JPPT | Single-Center Retrospective Study

Review of Tobramycin Dosing in Pediatric Patients With Cystic Fibrosis

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OBJECTIVE An institution's tobramycin pharmacokinetics (PK) database was reviewed to evaluate the efficacy and safety of empiric tobramycin dosing and monitoring strategies used in pediatric patients with cystic fibrosis (CF). The relationship between patient age and tobramycin dosing needed to achieve the area under the curve (AUC) goal was investigated.

METHODS Retrospective chart review was performed for patients who received tobramycin during a CF exacerbation from 2009 to 2019 who received PK monitoring by pediatric pharmacists. Tobramycin dosing needed to achieve an AUC of 100 mg·hr/L was calculated for each patient. Serum creatinine and concomitant nephrotoxin use were collected as surrogate nephrotoxicity endpoints to evaluate safety.

RESULTS Goal AUC (100 ± 15 mg·hr/L) was achieved based on initial or repeat PK calculations in 43.5% (95% CI, 37.7–49.3) of 85 unique patients across 326 encounters. Patients with calculated recommended doses of 9.5 to 11.9 mg/kg every 24 hours empirically achieved goal AUC in 77% (78/101) of encounters. The odds of achieving goal AUC were 56% higher for children aged 10 vs 5 years (OR = 1.56; 95% CI, 1.04–2.34; p = 0.033) and 32% higher for children aged 15 vs 10 years (OR = 1.32; 95% CI, 1.07–1.61; p = 0.008). Overall rates of acute kidney injury and concomitant nephrotoxin use were 10.8% (95% CI, 6.2–15.5) and 80.7% (95% CI, 74.3–87.1), respectively.

CONCLUSIONS Desired AUC was achieved by 43.5% of pediatric patients with CF using tobramycin 10 mg/kg every 24 hours. Older patient age was associated with higher initial AUC attainment and fewer dose modifications. Younger children may require higher weight-based dosing to meet AUC goals.

ABBREVIATIONS AKI, acute kidney injury; AUC, area under the curve; -CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane regulator; C_{max}; peak concentration; C_{min}, trough concentration; GEE, generalized estimating equation; K_e, elimination constant; N-AKI, Nephrotoxic Medication-Associated Acute Kidney Injury program; NINJA, Nephrotoxic Injury Negated by Just-in-Time Action program; PK, pharmacokinetics; SCr, serum creatinine; $T_{1/2}$, half-life; Vd, volume of distribution

KEYWORDS acute kidney injury; area under the curve; cystic fibrosis; pharmacokinetics; tobramycin

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Introduction

Cystic fibrosis (CF) is a rare, autosomal recessive disease characterized by a mutation in the CF transmembrane regulator (*CFTR*) gene that disrupts chloride channels and increases mucus viscosity throughout the body.[1] Approximately 30,000 Americans live with CF and develop progressive damage to numerous organ systems, including the pulmonary, pancreatic, musculoskeletal, genitourinary, and hepatic systems, often resulting in multi-organ dysfunction and significant complications.[2,3] Excessive thick mucus present in the lungs of CF patients contributes to inflammation, poor mucociliary clearance, and persistent microbial colonization, which periodically provokes acute, infectious pulmonary exacerbations. While pulmonary infections in CF patients tend to be polymicrobial in nature, *Pseudomonas aeruginosa* is a commonly implicated pathogen in these exacerbations. The percentage of patients colonized with *P. aeruginosa* increases dramatically with age, with a colonization rate of only 20% in pediatric patients under the age of 6 years compared with a rate of over 70% in adult patients aged 35 to 44 years.[3] The current recommended antibiotic regimen by the CF Foundation for patients of all age groups with a history of *P. aeruginosa* colonization includes dual anti-*Pseudomonal* drug coverage, most commonly an aminoglycoside and an anti-*Pseudomonal* beta-lactam.[4]

Extended-interval dosing of aminoglycosides is preferred for the treatment of Gram-negative infections because it expands the time of concentration-dependent bactericidal activity and provides sufficient time for drug clearance to reduce nephrotoxicity and ototoxicity risks.[4,5] The CF Foundation recommends once-daily

dosing of aminoglycosides over traditional thrice-daily dosing in CF patients of all ages.[4] The CF Foundation does not currently comment on appropriate dosing or pharmacokinetics (PK) monitoring of aminoglycoside use. Historically, peak and trough concentrations were used for PK monitoring of traditional aminoglycoside dosing. The shift toward extended-interval dosing of aminoglycosides has prompted some institutions to favor the use of AUC PK monitoring to index a patient's daily aminoglycoside exposure and to assess the need for dosing adjustments because higher AUC values have been linked to increased incidence of nephrotoxicity.[5]

