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Antonin Praet, Laurent Bourguignon, Florence Vetele, Valentine Bréant, Charlotte Genestet, et al.. Population Pharmacokinetic Modeling and Dosing Simulations of Tobramycin in Pediatric Patients with Cystic Fibrosis. *Antimicrobial Agents and Chemotherapy*, 2021, 65 (10), pp.e0073721. 10.1128/AAC.00737-21 . hal-04626819

HAL Id: hal-04626819

<https://hal.science/hal-04626819v1>

Submitted on 1 Oct 2024

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Population Pharmacokinetic Modeling and Dosing Simulations of Tobramycin in Pediatric Patients with Cystic Fibrosis

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ABSTRACT Initial dosing and dose adjustment of intravenous tobramycin in children with cystic fibrosis (CF) is challenging. The objectives of this study were to develop nonparametric population pharmacokinetic (PK) models of tobramycin in children with CF to be used for dosage design and model-guided therapeutic drug monitoring. We performed a retrospective analysis of tobramycin PK data in our children's CF center. The Pmetrics package was used for nonparametric population PK analysis and dosing simulations. Both the ratios of maximal concentration to the MIC (C_{max}/MIC) and daily area under the concentration-time curve to the MIC (AUC_{24}/MIC) were considered efficacy targets. Trough concentration (C_{min}) was considered the safety target. A total of 2,884 tobramycin concentrations collected in 195 patients over 9 years were analyzed. A two-compartment model including total body weight, body surface area, and creatinine clearance as covariates best described the data. A simpler model was also derived for implementation in the BestDose software to perform Bayesian dose adjustment. Both models were externally validated. PK/pharmacodynamics (PD) simulations with the final model suggest that an initial dose of tobramycin of 15 to 17.5 mg/kg/day was necessary to achieve C_{max}/MIC s of ≥ 10 for MICs up to 2 mg/liter in most patients. The AUC_{24}/MIC target was associated with higher dosage requirements and higher C_{min} . A daily dose of 12.5 mg/kg would optimize both efficacy and safety target attainment. We recommend performing tobramycin therapeutic drug monitoring (TDM), model-based dose adjustment, and MIC determination to individualize intravenous tobramycin therapy in children with CF.

KEYWORDS tobramycin, pharmacokinetics, cystic fibrosis, pediatrics, model-informed precision dosing, population pharmacokinetics

Nonfermenting Gram-negative bacilli are frequently responsible for bronchopulmonary infections in patients with cystic fibrosis (CF), in particular *Pseudomonas aeruginosa*. The treatment of pulmonary exacerbations is based on a combination of two antibiotics active against the identified or plausible bacteria, by the intravenous route (1, 2). Combination of an aminoglycoside with a beta-lactam active against *Pseudomonas aeruginosa* is a common therapy.

Tobramycin is a first-line aminoglycoside agent for the parenteral treatment of acute infections caused by *Pseudomonas aeruginosa* in CF patients. Like other aminoglycosides, it has a narrow therapeutic margin. Its antibacterial effect is concentration dependent. Both the ratio of maximal concentration (C_{max}) to the MIC and the ratio of

Citation Praet A, Bourguignon L, Vetele F, Breant V, Genestet C, Dumitrescu O, Doleans-Jordheim A, Reix P, Goutelle S. 2021. Population pharmacokinetic modeling and dosing simulations of tobramycin in pediatric patients with cystic fibrosis. *Antimicrob Agents Chemother* 65:e00737-21. <https://doi.org/10.1128/AAC.00737-21>.

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Received 9 April 2021

Returned for modification 10 May 2021

Accepted 12 July 2021

Accepted manuscript posted online 19 July 2021

Published 17 September 2021

TABLE 1 Characteristics of the study population

Characteristic	Value for data set ^a		
	Overall	Learning	Validation
No. (%) of patients	195 (100)	146 (74.9)	49 (25.1)
No. of females/males	99/96	72/74	27/22
Age (yrs) ^b	11.4 ± 5.1 (0.33–20.0)	11.4 ± 4.2 (0.3–20.0)	11.2 ± 5.4 (0.5–18.0)
TBW (kg) ^b	35.4 ± 15.9 (3.8–91.5)	35.6 ± 13.4 (3.8–91.5)	34.5 ± 15.9 (7.6–68.5)
IBW (kg) ^b	36.8 ± 16.4 (2.9–75.6)	37.0 ± 13.8 (2.9–75.6)	36.2 ± 16.9 (7.6–72.8)
Height (m) ^b	1.39 ± 0.28 (0.51–1.85)	1.39 ± 0.23 (0.51–1.85)	1.38 ± 0.29 (0.66–1.83)
BSA (m ²) ^b	1.17 ± 0.37 (0.25–2.03)	1.17 ± 0.31 (0.25–2.03)	1.15 ± 0.38 (0.39–1.87)
CL _{CR} (ml/min/1.73 m ²) ^b	125.5 ± 34.3 (58.8–351.0)	126.1 ± 35.2 (58.8–351.0)	123.6 ± 31.8 (59.2–233.3)
CL _{CR} (ml/min) ^b	82.6 ± 29.8 (16.5–192.6)	83.4 ± 22.9 (16.5–192.6)	80.2 ± 29.0 (24.8–170.9)
Initial tobramycin dose (mg/24 h)	288.2 ± 124.0 (40–600)	288.1 ± 124.8 (40–600)	288.3 ± 98.2 (70–500)
Initial tobramycin dosage (mg/kg/24 h)	8.4 ± 1.6 (3.1–14.5)	8.3 ± 1.5 (3.1–12.7)	8.4 ± 1.6 (3.1–14.5)
Total no. of tobramycin courses	754	559	195
Total no. of observed tobramycin concns per subject	15 ± 12 (2–94)	15 ± 17 (2–94)	16 ± 17 (2–69)
Total no. of observed tobramycin concentrations	2,884	2,120	764
Total no. of peaks (0.5–2 h postdose)	696	515	181
Tobramycin peak (mg/liter) (0.5–2h postdose)	25.4 ± 7.1 (9.4–55.5)	25.4 ± 7.3 (9.4–55.5)	25.6 ± 6.8 (10.8–45.1)

