



Differences in the Pharmacokinetics of Gentamicin between Oncology and Nononcology Pediatric Patients

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ABSTRACT Dosing gentamicin in pediatric patients can be difficult due to its narrow therapeutic index. A significantly higher percentage of fat mass has been observed in children receiving oncology treatment than in those who are not. Differences in the pharmacokinetics of gentamicin between oncology and nononcology pediatric patients and individual dosage requirements were evaluated in this study, using normal fat mass (NFM) as a body size descriptor. Data from 423 oncology and 115 nononcology patients were analyzed. Differences in drug disposition were observed between the oncology and nononcology patients, with oncology patients having a 15% lower central volume of distribution and 32% lower intercompartmental clearance. Simulations based on the population pharmacokinetic model demonstrated low exposure target attainment in all individuals at the current clinical recommended starting dose of 7.5 mg/kg of body weight once daily, with 57.4% of oncology and 35.7% of nononcology subjects achieving a peak concentration (C_{max}) of ≥ 25 mg/liter and 64.3% of oncology and 65.6% of nononcology subjects achieving an area under the concentration-time curve at 24 h postdose (AUC_{24}) of ≥ 70 mg · h/liter after the first dose. Based on simulations, the extent of the impact of differences in drug disposition between the two cohorts appeared to be dependent on the exposure target under examination. Greater differences in achieving a C_{max} target of > 25 mg/liter than an AUC_{24} target of ≥ 70 mg · h/liter between the cohorts was observed. Further investigation into whether differences in the pharmacokinetics of gentamicin between oncology and nononcology patients are a consequence of changes in body composition is required.

KEYWORDS pediatrics, gentamicin, NONMEM, body composition, normal fat mass, pediatrics

Gentamicin is an aminoglycoside antibiotic used to treat Gram-negative bacterial infections in critically ill pediatric patients. Achieving adequate gentamicin exposure for antimicrobial efficacy in these individuals is challenging, as gentamicin displays large pharmacokinetic (PK) variability, and it has a narrow therapeutic window. Part of this variability in critically ill pediatric patients is due to pathophysiological changes associated with an infection as well as changes in patient size and/or body composition and organ maturation over time (1, 2). Population PK models may help to explain this variability and predict drug exposure in specific individuals under different dosing regimens.

Information on the PKs of gentamicin in pediatric patients older than 2 years of age is limited mainly to oncology patients (2, 3). In addition, most gentamicin PK models developed to date have used a mechanistic covariate model-building approach, where covariate relations are predefined and incorporated into the model as fixed effects (1, 2). Preselection among correlated covariates may lead to the omission of other important covariate-parameter relations (4), or the true influence of two (or more) highly

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correlated covariates on the same parameter may not be identified (5). The full random-effect modeling (FREM) approach has been proposed to address this limitation, by testing all covariates of interest on each parameter of the model at the same time, potentially limiting bias in parameter estimation (6).

Differences in body composition between oncology and nononcology patients have been reported, which may lead to differences in the PKs of gentamicin between these two populations. It has been shown that pediatric oncology patients have a significantly high fat mass (FM) of 30.4%, compared to 14.9% in nononcology patients (7, 8). The higher percentage of body fat in oncology patients may be related to excess weight gain, particularly in leukemia patients, due to long-term glucocorticoid therapy usage (8). A 28% increase in body fat and a 5% decrease in lean body mass have been observed in pediatrics with acute lymphoblastic leukemia at the completion of 6 months of therapy (9). Whether these differences affect the PKs of gentamicin is unknown. No studies have investigated whether the PKs of gentamicin are different between oncology and nononcology patients and, consequently, whether a different dosing regimen may be required between the two cohorts when considering different drug exposure targets. Gentamicin efficacy has been related to achieving specific drug exposure targets (namely, a peak concentration [C_{max}] of ≥ 25 mg/liter [10] and an area under the concentration-time curve at 24 h postdose [AUC_{24}] of ≥ 70 mg · h/liter [11]).

In this study, we aim to investigate whether the PKs of gentamicin are different between oncology and nononcology patients and, consequently, whether different doses of gentamicin are required across these cohorts to achieve currently recommended exposure targets.