The preferred aminoglycoside used in CF patients with acute pulmonary exacerbations is tobramycin because of concerns of increased nephrotoxicity with gentamicin.[6] A national survey[7] of pediatric CF-accredited care centers in the United States demonstrated that tobramycin dosed 10 mg/kg every 24 hours was the most common dosing strategy empirically started for the treatment of pulmonary exacerbations. However, the efficacy of this dosing strategy has yet to be thoroughly investigated. Each patient with CF receiving tobramycin at the study center receives therapeutic drug monitoring services by pediatric pharmacists, who thoroughly document the results of their PK calculations in an internal database. This well-established database facilitated a retrospective analysis of extended-interval tobramycin dosing in pediatric CF patients.

The main objective of this study was to review our institution's internal tobramycin PK database to evaluate the efficacy and safety of empiric tobramycin dosing and monitoring strategies used in order to standardize future practice. Efficacy was investigated using the primary endpoint of target AUC attainment, while safety was evaluated using surrogate endpoints for nephrotoxicity (i.e., serum creatinine and concomitant nephrotoxin use). The study also examined the weight-based dosing requirements to meet desired AUC values based on patient age.

Materials and Methods

Patients and Setting. This retrospective study was conducted at a comprehensive pediatric hospital affiliated with a large academic medical center and accredited by the CF Foundation as a CF Care Center. Patients included in the study had a confirmed diagnosis of CF and were treated for an acute pulmonary exacerbation with tobramycin that was pharmacokinetically managed by a pediatric pharmacist using serum drug concentrations during the period extending from January 2009 through December 2019. Patients aged 18 years or older were still included in the study as long as their exacerbation was managed by pediatric pulmonologists and their tobramycin was monitored by pediatric pharmacists. Patients were excluded if they did not have CF, if they had been treated with tobramycin in the outpatient setting, or if serum drug concentrations were suspected to be contaminated, either through discussion with bedside nursing staff or laboratory personnel or based on the results of repeat serum concentrations.

Data Collection. Retrospective chart review supplemented data previously collected by pharmacists at the time of their initial evaluation and PK calculations. Collected data included patient demographics, weight (in kilograms), height (in centimeters), baseline and peak serum creatinine (SCr) values, initial and final tobramycin dose during admission, serum tobramycin concentrations, calculated time between the completion of tobramycin infusions and the drawing of serum tobramycin concentrations, calculated PK parameters, use of concomitant nephrotoxins defined by the Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) program (now known as the Nephrotoxic Medication Associated Acute Kidney Injury [N-AKI] program), use of inhaled tobramycin, and number of tobramycin dose changes.

Definitions and PK Equations. Blood for the determination of tobramycin drug concentrations in serum was obtained after administration of the second tobramycin dose. The first blood draw was obtained either 30 or 60 minutes after the completion of the tobramycin dose infused over 30 or 60 minutes, respectively, while the second blood draw occurred 10 to 12 hours after the dose to ensure that a measurable concentration was obtained. The PK equations used to determine tobramycin PK characteristics are outlined in the Supplemental Table and were previously coded into the internal pediatric CF database to calculate elimination constant (K_e), half-life ($T_{1/2}$), peak serum concentrations (C_{max}), trough serum concentrations (C_{min}), volume of distribution (Vd), clearance, AUC, and the dose required to achieve an AUC of 100 mg·hr/L (within the acceptable range of 85–115 mg·hr/L). The relationship between patient age and the weight-based tobramycin dose predicted to achieve an AUC value of 100 mg·hr/L was investigated. Each date that PK calculations were performed was treated as a separate encounter by the study investigators; therefore, a single inpatient admission could generate one or multiple opportunities to assess achievement of target AUC. Nephrotoxicity was defined as an increase in SCr of 50% or more (based on the lowest SCr value obtained in the previous 6 months) during inpatient admission. The SCr values during patient hospitalization were historically obtained per provider discretion. In February 2016, the NINJA (N-AKI) program was implemented, introducing daily SCr monitoring for all pediatric patients receiving greater than 3 days of intravenous tobramycin therapy and continued until 2 days after nephrotoxin exposure in an effort to increase detection of AKI as well as reduce rates of AKI in rates of AKI.[8] The overall rate of AKI as well as the available rate of AKI before and after the implementation of N-AKI were evaluated. Urine output data were