^aData are given as means ± standard deviations (minimum–maximum) unless otherwise stated.

^bCovariate values are given for the first TDM occasion.

daily area under the concentration-time curve (AUC₂₄) to the MIC have been suggested as pharmacokinetic/pharmacodynamic (PK/PD) predictors of efficacy, and target values have been defined (3–7). Overexposure to aminoglycosides has been associated with a risk of nephrotoxicity and ototoxicity (8), and concentration targets have also been suggested to optimize safety. For those reasons, therapeutic drug monitoring (TDM) of tobramycin is recommended to individualize the dosage and achieve the concentration target in each patient (9).

Children with CF are considered a special population regarding antimicrobial therapy. Pulmonary exacerbations are severe infections. Those exacerbations are recurrent, and pathogens such as *Pseudomonas aeruginosa* may acquire resistance to drugs and display higher MICs. In addition, it has been shown that patients with CF display altered PK of antimicrobials compared with patients without CF, including higher total body clearance and higher volume of distribution of hydrophilic drugs (10). All those characteristics support higher dosage requirements in children with CF. The usual initial dosage of tobramycin in CF patients is about 10 mg/kg/24 h (11–13). However, the ability to reach PK/PD targets of efficacy with such regimens is unclear (14). It remains challenging to determine safe and effective dosing for each individual. There is a need for dosage individualization and precision dosing of tobramycin in children with CF. Tobramycin TDM remains a valuable approach in this context, but a wider use of model-based dosing is desirable (15).

The aims of this study were (i) to develop nonparametric population PK models of tobramycin in children with CF to be used for dosage design and model-based TDM and (ii) to identify initial dosage regimens optimizing the achievement of efficacy and safety exposure targets.

(This work was presented in part as an oral abstract at the 39th RICAI meeting, Paris, 16 to 17 December 2019.)

RESULTS

Population model building and validation. A total of 2,884 measured tobramycin concentrations were collected in 754 courses of tobramycin from 195 subjects (99 female, 96 male). No outlier data were excluded in the analysis. Table 1 shows the main characteristics of this pediatric study population.

A two-compartment model best fit the data in the learning set ($n = 146$ patients). This model was associated with a 130-point decrease in the Akaike information criterion (AIC) compared with a one-compartment model without any covariate. A multiplicative term

TABLE 2 Population pharmacokinetic parameters of tobramycin estimated with the final model on the entire data set ($n = 195$ patients)^a

Pharmacokinetic parameter	Mean	SD	Coefficient of variation (%)	Interindividual variance	Median
$V_{1,0}$ (liters/kg)	0.23	0.10	42.6	0.01	0.23
CL_0 [(liters/h)/(ml/min)/m ²]	0.009	0.013	138.1	0.001	0.002
CL_r (liters/h/m ²)	2.82	1.00	35.6	1.01	2.93
K_{cp} (h ⁻¹)	1.12	1.22	109.4	1.49	0.52
K_{pc} (h ⁻¹)	2.25	3.04	135.1	9.23	0.86

^a $V_{1,0}$, typical central volume of distribution; CL_0 , clearance; CL_r , nonrenal clearance; K_{cp} , rate constant of transfer from central to peripheral compartment; K_{pc} , rate constant of transfer from peripheral to central compartment. The relationships between PK parameters and covariates were described as follows: $CL = (CL_0 \times CL_{CR} + CL_r) \times BSA$ and $V_1 = V_{1,0} \times \text{weight}$.

(gamma in the nonparametric adaptive grid algorithm [NPAG]) combined with the assay error polynomial resulted in the best residual error model.

Total body weight (TBW) was found to significantly influence tobramycin central distribution volume. The best equation describing the relationship was a linear equation, i.e., with volume expressed in liters per kilogram. Tobramycin total body clearance was modeled as the addition of nonrenal and renal clearance, the latter being correlated with creatinine clearance (CL_{CR}), calculated in milliliters per minute. Using CL_{CR} estimated for a standard body surface area of 1.73 m² was associated with poorer fit. In addition, body surface area (BSA) was found to significantly influence tobramycin clearance, in a linear fashion. Table 2 summarizes the estimated PK parameter values with the final model on the entire data set.

The final model adequately described the learning data set, as shown by the plot of observations versus predictions in Fig. 1. Predictive performances were acceptable, with little bias and low imprecision. Results were consistent in the validation data set ($n = 49$ patients), as shown in Table 3. Internal validation was confirmed by the prediction-corrected visual predictive check (VPC) plot shown in Fig. 2.

Performance of a simpler model to be implemented in the BestDose software.