RESULTS

Patients. Data were collected from 115 patients (72 males [62.6%]) admitted primarily for nononcology indications. These patients contributed 487 gentamicin concentration-time data points. This data set was pooled with a previously collected data set from 423 patients (219 males [52.0%]) who were admitted primarily for oncology indications (2). These patients contributed 2,422 gentamicin concentration-time data points. Within the combined data set, the patients' mean (standard deviation [SD]) total body weight (TBW) was 24.6 kg (17.5 kg), fat-free mass (FFM) was 18.8 kg (12.4 kg), postmenstrual age (PMA) was 361.9 weeks (241.8 weeks), and serum creatinine (SCR) was 38.9 μ mol/liter (36.1 μ mol/liter). One hundred twenty-four patients (23.0%) were younger than 2 years of age, of which 3 patients (2.42%) were neonates (postnatal age [PNA], <28 days) and 121 patients (97.6%) were infants (PNA, ≥ 28 days and <2 years). Two hundred seventy-nine patients (51.9%) were 2 to 10 years old, and 135 patients (25.1%) were older than 10 years of age. A summary of patient clinical and demographic characteristics is shown in Table 1. A comparison of gentamicin data between the oncology and nononcology patients stratified by different PNA, FFM, and SCR groups is illustrated in Fig. S1 in the supplemental material. The mean PNA in the nononcology and oncology cohorts were 5.5 and 6.4 years, respectively. Within the oncology cohort, the most common cancer was leukemia, diagnosed in 189 patients (45%), followed by blastomas, diagnosed in 55 patients (13%). Reasons for admission in the nononcology population were multifactorial, with the most common being appendicitis in 12.2% of patients and kidney disease/urinary tract infection in 10.4% of patients (Fig. S2).

Full random-effect covariate model. Inclusion of height, serum albumin, and being an oncology patient did not have a clinically significant effect (greater than 20% or less than -20% for the 5th and 95th percentile extremes of the covariate) on gentamicin clearance (CL) and the peripheral volume of distribution (V_2) (Fig. 1) when added to a previously built model (2) using the FREM approach. Being a nononcology patient was, however, associated with a significant mean increase in the central volume of distribution (V_1) (95% confidence interval [CI] of 25.7% (13.6% to 37.5%)) (Fig. 1). Sampling importance ratio (SIR) evaluation supported the model (Fig. S3), and the covariate effects identified were carried forward to the next steps of model building.

TABLE 1 Demographic and clinical characteristics of patients

Patient characteristic ^a	Value for group		P value ^d	Value for all patients (n = 538)
	Oncology patients (n = 423)	Nononcology patients (n = 115)		
Mean total body wt (kg) (SD)	25.2 (17.1)	22.3 (18.8)	0.150	24.6 (17.5)
Mean fat-free mass (kg) (SD)	19.3 (12.0)	17.0 (13.4)	0.100	18.8 (12.4)
Mean postnatal age (yr) (SD)	6.36 (4.47)	5.53 (5.24)	0.119	6.19 (4.65)
Mean postmenstrual age (wk) (SD)	371.2 (232.4)	327.6 (272.3)	0.119	361.9 (241.8)
Mean ht (cm) (SD)	115.6 (30.4)	103.9 (38.2)	0.003	113.0 (32.5)
No. of patients of age (%)				
≤2 yr	73 (17.3)	51 (44.3)	<0.01	124 (23.0)
2–10 yr	247 (58.4)	32 (27.8)	<0.01	279 (51.9)
>10 yr	103 (24.3)	32 (27.8)	0.521	135 (25.1)
No. (%) of male patients				
Mean serum creatinine concn (μmol/liter) (SD) ^b	219 (52)	72 (62.6)	0.049	291 (54.1)
Mean creatinine clearance rate (ml/min/1.73 m ²) (SD) ^c	36.8 (13.3)	47.1 (73.5)	0.102	38.9 (36.1)
Median gentamicin dose (mg/kg) (IQR)	108.0 (23.9)	87.6 (36.7)	<0.001	102.4 (28.6)
No. of gentamicin concn	7.05 (5.96–7.43)	5.90 (3.73–7.15)	<0.01	6.95 (5.81–7.42)
Median no. of gentamicin concn/patient (IQR)	2,422	487		2,909
Median no. of gentamicin concn/dose (IQR)	4 (2–7)	2 (1–5)	<0.01	3 (2–7)
No. (%) of gentamicin concn below limit of quantification	2 (1–4)	2 (1–4)		2 (1–4)
	372 (15.4)	60 (12.3)	0.098	432 (14.8)

^aIQR, interquartile range.

^bSerum creatinine concentration below the lowest reportable limit set to an expected creatinine concentration physiological mean (23).

^cCreatinine clearance was calculated using the Flanders metadata formula (32), with the serum concentration below the lowest reportable limit set to an expected creatinine concentration physiological mean (23).

^dSignificance levels calculated using an independent two-sample t test, a two-sample Wilcoxon test, and Pearson’s chi-squared test for means, medians, and proportions, respectively, comparing oncology patient demographics to those of nononcology patients.