Table 1. Patient Demographics and Select Outcomes*

Characteristic	Data by Patient (N=85)	Data by Encounter (N=326)
Age, yr		
Mean (CI)	13.6 (12.5 to 14.7)	
Mean ± SD		13.8 ± 5.07
Median (IQR)		15.5 (11.0–17.6)
Female sex	49/85 (57.6)	175/326 (53.7)
AKI†		
Overall	10.8 (6.2 to 15.5)	26/302 (11.9)
Before N-AKI	5.8 (1.7 to 9.9)	14/205 (6.8)
After N-AKI	22.5 (10.0 to 35.0)	22/97 (22.7)
Change between After and Before N-AKI	16.6 (3.1 to 30.2)	15.9 (6.8 to 24.8)
Concomitant nephrotoxin		
Overall	80.7 (74.3 to 87.1)	258/326 (79.1)
Before N-AKI	85.0 (78.2 to 91.7)	190/229 (83.0)
After N-AKI	70.4 (58.7 to 82.1)	68/97 (70.1)
After and before Change between After and Before N-AKI	−14.6 (−27.4 to −1.7)	−12.9 (−23.2 to −2.5)
Concomitant use of inhaled tobramycin‡	15.5 (10.2 to 20.8)	52/326 (16.0)
Met goal AUC	43.5 (37.7 to 49.3)	142/326 (43.6)

AKI, acute kidney injury; AUC, area under the curve; SCr, serum creatinine

* Data presented as n/total (percentage) or mean (CI) unless otherwise noted

† Nephrotoxic Injury Negated by Just-in-Time Action (NINJA), now known as Nephrotoxic Medication-Associated Acute Kidney Injury (N-AKI), was implemented at the study center in February 2016. This program recommended daily SCr monitoring for all pediatric patients receiving greater than 3 days of intravenous tobramycin therapy and continued 2 days after nephrotoxin exposure.

‡ Refers only to concomitant use of inhaled and intravenous tobramycin during hospitalization. Inhaled medications on chronic outpatient medication list were unknown.

not included in the analysis because strict intake and output information was not consistently documented.

Data Analysis. Descriptive statistics were used to evaluate the data. Median and IQR were calculated for continuous variables at the level of individual encounters (ignoring clustering), while the mean and 95% CI were derived using generalized estimating equations (GEE). Frequencies and percentages were used to describe categorical variables. The GEEs were used to estimate and test for associations between key outcomes and explanatory variables because of the cluster-correlated nature of the data, which included multiple encounters from the same subject.[9,10] The GEE models for binary outcomes of interest (goal AUC attainment, AKI during hospital stay, concomitant nephrotoxin use, and use of inhaled tobramycin) used either the logit or identity link to respectively produce OR or differences in percentages as the measures of association with 95% CIs. The models relied on an exchangeable correlation structure and robust standard errors. Continuous predictors (e.g., age and dosage) in these models used restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles to avoid assuming a strictly linear association with the response. Several PK parameters were log-transformed prior to analysis to improve symmetry.[11]

Results

Data from 326 encounters involving 85 unique patients were identified for inclusion in this retrospective analysis between January 2009 and December 2019. One-third (33%) of the patients had only 1 encounter; 51% had between 2 and 7 encounters; and 16% had between 8 and 16 encounters, with the time between encounters or inpatient PK analysis ranging from less than a day to 5.8 years. The sample was 58% female. The age at time of the encounter ranged from 84 days to approximately 21 years (median, 15.5; IQR, 11.0–17.6). Inhaled tobramycin was administered in 15.5% (95% CI, 10.2–20.8) of encounters. Patient demographics are shown in Table 1, and the PK parameter estimates are summarized in Table 2.