The model's parameters and its predictive performance in the external and entire data sets are provided as supplemental material. Despite the simplification, the model provided

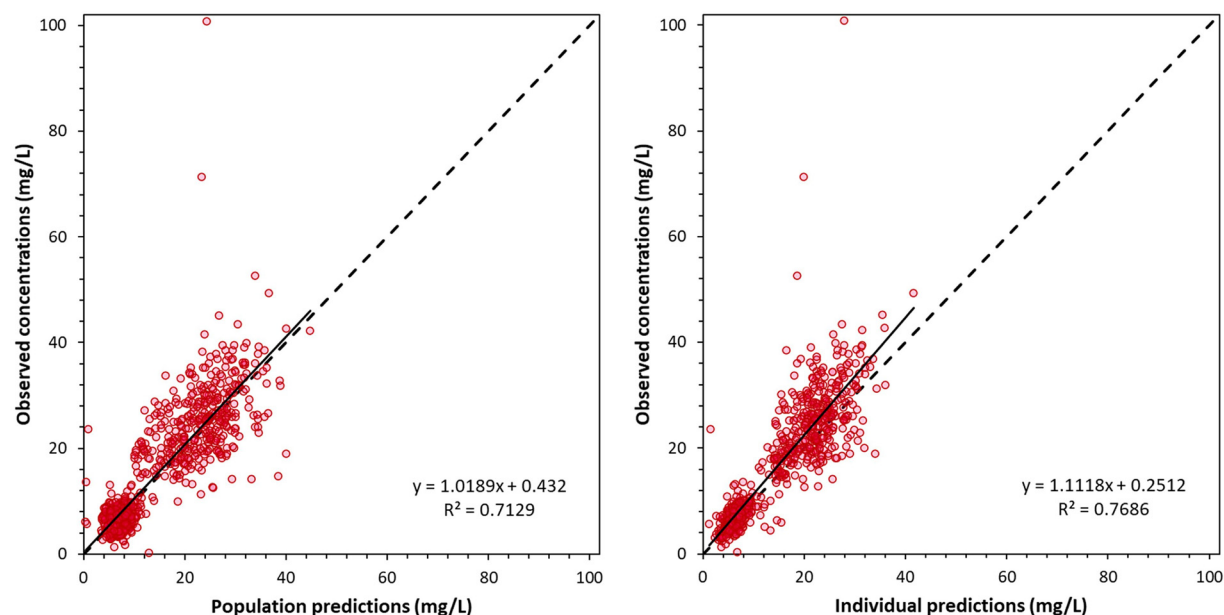


FIG 1 Goodness of fit of the final pharmacokinetic model in the validation data set ($n = 49$). Observed tobramycin concentrations (y axis) are plotted against population predictions (left) and individual model predictions (right). The dashed line represents the identity line ($y = x$); the solid black line represents the linear regression line.

TABLE 3 Predictive performance of the final model

Parameter	Prediction value for data set					
	Learning (<i>n</i> = 146)		Validation (<i>n</i> = 49)		Entire (<i>n</i> = 195)	
	Population	Individual	Population	Individual	Population	Individual
Mean error (mg/liter)	−0.48	−0.96	−0.72	−1.81	−0.06	−1.64
Median absolute error (mg/liter)	0.18	0.14	0.22	0.16	0.22	0.28
Root mean squared error (mg/liter)	5.23	4.69	6.05	5.78	5.51	5.03

a fairly good description of the data and appears suitable for model-based TDM of tobramycin in pediatric CF patients.

Dosing simulations and PTA. Simulation results and PTA analysis are summarized in Fig. 3 and Table 4. Regarding the C_{\max} /MIC target, the usual dosage of 10 mg/kg was associated with acceptable probability of target attainment (PTA) for MICs of ≤ 1 mg/liter. Considering the EUCAST MIC breakpoint of 2 mg/liter, which is intermediate between USCAST and CLSI breakpoint values, the lowest dosage achieving a PTA of $\geq 90\%$ was 17.5 mg/kg. Of note, the 15-mg/kg dosage was very close to acceptance, with a PTA of 89.2%. None of the tested regimens was associated with acceptable PTA for a MIC of 4 mg/liter (CLSI breakpoint).

With regard to the AUC_{24} /MIC target, a dosage of ≥ 20 mg/kg was necessary to achieve an acceptable PTA for MICs up to 1 mg/liter. However, none of the nine tested tobramycin regimens could attain over 90% PTA for MICs of ≥ 2 mg/liter.

All tested regimens with a dosage of ≥ 10 mg/kg were associated with a substantial proportion of C_{\min} greater than the safety targets. Figure 4 shows the probability of efficacy and safety as a function of tobramycin dose, assuming a MIC of 2 mg/liter. With regard to C_{\max} /MIC and C_{\min} targets, the dosage that would maximize both efficacy and safety was 12.5 mg/kg. No optimal dose could be defined when the AUC_{24} /MIC target was used as the efficacy target, because of low target attainment for all simulated doses.