Mechanistic-based covariate model. The inclusion of normal fat mass (NFM) as a body size descriptor on all structural parameters (difference in the objective function value [ΔOFV] of −12.9) and different V₁ and intercompartmental clearance (Q) estimates for oncology patients and nononcology patients improved the model fit (ΔOFV of −42.7). The typical CL was estimated to be 4.58 liters/h/62.8 kg (NFM). V₁ values for oncology and nononcology patients were 18.1 liters/57.5 kg (NFM) and 21.4 liters/57.5 kg (NFM), respectively. Additionally, the stochastic model was extended to a full variance-covariance matrix (ΔOFV of −25.3), allowing for separate between-subject variability (BSV) estimates on V₁

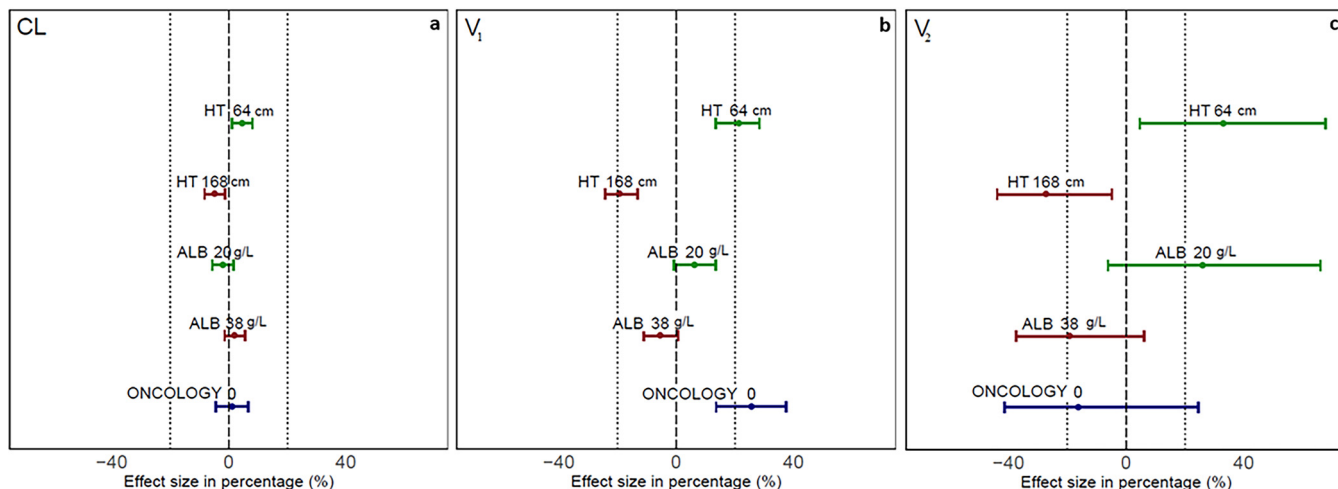


FIG 1 Predicted relative effect size of height (HT), serum albumin (ALB), and being an oncology patient (ONCOLOGY) on gentamicin clearance (CL) (a), volume of distribution of the central compartment (V₁) (b), and volume of distribution of the peripheral compartment (V₂) (c). For continuous covariates (HT and ALB), the lines illustrate 95% effect size uncertainty at the 5th (green lines) and 95th (red lines) percentile extremes of the covariate, respectively. For the categorical covariate (ONCOLOGY), the blue line compares the plotted category (nononcology = 0) versus the most frequent category in the data set (oncology = 1). The dashed lines represent the no-effect line (relative effect size of 0%), and the dotted lines show a clinically significant effect (greater than 20% or less than −20%).

TABLE 2 Population PK model parameter estimates and covariate effects associated with the final model for gentamicin^a

Parameter	Value	RSE (%) ^c	BSV CV (%)	RSE (%) ^c	BOV CV (%)	RSE (%) ^c
CL (liters/h/62.8 kg NFM) ^b	4.58	1.55	16.5	17.1	20.7	5.62
V ₁ in oncology patients (liters/57.5 kg NFM) ^b	18.1	2.43	23.8	22.9		
V ₁ in nononcology patients (liters/57.5 kg NFM) ^b	21.4	4.78	26.0	31.9		
Q in oncology patients (liters/h/56.1 kg NFM)	0.57	4.88	29.4	40.0		
Q in nononcology patients (liters/h/56.1 kg NFM)	0.84	12.2	59.8	38.4		
V ₂ (liters/56.1 kg NFM)	18.2	13.6	67.6	35.6		
Covariate model						
θ _{serum creatinine}	0.58	4.26				
F _{fat} on CL	0.48	27.2				
F _{fat} on V ₁	0.10	31.7				
F _{fat} on Q	0 fix					
F _{fat} on V ₂	0 fix					
Residual-error model						
Proportional (%)	29.3	2.21				
Additive (mg/liter)	0.05	16.9				

^aBOV, between-occasion variability; BSV, between-subject variability; CV, coefficient of variation; F_{fat}, fat factor; FFM, fat-free mass; NFM, normal fat mass; OFV, objective function value; Q, intercompartmental clearance; V₁, volume of distribution of the central compartment; V₂, volume of distribution of the peripheral compartment.