For our primary outcome, 43.5% (95% CI, 37.7–49.3) of PK encounters resulted in the patient meeting the AUC goal of 85 to 115 mg·hr/L. The odds of achieving goal AUC increased with increasing age up to 15 years, based on our GEE model. The relationship between goal attainment and age was not linear, as shown in Figure 1. Ages of 5, 10, and 15 years were chosen as examples to describe how odds of goal attainment change as a function of age. Patients with an age of 10 years compared with patients aged 5 years had 56% higher odds of attaining goal AUC (OR = 1.56; 95% CI,

Table 2. Pharmacokinetic Parameter Estimates for Study Patients

PK Parameter	Median (IQR)	Mean (95% CI)
K_e, hr^{-1}		
Overall	0.32 (0.28–0.35)	0.31 (0.30–0.32)*
<6	0.32 (0.27–0.36)	0.31 (0.29–0.34)*
6–14	0.32 (0.29–0.37)	0.33 (0.32–0.34)*
≥15	0.31 (0.28–0.34)	0.30 (0.29–0.32)*
$T_{1/2}$, hr		
Overall	2.19 (1.98–2.46)	2.21 (2.15–2.27)*
<6	2.16 (1.95–2.54)	2.21 (2.07–2.37)*
6–14	2.14 (1.89–2.38)	2.10 (2.03–2.18)*
≥15	2.24 (2.05–2.49)	2.27 (2.19–2.36)*
C_{max}, mg/L		
Overall	25.8 (21.5–30.3)	24.9 (23.9–25.9)*
<6	21.3 (15.2–25.9)	19.6 (17.1–22.4)*
6–14	25.0 (21.1–28.3)	24.5 (23.4–25.6)*
≥15	27.1 (23.1–31.4)	26.7 (25.6–27.8)*
C_{min}, mg/L		
Overall	1.94 (0.88–3.89)	1.82 (1.50–2.21)*
<6	2.12 (0.85–5.48)	2.58 (1.64–4.05)*
6–14	1.58 (0.62–3.08)	1.20 (0.91–1.58)*
≥15	2.15 (1.15–4.31)	2.13 (1.69–2.70)*
Vd, L		
Overall	17.8 (13.5–21.7)	17.7 (16.4–19.0)
<6	5.6 (4.2–8.4)	7.0 (5.4–8.6)
6–14	16.1 (12.8–19.0)	16.8 (15.7–17.9)
≥15	20.1 (17.4–23.5)	21.0 (19.8–22.1)
CL, L/hr		
Overall	94.5 (71.9–114.2)	91.0 (84.4–97.6)
<6	30.4 (22.2–45.3)	37.2 (29.3–45.0)
6–14	89.8 (70.2–106.1)	92.6 (86.4–98.7)
≥15	103.4 (90.0–122.2)	104.5 (98.6–110.4)
Vd/kg, L/kg		
Overall	0.39 (0.33–0.48)	0.40 (0.38–0.42)*
<6	0.51 (0.44–0.64)	0.52 (0.46–0.58)*
6–14	0.42 (0.36–0.50)	0.43 (0.40–0.45)*
≥15	0.36 (0.31–0.43)	0.37 (0.35–0.39)*
CL/kg, L/kg·hr		
Overall	2.05 (1.68–2.59)	2.10 (1.98–2.23)*
<6	2.84 (2.20–3.44)	2.64 (2.27–3.07)*
6–14	2.25 (1.91–2.81)	2.34 (2.18–2.52)*
≥15	1.87 (1.55–2.22)	1.87 (1.75–1.99)*
AUC, mg·hr/L		
Overall	95.0 (78.0–113.7)	92.4 (88.6–96.4)*
<6	78.0 (60.8–95.4)	77.4 (69.4–86.3)*
6–14	88.1 (72.8–106.4)	86.3 (81.7–91.2)*
≥15	102.7 (86.6–117.8)	100.4 (95.9–105.0)*

AUC, area under the curve, CL, clearance; C_{max}, peak concentration; C_{min}, trough concentration; GEE, generalized estimating equation; K_e, elimination constant; PK, pharmacokinetics; $T_{1/2}$, half-life; Vd, volume of distribution

* Median and IQR are computed for individual encounters (ignoring clustering), while the mean and 95% CIs are based on GEEs that accounts for clustering. Values marked with an asterisk are geometric means from having initially log-transformed data for the indicated parameter prior to analysis. Sample size is n = 326 for the entire cohort and is 35 (<6 yr), 114 (6–14 yr), and 177 (≥15 yr) for each subgroup.