Figure 5 shows the median values and percentiles of the simulated PK/PD indices (AUC_{24} /MIC and C_{\max} /MIC) as a function of MIC for dosages of 10 and 17.5 mg/kg/day. This allows to examine the ability to achieve values of the PK/PD indices different from the specific target (16). For example, a ratio of AUC_{24} for free, unbound drug ($fAUC_{24}$) to MIC of >50 has been suggested as acceptable for tobramycin in CF patients (5). Of note, this is virtually equivalent to an AUC_{24} /MIC ratio of >50 , since tobramycin protein

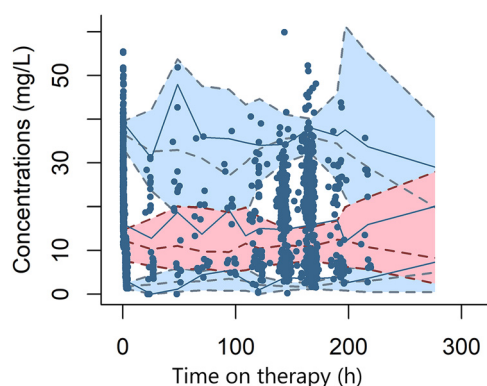


FIG 2 Prediction-corrected visual predictive check obtained with the final model for the learning data set. The blue dots represent the observed tobramycin concentrations. The blue areas show the 90% prediction interval of the 5th and 95th percentiles of simulated concentrations, and the red area is the 90% prediction interval of the median of simulated concentrations. The solid and dashed blue lines (within the colored area) represent the 5th, 50th, and 95th percentiles of observed and simulated concentrations, respectively.

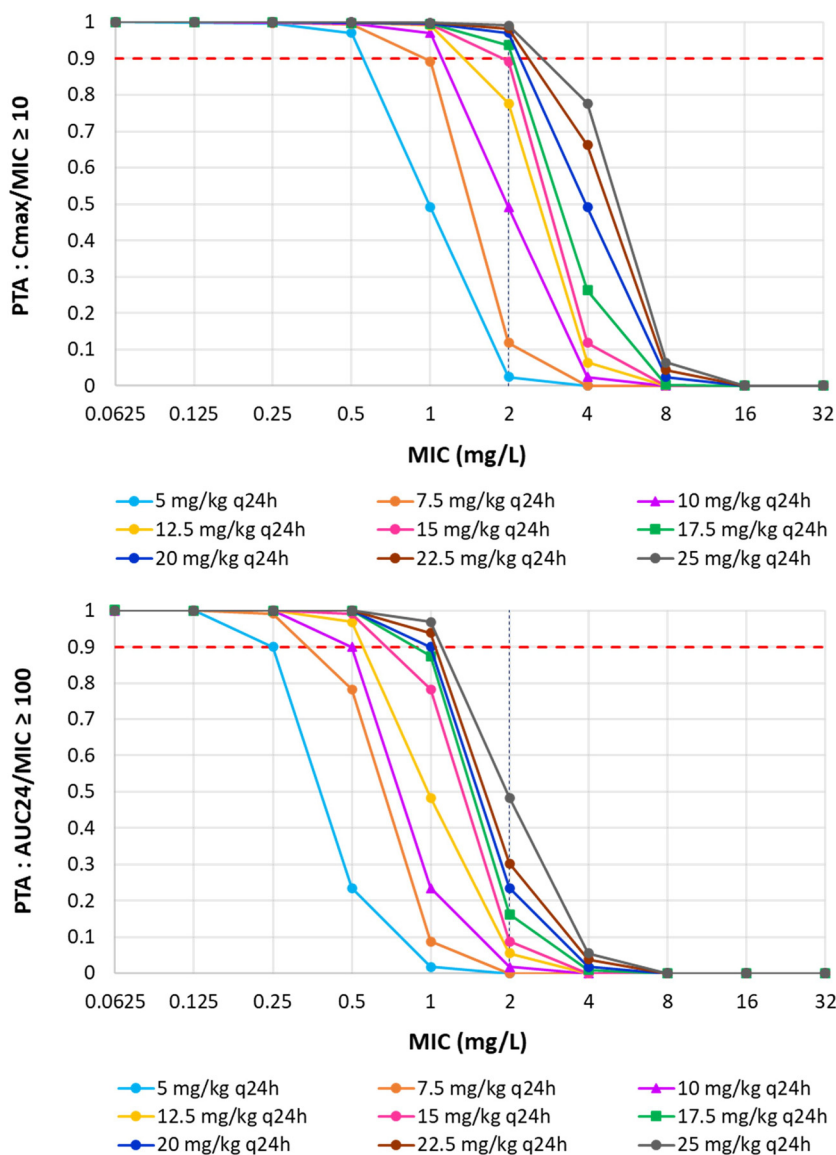


FIG 3 Probability of target attainment for an C_{max}/MIC of ≥ 10 (top) and an AUC_{24}/MIC of ≥ 100 (bottom) at day 1 for various tobramycin daily dosages, as a function of tobramycin bacterial MIC. The horizontal dashed red line shows acceptable PTA of 90%. The vertical dashed black line indicates the EUCAST tobramycin MIC breakpoint for *Pseudomonas* spp.

binding is very low (17). As shown in Fig. 4, this target of an AUC_{24}/MIC ratio of >50 can be achieved with high probability for MICs up to 0.5 mg/liter and 1 mg/liter for dosages of 10 mg/kg/day and 17.5 mg/kg/day, respectively.

DISCUSSION

The present study, which is one of the largest population PK analysis of tobramycin in pediatric patients with CF, shows some important findings.