^bFor clearance (CL), standard NFM (NFM_{std}) is calculated as NFM_{std} = 56.1 + 0.48 × (70 - 56.1) = 62.8 kg; for V₁, standard NFM is calculated as NFM_{std} = 56.1 + 0.10 × (70 - 56.1) = 57.5 kg.

^cRelative standard errors (RSE) for both fixed- and random-effect values were obtained using the sampling importance resampling (SIR) method.

and Q for oncology and nononcology patients (ΔOFV of -29.9). The contribution of fat (F_{fat}) on the PK parameters was estimated for CL and V₁, with values of 0.48 and 0.10, respectively, whereas the contribution of fat on Q and V₂ was negligible and fixed to 0. Again, model evaluations were supported by using the SIR technique to obtain uncertainty in model parameters (Fig. S4). Typical PK parameter estimates for the final model are shown in Table 2. Prediction- and variability-corrected visual predictive check (VPC) and normalized prediction distribution error (NPDE) plots displayed good agreement between the observed and predicted data (Fig. 2). Final parameter estimates are summarized in Table 2.

Pharmacokinetic simulations. The demographic characteristics of simulated oncology subjects (mean TBW [SD] of 24.8 kg [15.7 kg], mean FFM [SD] of 19.2 kg [11.4 kg], mean PMA [SD] of 377.1 weeks [287.1 weeks], and mean SCR [SD] of 36.7 μmol/liter [12.4 μmol/liter]) and nononcology subjects (mean TBW [SD] of 23.4 kg [25.4 kg], mean FFM [SD] of 17.6 kg [17.6 kg], mean PMA [SD] of 351.3 weeks [434.5 weeks], and mean SCR [SD] of 42.5 μmol/liter [23.9 μmol/liter]) were in agreement with values from the original data sets (Table 1).

After an initial once-daily dose of 7.5 mg/kg of body weight, simulations showed that 57.4% of oncology subjects and 35.7% of nononcology patients would achieve a C_{max} of ≥25 mg/liter at 0.5 h postdose after the end of the infusion and that 64.3% of oncology and 65.6% of nononcology subjects would achieve an AUC₂₄ of ≥70 mg · h/liter on day 1 (Table 3). After an initial dose of 9 mg/kg, more than 80% of oncology subjects would achieve both targets (C_{max} and AUC₂₄). However, a higher dose would be required in nononcology subjects to achieve both targets in the same proportion of subjects. Gentamicin exposure and the proportion of subjects achieving specified targets under all tested doses (12) are shown in Table 3 and Fig. S5.

DISCUSSION

A population PK model of gentamicin was developed to characterize the PKs of this agent in different pediatric cohorts and can be used for gentamicin dosing support and dosage adjustment. Differences in the distribution of gentamicin between oncology and nononcology patients were observed and described using allometrically scaled NFM. NFM is a theory-based size descriptor, which partitions TBW into FFM and FM to account for differences in body composition (13, 14). The influence of FM is described by the fraction of FM (F_{fat}) associated with a PK parameter. F_{fat} reflects the contribution of fat, in addition