Figure 1. Odds of AUC attainment by age. Odds of AUC goal attainment (vertical axis) and age in years (horizontal axis). The solid red line shows how odds of reaching the goal increase with advancing age. The surrounding dotted lines are pointwise 95% CIs for the odds at any given age. Solid circles show observed odds of meeting the goal when data are aggregated to the nearest integer age; the size of the circle is proportional to the number of encounters at the (coarsened) age. A rug of tick marks along the lower and upper edge of the plotting region indicates actual age for those who failed to meet the goal (red; lower edge) and those who successfully met the goal (blue; top edge).

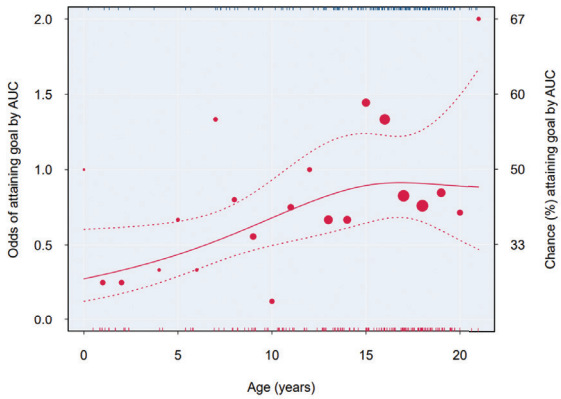
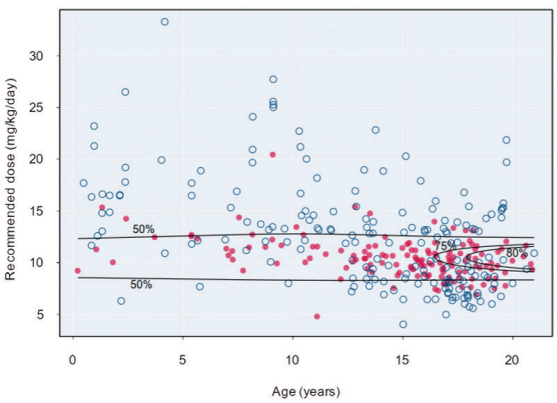


Figure 2. Rate of AUC attainment based on recommended weight-based dosing (vertical axis) and age (horizontal axis). Solid red circles signify encounters in which the goal was met and hollow blue circles those that failed to meet the goal. Contour lines enclose regions in which the estimated chances of meeting the goal are 50%, 75%, or 80%. Low changes (50%; 1:1 odds) cover the entire age range over a narrow range of recommended doses. Higher changes apply over a comparable range of doses but involve only older children (~16 years or older).



1.04–2.34; p = 0.033); patients aged 15 vs those aged 10 years had 32% greater odds of attaining goal AUC (OR = 1.32; 95% CI, 1.07–1.61; p = 0.008); and patients aged 20 vs those aged 15 years had similar odds of achieving goal AUC (OR = 1; 95% CI, 0.55–1.80; p = 0.988). There was no evidence to suggest that sex had an association with goal AUC attainment or modified the existing relationship between age and meeting the goal (p = 0.512).

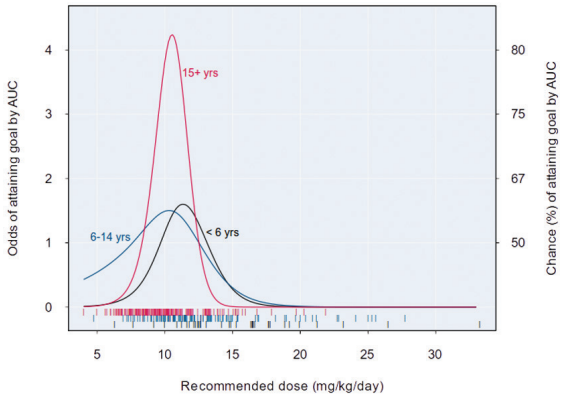
Recommended dose (milligrams per kilogram per day) had a strong nonlinear association with the odds of reaching goal AUC, with increasing odds up to approximately 10.7 mg/kg/day and then decreasing odds for larger doses. For recommended doses between 9.5 and 11.9 mg/kg/day, 77% of encounters met the AUC goal. The relationship between age (horizontal axis) and recommended dose (vertical axis) is shown in Figure 2. Low chances (50%) cover the entire age range over a fairly restricted range of recommended doses, but greater chances (75% and 80%) only apply to encounters involving older children (those aged 16 years or older) over an even narrower range of doses. Similar statements can be made if encounters are grouped according to specific age ranges: <6 years (n = 35; range, 0.23–5.8 years), 6 to 14 years (n = 114; range, 6.9–14.9 years), and ≥15 years (n = 177; range, 15.0–20.9 years). Estimated odds of attaining the goal AUC were highest for the most advanced age group, although all age groups demonstrated the same narrow range of recommended doses where odds are still the highest.