Our final model has two compartments. The adequacy of a one- versus a two-compartment model to describe aminoglycoside PK in routine TDM has been discussed in previous works (18–24). Aminimanizani et al. performed a rich PK data analysis of tobramycin in patients with CF. Their results confirmed the two-compartment kinetics of the drug when dosed once daily (25). Despite the sparse sampling design, our analysis confirmed this result. The use of a one-compartment model to analyze TDM data should be discouraged, as it likely to underestimate trough concentrations. This is especially

TABLE 4 Probability of achieving tobramycin efficacy and safety targets

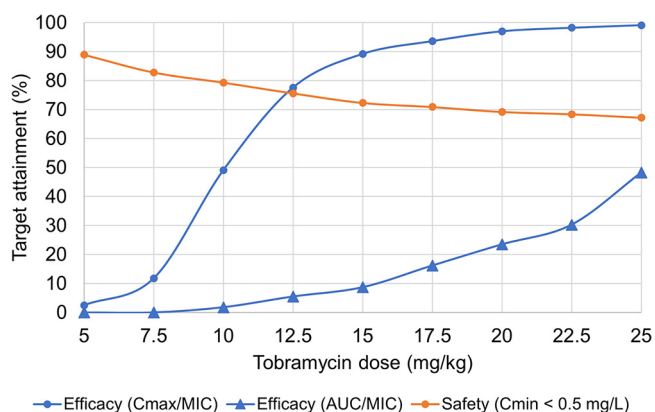
Dosage (mg/kg/day)	Median value of PD index (95% confidence interval) for MIC of 2 mg/liter		% PTA for MIC of 2 mg/liter		% of C_{min} (mg/liter) at:	
	C_{max}/MIC	AUC_{24}/MIC	$C_{max}/MIC \geq 10$	$AUC_{24}/MIC \geq 100$	>0.5	>1
5	5.0 (2.3–10.0)	19.8 (9.7–48.4)	2.5	0.0	11.1	3.6
7.5	7.5 (3.5–15.0)	29.8 (14.6–72.6)	11.8	0.0	17.2	7.3
10	10.0 (4.7–20.0)	39.7 (19.4–96.8)	49.1	1.8	20.7	11.1
12.5	12.5 (5.8–25.0)	49.6 (24.3–121.0)	77.6	5.5	24.4	14.9
15	15.0 (7.0–30.0)	59.5 (29.2–145.2)	89.2	8.7	27.7	17.2
17.5	17.4 (8.2–35.0)	69.5 (34.0–169.4)	93.6	16.2	29.1	19.3
20	19.9 (9.3–40.0)	79.4 (38.9–193.6)	97.0	23.5	30.8	20.7
22.5	22.4 (10.5–45.0)	89.3 (43.7–217.8)	98.2	30.3	31.6	22.3
25	24.9 (11.7–50.0)	99.2 (48.6–242.0)	99.1	48.3	32.8	24.4

important when the trough concentration is not measured but only estimated, as was done in our pediatric cohort, as well as for AUC estimation. Regarding PK parameter values and covariates, our results are in agreement with published results. Most population PK models of tobramycin previously published for pediatric CF patients incorporated TBW as a significant covariate influencing tobramycin body clearance and volume of distribution (19–23). Renal function was also found to influence tobramycin clearance parameter in some studies (18, 19, 24). Using CL_{CR} estimated in milliliters per minute provided a better fit than the standard estimate in milliliters per minute per 1.73 m^2 . This finding is consistent with that of Crass and Pai (18), who nicely showed that estimated glomerular filtration expressed for standard BSA greatly overestimates tobramycin clearance in children with CF. They recommended using estimated glomerular filtration rate calculated in absolute units for PK, as it better reflects the change in tobramycin clearance with age. In our analysis, tobramycin clearance was also influenced by body size, with body surface area being a better descriptor than TBW.

Interestingly, allometric scaling did not provide better results than a linear relationship for both volume and clearance. The population estimate of central volume of distribution was 0.23 ± 0.10 liters/kg, very similar to previous results in children with CF (18, 22). The mean total body clearance of tobramycin was 3.97 ± 1.52 liters/h (0.12 ± 0.04 liters/h/kg), which is also similar to previous population studies in children with CF (18, 22).

We also derived a simpler model to be used for model-based TDM of tobramycin with the BestDose software. The model file is available upon request. Both the final population model and the simpler model have been validated with an external data set and provided good predictive performance.

Dosing simulations were performed to assess the ability of various tobramycin daily doses to achieve two PK/PD targets of efficacy and a PK safety target. Several findings are

**FIG 4** Simulated dose-response curves for efficacy and safety. Target attainment rates for efficacy are those reported in Table 4, for a MIC of 2 mg/liter.