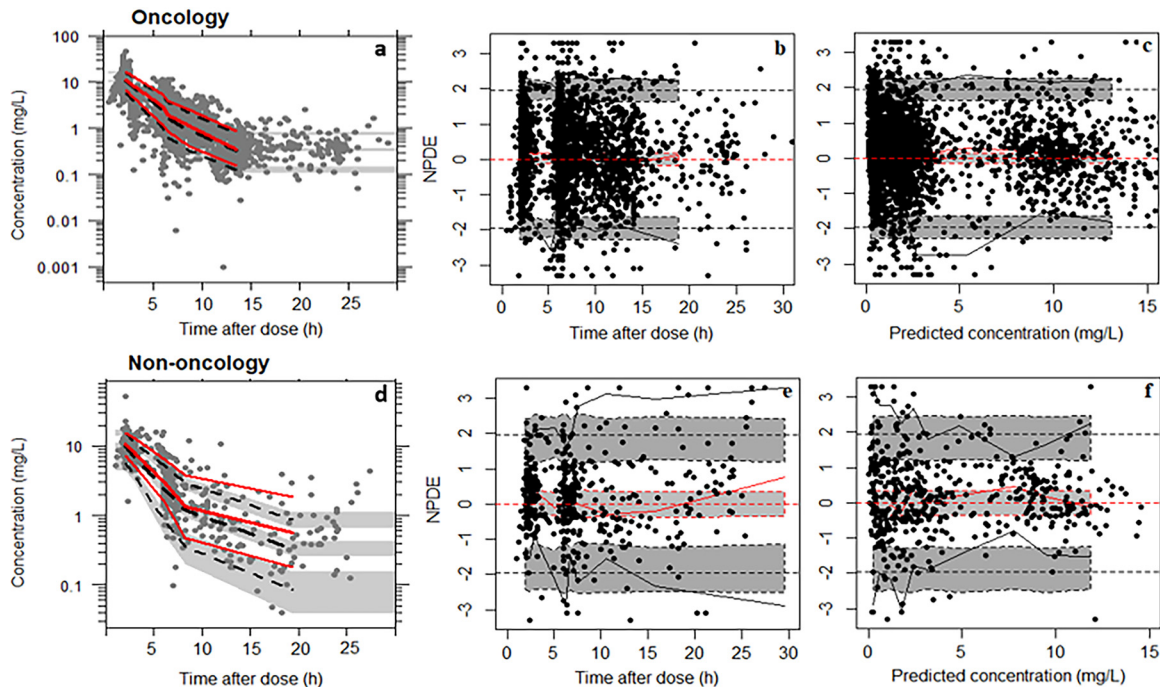


FIG 2 Prediction- and variability-corrected visual predictive check and normalized prediction distribution error (NPDE) plots using the final model. Medians and 90th and 10th percentiles of observed data (red lines), medians and 90th and 10th percentiles of simulated data (black dashed lines), and 95% confidence intervals of simulated data (gray area) are shown. (a) Gentamicin concentration (milligrams per liter) versus time after dose (hours) in oncology patients; (b) NPDE versus time after dose (hours) in oncology patients; (c) NPDE versus population-predicted concentrations (milligrams per liter) in oncology patients; (d) gentamicin concentration (milligrams per liter) versus time after dose (hours) in nononcology patients; (e) NPDE versus time after dose (hours) in nononcology patients; (f) NPDE versus population-predicted concentrations (milligrams per liter) in nononcology patients.

to FFM, to describe changes in function or structure (e.g., CL or volume of distribution [V]) (14).

PK parameter estimates in this study are in agreement with those of another recent study involving more than 2,000 pediatric patients (PMA range, 21 to 1,026 weeks), where the following PK parameter estimates were reported: CL of 4.57 liters/h/70 kg TBW, V_1 of 18.1 liters/70 kg TBW, Q of 1.07 liters/h/70 kg TBW, and V_2 of 17.1 liters/70 kg TBW (15). In our study, oncology patients had lower V_1 (18.1 liters/57.5 kg NFM) and Q (0.57 liters/h/56.1 kg NFM) values than nononcology patients (V_1 of 21.4 liters/57.5 kg NFM and Q of 0.84 liters/h/56.1 kg NFM). These differences between the two cohorts may be explained by differences in their severity of illness and/or differences in their body composition. Reasons for hospital admission within the nononcology cohort were multifactorial, with 22% of patients being treated for an infection-related disease, 10% being admitted because of an accident, and 8% recovering from a liver transplant (see Fig. S2 in the supplemental material). It should be noted that in this study, the nononcology cohort had a higher proportion of pediatric patients younger than 2 years of age than in the oncology cohort (Table 1). To evaluate if differences in V_1 between the cohorts were due to age-dependent changes, a sensitivity analysis was performed by excluding patients younger than 2 years of age in both cohorts; however, high V_1 and Q values for gentamicin were still identified in nononcology compared to oncology patients.

Murphy et al. (8) reported that the percentage of body fat in oncology patients is higher (30.4%) than in nononcology patients (14.9%) of a similar TBW. Others reported that pediatric acute lymphoblastic leukemia patients' body fat increases by 28% at the completion of 6 months of therapy, while the ratio of lean body mass to TBW is reduced by 5% (9). When gentamicin is dosed based on TBW, it may be expected that oncology patients have a lower gentamicin V and higher initial serum drug concentrations, due to their high percentage of FM and decreased body water relative to their total body

TABLE 3 Simulated gentamicin exposure following a first dose of 7.5 mg/kg q24h, 9 mg/kg q24h, 10 mg/kg q24h, and 12 mg/kg q24h in oncology and nononcology patients^a