Regarding surrogate endpoints for nephrotoxicity, the rate of AKI was 10.8% (95% CI, 6.2–15.5) across the entire study time period. The percentage of AKI events increased by 16.6 percentage points (95% CI, 3.1–30.2; p = 0.016) after N-AKI implementation on February 1, 2016, compared with earlier (22.5% vs 5.8%). Between those same time periods, use of concomitant nephrotoxins during admission decreased by 14.6 percentage points (95% CI, 1.7–27.4; p = 0.026; 70.4% after N-AKI vs 85.0% before).

Discussion

Extended-interval dosing of tobramycin has been endorsed by the CF Foundation[4] for the treatment of pulmonary exacerbations in patients of all ages since 2008. While data promoting the use of extended-interval dosing were originally more prevalent for adult CF patients, results from the TOPIC study helped garner support for its use in pediatric patients because it uncovered lower rates of nephrotoxicity with once-daily dosing compared with traditional dosing in children.[12] While the CF Foundation provides a clear stance on extended-interval dosing of tobramycin, insufficient evidence is currently available for the organization to provide specific recommendations for empiric weight-based dosing or for goal PK parameters.[4] Available PK literature surrounding aminoglycoside use in CF patients has suggested

Figure 3. Recommended weight-based dosing to achieve AUC for 3 specific age groups. Chances are highest for those at least 15 years old and lower for younger age groups. All age groups have identifiable peaks over a similar narrow range of recommended dose. Rug tick marks along the bottom edge show recommended dose for each individual according to age group.



targets for both C_{max} (20–30 mg/L[12–14]; 25–30 mg/L[7]; 25–35 mg/L[15]) and C_{min} (<1 mg/L)[7,12–14] and for AUC (100,[7,16] 70–100,[17] 80–100,[18,19] 80–110,[14] and 90–110[14] mg·hr/L), but no clear preference between the two strategies has been established, leaving each institution to develop its own protocol.

Clinicians at our center have chosen to initiate new pediatric patients with CF on tobramycin at 10 mg/kg every 24 hours and to modify dosing as needed to achieve a goal AUC of 100 ± 15 mg·hr/L. Empiric dosing for patients previously treated with tobramycin at our center may deviate from the standard 10 mg/kg every 24 hours if historical PK calculations suggested a different dosing regimen may be more successful. Pediatric pharmacists noticed over time that younger patients seemed to require more frequent dose increases to meet target PK parameters. Recent data[13] have suggested that children younger than 6 years may require 12 mg/kg every 24 hours dosing to meet desired C_{max} and C_{min} parameters. This publication prompted us to examine our PK database to evaluate the adequacy of current tobramycin dosing strategies in pediatric CF patients and to further investigate the relationship between weight-based dosing and age to add to the body of literature and to standardize our future practice.

Results pertaining to the primary outcome indicate that slightly less than half of the included PK encounters met the desired AUC range of 85 to 115 mg·hr/L. It is not currently common practice at our center to obtain confirmatory tobramycin serum drug concentrations after dose adjustments unless significant changes in renal function are observed. Therefore, this AUC attainment rate solely reflected the success of empiric dosing, and additional tobramycin concentrations obtained during admission were based on the discretion of pediatric pharmacists for reasons such as changing renal function. Our findings suggest that common tobramycin dosing strategies may inadequately achieve goal PK parameters in this patient population. Further study is likely warranted to identify ways to optimize empiric tobramycin dosing in pediatric patients with CF to better meet desired PK parameters.