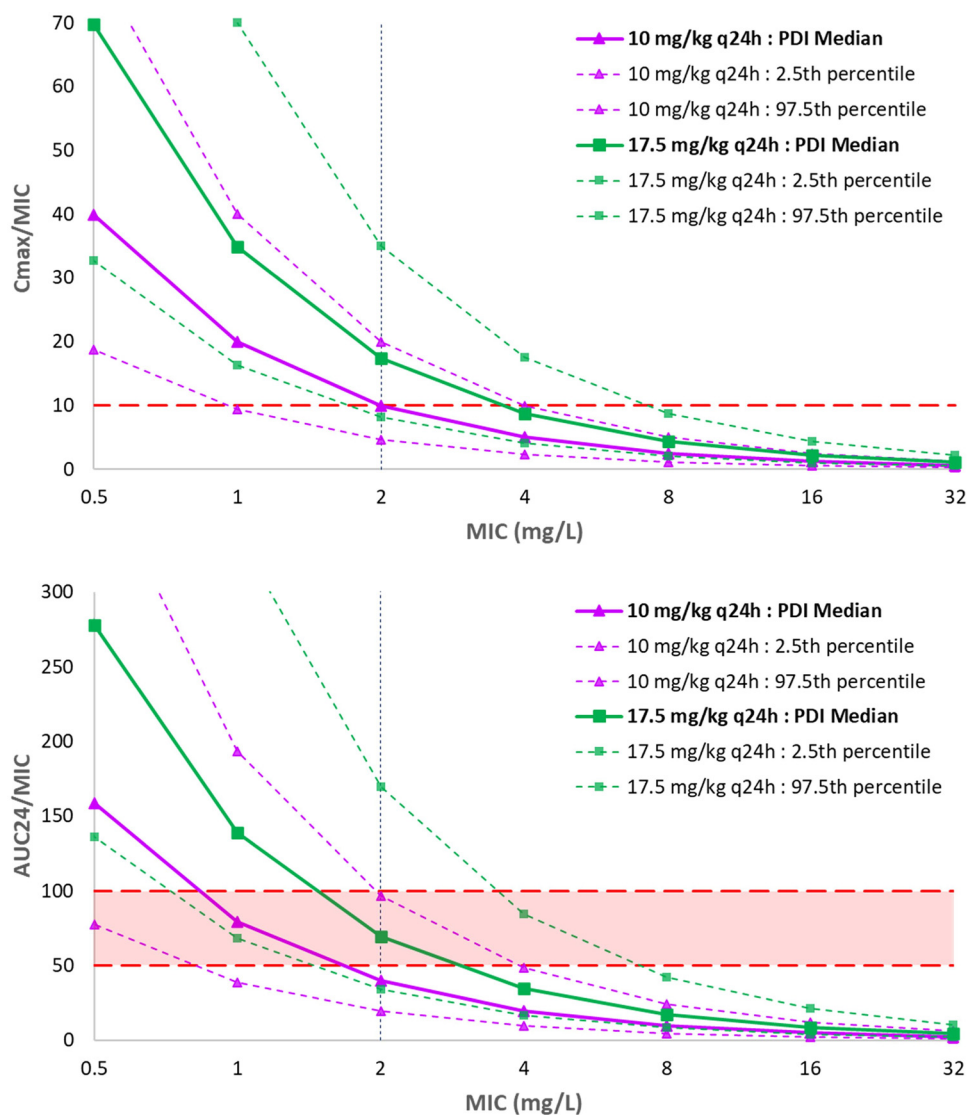


FIG 5 Simulated values of PK/PD efficacy indices as a function of MIC. (Top) C_{max}/MIC ; (bottom) AUC_{24}/MIC . Results are shown for tobramycin dosage regimens of 10 mg/kg/day and 17.5 mg/kg/day. The solid line represents the median value. The dashed lines represent the values of the PK/PD index in the percentile range from 2.5 to 97.5. In the top panel, the horizontal dashed red line shows the target value of C_{max}/MIC . In the bottom panel, the horizontal dashed red lines delimit the target interval of AUC_{24}/MIC . In both panels, the vertical dashed black line indicates the EUCAST tobramycin MIC breakpoint for *Pseudomonas* spp.

relevant for clinical practice. First, the usual tobramycin dosage of 10 mg/kg/24 h that is suggested in guidelines for patients with CF is not adequate, as it is associated with insufficient PTA. Our results suggest that 15 to 17.5 mg/kg would be necessary to optimize the achievement of the C_{max}/MIC target for MICs up to 2 mg/liter. Those higher dosages would still be insufficient to achieve the AUC_{24}/MIC target, which raises questions about the most relevant index to be used in clinical practice. A C_{max}/MIC ratio of ≥ 8 to 10 is the historical target based on clinical data (3, 4). There is also evidence supporting the relevance of an AUC/MIC ratio of ≥ 70 to 100, including one study in patients with CF (5–7). Some recent TDM guidelines have recommended the use of both targets (26). However, as reported in a previous study from our group, it should be recognized that those targets are not interchangeable and are associated with large differences in terms of aminoglycoside dosage requirements (27). In patients without renal impairment, reaching the AUC/MIC target requires much larger daily doses than C_{max}/MIC -based monitoring. Our results show that doses larger than 10 mg/kg/day would be associated with increased C_{min} and a

higher proportion of C_{\min} values greater than 0.5 to 1 mg/liter at 24 h, which raises safety concerns. As reported in a previous study from our group (27), the efficacy and safety targets of aminoglycosides are conflicting.

As one could expect, the MIC strongly influences the PTA and optimal dosing of tobramycin. The variability of tobramycin MIC breakpoints for *Pseudomonas aeruginosa* is an issue in this context, with a 4-fold difference between USCAST and CLSI breakpoints. Obviously, both C_{\max} /MIC and AUC/MIC targets can be better achieved with conventional dosages when a lower MIC breakpoint, such as the USCAST reference of 1 mg/liter, is used. This lower breakpoint value was suggested in 2016, based on PK/PD data, considering the poor rate of achievement of the AUC/MIC target with conventional dosing (14). Our results also support this alternative approach, which may be safer than using larger doses. However, it should be reminded that a significant proportion of *Pseudomonas aeruginosa* clinical isolates from patients with CF show MICs greater than 1 mg/liter (28).