Population	Dose (mg/kg)	Median C _{max} (mg/liter) (95% PI)	Median AUC ₂₄ (mg · h/liter) (95% PI)	% of patients achieving C _{max} ≥ 25 mg/liter			% of patients achieving AUC ₂₄ ≥ 70 mg · h/liter				
				Total	<2 yr old	2–10 yr old	>10 yr old	Total	<2 yr old	2–10 yr old	>10 yr old
Oncology	7.5	26.1 (18.0–39.4)	79.4 (45.8–140.0)	57.4	36.8	57.1	65.6	64.3	17.1	59.8	95.4
	9	31.4 (21.6–47.3)	95.3 (54.9–168.0)	83.7	72.3	84.4	85.3	81.8	38.2	81.3	98.6
	10	34.9 (24.0–52.6)	106.0 (61.1–187.0)	92.7	86.8	93.4	92.2	88.9	52.6	89.7	99.1
	12	41.8 (28.8–63.1)	127.0 (73.3–224.0)	98.8	97.4	98.9	99.1	96.8	81.6	97.6	99.5
Nononcology	7.5	23.0 (14.8–33.6)	84.0 (44.1–205.0)	35.7	28.5	35.5	45.9	65.6	53.6	61.3	95.1
	9	27.6 (17.8–40.3)	101.0 (53.0–247.0)	63.3	55.9	63.5	72.4	80.5	73.4	77.4	99.4
	10	30.7 (19.7–44.8)	112.0 (58.9–274.0)	77.7	70.6	78.2	85.9	87.1	81.7	85.3	100
	12	36.8 (23.7–53.8)	134.0 (70.6–329.0)	92.7	90.9	92.0	97.3	95.2	92.5	94.8	100

^aTotal is the percentage of patients who achieved the targets across the data set (n = 1,000). The percentage is also shown for each subgroup based on the respective number of patients within each group who achieved the targets, in oncology patients <2 years (n = 76), 2 to 10 years (n = 706), and >10 years (n = 218) and in nononcology patients <2 years (n = 252), 2 to 10 years (n = 563), and >10 years (n = 185) of age. AUC₂₄ area under the concentration-time curve at 24 h postdose; C_{max}, peak concentration 0.5 h after the first dose; PI, prediction interval.

weight. The higher percentage of body fat in oncology patients has been related to excess fat gain, particularly in leukemia patients, due to ongoing glucocorticoid steroid therapy and the consequential appetite stimulation for fatty food (8, 16, 17).

In this study, we included NFM as a body size descriptor to investigate the influence of FM on the PKs of gentamicin by the determination of F_{fat} . Different F_{fat} values for oncology and nononcology patients on each PK parameter did not produce a significant drop in the OFV, and difficulties in estimating F_{fat} were encountered, which could be due to the smaller nononcology cohort and the sparse samples per patient in both cohorts. In addition, the contribution of FM to V_1 was small, with an F_{fat} value of 0.10, whereas the contribution of FM to V_2 was negligible (0.002) and was therefore fixed to 0. The latter was not unexpected, as gentamicin does not distribute widely into fat (14). In contrast, an F_{fat} value of 0.48 was estimated for CL. Rhodin et al. (18) reported a contribution of FM to the glomerular filtration rate (GFR) of 21%. However, in the present study, a higher percentage of oncology patients (79%) was included than in Rhodin et al.'s (18) data set (38%), and this may explain our higher F_{fat} estimate. Han et al. (19) showed that absolute clearance was higher in obese than in normal-weight subjects. It should be noted that NFM is an estimator of body composition based on FFM for a typical patient with a specific sex, height, and body weight. The equation to predict FFM (20) does not differentiate between oncology and nononcology patients as such. If FFM would have been measured using the dual-energy X-ray absorptiometry (the "gold-standard") technique (21) in our patient cohort, a difference in PKs based on body composition could have possibly been determined. This could be a subject of future studies to further investigate potential reasons for the differences in the PKs of gentamicin between oncology and nononcology patients seen in this study.

The FREM approach was applied in this study. FREM is a novel method, which has been proposed to reduce the risk of selection bias when correlated covariates are available for testing (6). In this study, FREM was applied to identify the effect size of different correlated covariates on the PKs of gentamicin. When using a FREM covariate modeling approach, assessment of covariate-parameter relationships is restricted to parameters that include BSV. Our base model did not include BSV on Q , and therefore, covariate effects were not assessed on the parameter Q .

Simulations showed that when a C_{max} exposure target of ≥ 25 mg/liter was considered, nononcology subjects appeared to require a higher gentamicin starting dose than oncology patients, but when an exposure target of an AUC_{24} of ≥ 70 mg · h/liter was considered, different doses between the two cohorts would likely not be required. The pattern of our findings (proportion of patients achieving a target) would remain the same if MIC-based targets (e.g., C_{max}/MIC or AUC_{24}/MIC values) were used, although absolute proportions would change. Thus, our model can be applied to estimate optimal drug exposure based on different exposure targets, including ones used at other hospital sites. It is important to mention that it was previously suggested that AUC_{24} , rather than C_{max} , is more closely linked to bacterial kill (22). Higher initial doses maximize bacterial kill at 24 h postdose, by limiting the bacterial pool susceptible to developing adaptive resistance to gentamicin. A higher initial dose of antibiotic has been shown previously to achieve a higher bacterial killing rate and avoid lingering bacterial mutation problems (11, 12). Based on the simulations, a dose of 10 mg/kg would achieve both targets (C_{max} and AUC_{24}) in more than 70% of oncology and nononcology subjects. In this study, the potential toxicity associated with each dose was not considered. However, toxicity associated with these doses was investigated previously (12).