Analysis of the relationship between weight-based dosing, patient age, and achievement of goal AUC identified patients with the highest odds of meeting desired PK goals. The majority of patients receiving tobramycin at a dosing of 9.5 to 11.9 mg/kg/day had calculated AUCs within the goal range, implying that most pediatric patients require tobramycin doses of at least 10 mg/kg every 24 hours to reach PK targets. With regard to patient age, older pediatric patients experienced greater PK success compared with younger patients. Both adult and pediatric literature[7,16,20–22] have documented PK success with dosing tobramycin at 10 mg/kg every 24 hours when using C_{max} and C_{min} as PK targets. Similarly, older pediatric patients and younger adults may experience better AUC attainment with doses near 10 mg/kg/day because their PK properties mirror those of adult patients with CF more than those of younger children. Arends and Pettit[13] published a retrospective study of CF patients younger than 6 years of age who were receiving their first course of tobramycin therapy. Their results suggested that younger CF patients may require larger empiric tobramycin doses of 12 mg/kg every 24 hours to achieve goal PK values (C_{max} = 20–30 mg/L and undetectable C_{min}).[13] In comparing the results of the present to those of the previous study, Figure 3 illustrates that pediatric patients with CF under the age of 6 years likely require higher weight-based dosing that nears 12 mg/kg/day, with both studies including approximately 30 patients in this age group.[13] However, the present study only showed a nonsignificant trend toward higher weight-based dosing for children less than 6 years of age, and additional research is needed before an empiric dose of 12 mg/kg/day can be widely adopted in this patient age group. While this empiric dosing is described in milligrams per kilograms per day, we mostly administer tobramycin every 24 hours and very rarely divide the total daily dose for administration every 12 hours. Further study is needed to determine the effect of using modified dosing intervals, such as every 12 hours, on achievement of goal PK parameters in younger children with CF.

Tobramycin appeared to be relatively safe based on surrogate endpoints for nephrotoxicity, with an AKI rate of approximately 10% during the study period. Our implementation of N-AKI was associated with the identification of a significantly higher rate of AKI compared with previous years, likely because of an increase in SCr monitoring.[8] Because AKI was solely defined based on SCr in this study, absent or limited SCr values obtained

prior to the implementation of N-AKI would reduce the ability to detect AKI in patients treated with tobramycin prior to the implementation of the N-AKI monitoring. It is reassuring that the rate of concomitant nephrotoxin use substantially decreased after the N-AKI protocol was adopted because it implies the risk of aminoglycoside-related nephrotoxicity is being more carefully considered.

This study was modest in size and included patients across the pediatric age continuum but is not without its limitations. Clinical markers related to tobramycin efficacy, namely pulmonary function tests, length of inpatient stay, or time between pulmonary admissions, were not collected because of resource constraints. It is not our standard practice to collect repeat serum tobramycin serum concentrations after dose adjustments unless important changes in renal function or clinical status are observed. This approach may have contributed to a falsely low rate of AUC attainment if positive findings were excluded from the study. The analysis also did not investigate how changes in clinical status, including hydration, edema, and critical illness, could alter tobramycin PK parameters, particularly drug clearance. Concurrent use of inhaled tobramycin may have also confounded our PK calculations. The incidence of concurrent inhaled and intravenous tobramycin was relatively low (15.5% of patients). These changes may explain why some patients' AUCs were not at goal upon rechecking, despite using recommended dosing based on PK parameters observed earlier in their hospital stay. The investigators had originally planned to evaluate ototoxicity rates as a part of the safety analysis; however, audiogram testing was rarely performed in the inpatient setting, making this analysis infeasible. Data surrounding the use of CFTR modulators were not collected; the potential effect of CFTR modulators on tobramycin PK has not been thoroughly evaluated in the literature. Retrospectively analyzing the internal PK database identified associations between weight-based dosing, age, and reaching goal AUC. However, the data set was not robust enough to clearly define weight-based dosing recommendations based on patient age.

Conclusion

This study demonstrated that routine empiric dosing of tobramycin at 10 mg/kg every 24 hours in pediatric patients with CF resulted in achieving goal AUC less than 50% of the time. Daily tobramycin doses of 9.5 to 11.9 mg/kg and increasing patient age were both associated with greater rates of goal AUC attainment, with younger children tending to require higher weight-based dosing to achieve AUC targets. The implementation of a protocol encouraging frequent SCr monitoring and reduction of concomitant nephrotoxin agents elevated rates of AKI detection and brought greater attention to prevention and early identification of aminoglycoside-associated nephrotoxicity. Further research will aid pediatric practitioners in identifying optimal tobramycin dosing strategies with pediatric patients with CF and will better define the relationship between weight-based tobramycin dosing and patient age to allow for the delivery of standardized care across pediatric CF Foundation–accredited centers.

Article Information

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