Our study has several limitations that should be considered. Data were collected in routine clinical practice, and errors may have occurred in drug administration and assay, as well as data collection. Despite the large number of patients and the long follow-up, the single-center nature of this study remains a limitation for generalizability. Regarding simulations, we considered high target values of the PK/PD indices C_{\max} /MIC and AUC/MIC. As suggested elsewhere (14), lower target values may be acceptable, and so lower tobramycin doses and exposure may be sufficient considering that tobramycin is not used alone but always in combination in patients with CF. On the other hand, the host and pathogen characteristics, as well as the severity of this disease, may justify a more aggressive dosing approach in this context.

Although aminoglycoside TDM and dosage individualization are recommended and widely performed in CF patients, it should be recognized that the PK/PD rationale is still unclear for those patients. Pulmonary exacerbations are different from pneumonia in non-CF patients. There is a lack of aminoglycoside exposure targets adapted to CF patients, for both efficacy and toxicity. Regarding antimicrobial PD, some studies reported a lack of correlation between *P. aeruginosa* susceptibility to tobramycin and ceftazidime and clinical outcome in CF patients (29, 30). Also, while MIC measurement seems relevant to define individual PK/PD targets, most often MIC determination is not performed, or when it is performed, the results are not available when antimicrobial therapy starts (13, 31). Thus, assuming the highest possible MIC and targeting the highest exposure for each exacerbation is questionable, considering the cumulative risk of toxicity (32). However, identifying the safe and effective exposure of antimicrobials in each CF patient is currently impossible. Further research is necessary to clarify the PK/PD relationships of aminoglycosides in CF patients.

Conclusion. To conclude, we have developed nonparametric PK models for initial dosing and model-based TDM of tobramycin in CF children. Dosing simulations suggest that an initial dose of tobramycin of 15 to 17.5 mg/kg would be necessary to achieve C_{\max} /MIC ratios of ≥ 10 for MICs up to 2 mg/liter in most patients. A dose of 12.5 mg/liter would optimize both efficacy and safety. Such higher dosages require further clinical efficacy and safety evaluation. The efficacy and safety concentration targets of tobramycin are conflicting. We believe that dose individualization based on tobramycin TDM, model-based dose adjustment, and MIC determination remains the best way to ensure safe and effective therapy in children with CF, and we recommend such practice.

MATERIALS AND METHODS

Study design, patients, and data collection. This was a single-center, noninterventional, retrospective study of tobramycin PK data collected in routine clinical care of CF pediatrics followed at the Lyon CF pediatrics reference center (Centre de Ressources et de Compétences de la Mucoviscidose pédiatrique de Lyon, CRCM). All patients who were treated with intravenous (i.v.) tobramycin for pulmonary exacerbation from January 2010 to December 2018 and had TDM were included. As we performed a retrospective analysis of anonymized data collected in routine care, patients' consent and ethics approval were not required, as stated in French regulations for clinical research (33).

In our CF pediatric center, i.v. tobramycin is administered once daily for 14 days to treat pulmonary exacerbations, in accordance with guidelines (1). Model-based TDM of tobramycin in CF pediatric patients has been routine practice for more than 20 years in our center. TDM results are used to estimate individual

PK parameter values in each patient and adjust tobramycin doses in order to achieve an AUC_{24} target of 70 to 100 mg·h/liter, irrespective of MIC. The BestDose software (formerly USC*PACK and MM-USC*PACK) is used for nonparametric, Bayesian estimation of PK parameters and computation of dose adjustment (34). TDM data collected in this routine activity were retrieved for population PK analysis.

In detail, two samples were collected after the first dose, about 30 min and 3 h after the end of the infusion. The same sampling procedure was repeated on day 8 of therapy. The sampling times were recorded for each patient according to standard practice. Tobramycin plasma concentrations were determined by using an automated immunoturbidimetric assay (particle-enhanced turbidimetric immuno assay [PETIA]). The lower limit of quantification of the method was 0.2 mg/liter. Coefficients of variation of repeatability were less than 4%, within the acceptance range (<8 to 10%) of our national quality insurance program.

Other data collected were tobramycin dosing history, age, sex, total body weight (TBW), height, and serum creatinine. Other covariates were calculated from those data: body surface area (BSA, in square meters) estimated by the Gehan and George equation (35), ideal body weight (IBW, in kilograms) estimated by the Peck equation (36), and creatinine clearance (CL_{CR}) estimated by the new Schwartz equation (37). As the Schwartz equation provides estimated CL_{CR} in milliliters per minute per 1.73 m², the estimates were denormalized by using the individual BSA to get CL_{CR} in milliliters per minute as well (18).

Pharmacokinetic analysis. (i) Model building. The data set was randomly divided into a learning (74.9%; $n = 146$) and a validation (25.1%; $n = 49$) data set for the PK analysis. The learning set was used for model selection and initial estimation of pharmacokinetic parameters. The validation data set was then used for external validation of the final model built in the first step. A final run with the entire data set was done to get the largest model to be used for dosing simulations.

Population PK modeling was performed by using the nonparametric adaptive grid algorithm (NPAG) implemented in the Pmetrics R package (Laboratory of Applied Pharmacokinetic, University of Southern California, Los Angeles, CA, USA) (38). One- and two-compartment models (associated with zero-order input and first-order elimination) were fitted to tobramycin concentrations without any covariates in the learning data set to assess the best structural model. The residual error model was based on the assay error pattern described by a polynomial combined with either a multiplicative (gamma) or additive (lambda) term, as available in Pmetrics, to describe other sources of noise. The influence of TBW, IBW, BSA, age, and height on tobramycin central volume of distribution and total body clearance was assessed, by using various relationships, including linear equations and power equations, including allometric scaling for body size descriptors.