In conclusion, small to moderate differences in gentamicin PKs (V_1 and Q) between oncology and nononcology patients were observed, with nononcology patients having a higher V_1 and a higher Q . This means that nononcology patients achieve a lower C_{max} but a higher AUC_{24} under any given dosing regimen than oncology patients. The biologically effective body size determining CL of gentamicin is proportional to FFM plus 48% of FM. Although nononcology patients achieve a lower C_{max} than oncology patients, no clinically significant differences in AUC_{24} were observed between the two

populations. The model developed in this study can be used to support dosing recommendations for oncology and nononcology patients to achieve any desired target. A common clinically used initial once-daily dose of gentamicin of 7.5 mg/kg may not achieve an optimal C_{\max} target in either cohort (<60% of simulated subjects achieved this target). In addition, further investigation of whether PK differences in gentamicin between oncology and nononcology patients are a consequence of their differences in body compositions is still required.

MATERIALS AND METHODS

Patients. Data were collected retrospectively from the medical charts of nononcology and oncology pediatric patients who had gentamicin concentrations measured during routine therapeutic drug monitoring (TDM) between 2008 and 2013 at the Children's Hospital Queensland, Brisbane, Australia. Ethics approval for collecting data for this study was obtained from the University of Queensland Human Research Ethics Unit (approval number 2012001308) and the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (approval number HREC/12/QRCH/162).

Information on gentamicin dosing regimens, the timing of dose administration, gentamicin serum drug concentrations, and the time of sample collection for drug measurement along with patient demographic and clinical information such as age, sex, TBW, height, serum albumin, diagnosis, indication, and SCR concentration were recorded. SCR values reported to be <30 $\mu\text{mol/liter}$ (lowest reportable limit of quantification) were replaced with the mean expected physiological creatinine concentration for a child of the relevant age and sex (23). Patients in critical care were excluded from the analysis.

Gentamicin treatment and blood sampling. Gentamicin was administered as a 30-min intravenous infusion. As per local hospital guidelines, patients <10 years old or septic patients received an initial dose of 7.5 mg/kg every 24 h (q24h), and patients ≥ 10 years old received 6 mg/kg q24h. TDM was performed after the first dose of directed therapy. Blood samples for measurement of gentamicin serum concentrations were generally collected at 2 to 3 and 6 to 8 h postdose.

Gentamicin assay. The gentamicin drug concentration in serum was measured using a fluorescence polarization immunoassay method. From 2008 to August 2011, a Beckman Coulter Petinia immunoassay run on a Beckman Coulter DXC800 analyzer was used. From August 2011 to November 2011, an Abbott CMA immunoassay run on the Abbot Architect i1000 immunoassay analyzer was used. From November 2011 to December 2012, a Beckman Coulter CEDIA immunoassay run on a Beckman Coulter DXC800 analyzer was used. From December 2012 onward, a Beckman Coulter Petinia immunoassay run on a Beckman Coulter DXC800 analyzer was used. The assay lower limit of quantification (LLOQ) varied across immunoassay methods from 0.3 to 0.6 mg/liter. Within- and between-assay coefficients of variation were below 10% for all immunoassays employed.

Pharmacokinetic model development. (i) Base model. A previously reported PK model of gentamicin (2) was used as an initial starting model, which was a two-compartmental model that included the influence of the patient's postmenstrual age (PMA), FFM, and SCR concentration on gentamicin CL and the influence of FFM on V_1 , V_2 , and Q. BSV was modeled using an exponential model for CL, V_1 , and V_2 . The model included a correlation between CL and V_1 , and between-occasion variability (BOV) was included on CL. BOV was modeled using an additional random-effect parameter. Residual unexplained variability (RUV) was described using a combined-error model. Gentamicin drug concentrations reported as being below the LLOQ were replaced by LLOQ/2 values. Updated GFR maturation values were used in this study (maturation half-time $[TM_{50}] = 46.5$ weeks; Hill coefficient = 3.43; adult GFR = 119 ml/min) (24).

(ii) Covariate analysis. Covariate model building was performed using a mechanistic-based approach, as described previously (2). The specific aim was to explore the effect of NFM on gentamicin PKs and the contribution of FM on different PK parameters. To overcome limitations of the mechanistic approach, the FREM method was used to investigate whether other correlated covariates that were previously not considered (e.g., height and albumin) may have an influence on gentamicin PKs.

