12.2)	0.34 (0.3–0.44)	2 (1.6–2.3)	0.38 (0.35–0.44)	29 (19.8–32.6)	<0.01
1 to <3	7 (9)	9	12 (11.7–12)	0.44 (0.38–0.5)	1.6 (1.5–1.9)	0.33 (0.32–0.47)	31.8 (22.8–32.8)	<0.01
3 to <6	16 (23)	25	11.7 (11.4–12)	0.4 (0.34–0.52)	1.7 (1.3–2)	0.4 (0.3–0.5)	27 (21–33)	<0.01
All ages	31 (45)	50	11.7 (11.3–12)	0.4 (0.32–0.47)	1.7 (1.5–2.1)	0.37 (0.31–0.47)	27.3 (20.9–32.7)	<0.01

* Data presented as median (IQR), unless otherwise noted.

the PK parameters of once-daily tobramycin dosing in a study¹⁶ that included both children and adults with CF. Participants included patients as young as 9 months old through those who were 20 years of age. Weight was the only parameter to significantly influence the model, and tobramycin was dosed at 12 mg/kg. The estimated volume of distribution was 0.265 L/kg, similar to that of adult CF patients. The estimated clearance of 1.67 mL/min/kg was similar to previous study results of 1.73 mL/kg/min. This study demonstrated that 12 mg/kg resulted in serum concentrations at least 10 times the MIC for sensitive *P. aeruginosa*. Unfortunately, the previous study did not separate out the parameters between adult patients and pediatric patients, who typically have different pharmacokinetic parameters, making these study results important for guiding tobramycin dosing in this young age group.

Some limitations to this study include the design as a retrospective chart review, which greatly confines the data collected to what was recorded in the electronic medical record. The study group was small due to an institutional restriction on tobramycin during the early years of the study period. Serum creatinine levels and audiology assessments were not systematic; thus, changes in renal function or hearing may have been missed in some patients.

Conclusion

This study demonstrated that use of EID tobramycin in a small population of aminoglycoside-naïve patients with CF who were less than 6 years of age did not result in drug-related ototoxicity and resulted in some nephrotoxicity. Routine dosing of tobramycin at 12 mg/kg every 24 hours in CF patients less than 6 years of age resulted in recommended peak concentrations. Monitoring of renal function is recommended in this patient population. These data will help guide pediatric practitioners on the appropriate EID tobramycin dosing in CF patients who are less than 6 years old.

ARTICLE INFORMATION

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