In the learning data set, goodness of fit of candidate structural, error, and covariates models was assessed using a likelihood-derived criterion, i.e., the objective function [OF; $-2\log(L)$, where L is the likelihood], and the Akaike information criterion [AIC; $-2\log(L) + 2p$, where p is the number of model parameters]. When two models are compared, a lower AIC value indicates a better fit. Parameter values and plots of observed versus model-based predicted concentrations as well as residual plots were also examined. Bias and imprecision were derived from population and Bayesian posterior individual predictions. Mean prediction error (MPE; in milligrams per hour) (equation 1) was used as a measure of bias.

$$MPE = \frac{1}{n} \sum_{i=1}^n (C_{pred\ i} - C_{obs\ i}) \quad (1)$$

Median absolute percent error (MdAPE, in percent) (equation 2) and root mean squared error (RMSE; in percent) (equation 3) were used as measures of precision.

$$MdAPE = \text{median} \left(\left| \frac{C_{pred\ i} - C_{obs\ i}}{C_{obs\ i}} \right| \times 100 \right) \quad (2)$$

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^n (C_{pred\ i} - C_{obs\ i})^2} \quad (3)$$

Internal validation of the final model was performed by computation of visual predictive checks (VPCs). Each subject in the study population was used as a template for a 1,000-subject simulation based on the population PK model. Model predictions were then visually compared with observed tobramycin concentrations on a concentration-time plot.

(ii) External validation. External validation of the final model was performed in a data set from 49 patients not used in the model building. Nonparametric joint densities of pharmacokinetic parameters estimated by the NPAG algorithm in the learning set were used to calculate population predictions (zero cycle option in NPAG). In addition, those densities were used as priors for Bayesian estimation of individual parameters of the 49 patients and subsequent calculation of individual predictions. Plots of observations versus model predictions, as well as bias and precisions of model predictions, were evaluated as defined above.

(iii) Final analysis. A final run was performed to estimate population PK parameters in the entire data set, in order to get the richest possible population model to be used in subsequent simulations. The nonparametric population joint densities estimated in the learning set were used as initial prior for the run. The goodness of fit and predictive performances were assessed as described above.

(iv) Derivation of a simpler model for implementation in the BestDose software. A simpler model was derived for implementation into the BestDose software (Windows version) that is used in our institution for model-based TDM of tobramycin. Due to software requirements, the model was

parameterized in rate constants and volume instead of clearance and volume. Also, as this version of the software can accommodate only two covariates, the model was simplified and included only TBW and CL_{CR} as covariates influencing tobramycin volume of distribution in the central compartment (V_1) and elimination rate constant (k_{el}), respectively, in a linear manner. Predictive performance of this model was assessed in the external data set. A final run was also performed with the entire data set to get the richest possible nonparametric prior distribution of PK parameters.

Monte Carlo simulations and PTA. Monte Carlo simulations were performed with the final model to investigate the influence of tobramycin dosage on the probability of target attainment (PTA) considering two PK/PD indices of efficacy, C_{max}/MIC and AUC_{24}/MIC (39). We set target values at a C_{max}/MIC of ≥ 10 and an AUC_{24}/MIC of ≥ 100 , in accordance with published reports (3–5, 14). Of note, those targets are defined for total drug concentrations in plasma. Free-drug concentrations are not relevant for aminoglycosides, since their protein binding is very low (17). C_{max} was calculated as tobramycin concentration measured 30 min after the end of a 30-min infusion, in accordance with French guidelines.

We also evaluated the probability of achieving target values of trough concentration (C_{min}), which is considered a predictor of aminoglycosides nephrotoxicity. Two C_{min} target values were investigated in simulations based on the literature: < 0.5 mg/liter (11) and < 1.0 mg/liter (40–44).

Nine tobramycin dosing regimens were evaluated: 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25 mg/kg/day. Weight-based dosing was justified by the final model results, with body size influencing both central volume of distribution and clearance of tobramycin, as well as the wide use of such a dosing approach in routine pediatric practice.

A wide range of tobramycin MICs of ranging from 0.0625 to 32 μ g/ml was considered, to take into account tobramycin resistance of *Pseudomonas aeruginosa* (45). It is noteworthy that tobramycin MIC breakpoints for *Pseudomonas* spp. vary slightly between references. They are 4 mg/liter, 2 mg/liter, and 1 mg/liter according to CLSI, EUCAST, and USCAST, respectively (46).

PK/PD simulations with the final model were performed by computing tobramycin concentrations profiles in 1,000 virtual patients, for each tobramycin dosage regimen. Variability of influencing covariates was taken into account, with random selection of covariate values based on the variance-covariance of covariates observed in the study population and covariates values. We used the semiparametric simulation method available in Pmetrics, which respects the discrete nonparametric prior distribution estimated with NPAG (47).

The PTA was calculated as the proportion of virtual patients achieving the target index value after the first tobramycin dose for each dosage regimen. Acceptable PTA was set at 90% (48).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

ACKNOWLEDGMENTS

We thank all the members of the Lyon pediatric CRCM, with particular appreciation for the CF children and their families.

This work was not supported by any company or sponsor fund. It was performed as part of our routine activity that is supported by Hospices Civils de Lyon and the University of Lyon.

We have no conflicts of interest that are relevant to the content of this study.

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