(iii) Full random-effect covariate model. The FREM approach (6) was used to investigate the influence of additional continuous covariates that were not included in the initial starting model (2), such as height and serum albumin on CL, V_1 , and V_2 and being an oncology patient on all distribution and clearance parameters. This approach was selected as these additional covariates (height, serum albumin, and whether the patient belonged to the oncology cohort or not) were correlated with covariates already included in the model (FFM, PMA, and SCR). Therefore, FREM in this study was used as an explorative method.

Using FREM, covariates were included in the model as observed variables, and their distributions were modeled as random effects (6). Log-normal distributions were used to describe BSV in covariate values. Coefficients for covariate-parameter relations were determined from the ratio of covariance between parameter and covariate variability to the covariate variance (6). The covariate effect size on PK parameters for continuous covariates was obtained from the ratio of the parameter value, conditional on a known covariate value (5th and 95th percentiles), to the parameter value conditional on the observed covariate value (the mean). For categorical covariates, the covariate effect on PK parameters was obtained from the ratio of the parameter value conditional on a known value equal to the least common category (nononcology = 0) to the parameter value conditional on a known value equal to the most common category (oncology = 1). A clinically relevant effect was considered when the effect size was greater than 20% or less than -20% for the 95th and 5th percentile extremes of the covariate, respectively. The SIR (25) technique was used to obtain the relative standard errors and assess the

precision of the model parameters. Results were graphically examined by comparing the distribution of the Δ OFV of the proposed uncertainty distribution to a theoretical chi-square distribution, to assess the appropriateness of the proposal uncertainty given by the SIR. The uncertainty distribution was considered appropriate when the Δ OFV distribution of the last two iterations was overlaid with or below the theoretical distribution (26).

(iv) Mechanistic-based covariate model. Further development of the initial starting model was performed by including NFM (13), and replacing FFM, on all parameters. Both FFM and F_{fat} were used within the NFM calculation (equation 1), with F_{fat} estimated for each PK parameter. Standard values of an FFM of 56.1 kg and a TBW of 70 kg (equation 2) were used (14). F_{fat} values range between 0 and 1; if F_{fat} is estimated to be 0, then FFM alone is required to characterize the effect of patient size on the PK parameter, and conversely, if F_{fat} is 1, then the patients' entire TBW is required to characterize the effect of patient size on the PK parameter. Parameter-covariate relationships for CL, V_1 , Q , and V_2 are shown in equations 3 to 6, respectively. Maturation of GFR (GFR_{mat}), which affects gentamicin CL, was calculated using equation 7.

$$NFM(\text{kg}) = FFM + F_{fat} \times (TBW - FFM) \quad (1)$$

$$NFM_{std}(\text{kg}) = 56.1 + F_{fat} \times (70 - 56.1) \quad (2)$$

$$CL(\text{liters/h}) = CL_{pop} \times \frac{GFR_{mat}}{100} \times \left(\frac{SCR_{mean}}{SCR_i} \right)^{\text{exponent}} \quad (3)$$

$$V_1(\text{liters}) = V_{1pop} \times \frac{NFM}{NFM_{std}} \quad (4)$$

$$Q(\text{liters/h}) = Q_{pop} \times \left(\frac{NFM}{NFM_{std}} \right)^{0.75} \quad (5)$$

$$V_2(\text{liters}) = V_{2pop} \times \frac{NFM}{NFM_{std}} \quad (6)$$

$$GFR_{mat}(\text{ml/min}) = \left(\frac{NFM}{NFM_{std}} \right)^{0.75} \times \frac{PMA^{3.43}}{46.5^{3.43} + PMA^{3.43}} \times 119 \quad (7)$$

Here, TBW is total body weight, CL_{pop} is the typical population CL value, SCR_{mean} is the mean serum creatinine concentration calculated using a formula described previously by Ceriotti et al. (23), SCR_i is the individual patient serum creatinine concentration, V_{1pop} is the typical population V_1 value, V_{2pop} is the typical population V_2 value, and Q_{pop} is the typical population Q value. To investigate further differences in the PKs of gentamicin between oncology and nononcology patients, different fixed- and random-effect values of CL, V_1 , Q , and V_2 for oncology and nononcology patients were considered. Model selection was based on differences in OFVs between nested models, with a decrease of at least 3.84 points ($P < 0.05$) considered significant. In addition, prediction- and variability-corrected VPC and NPDE plots (27, 28) were generated to assist model selection.

(v) Software. Population modeling was performed using NONMEM software v.7.4. (Icon Development Solutions, Ellicott City, MD, USA) (29) with an Intel Fortran compiler and PsN (Perl-speaks-NONMEM) version 4.7.0 (30). Typical population PK parameters of gentamicin as well as BSV and RUV were estimated via the first-order conditional estimation method with interaction (FOCE+I). R Studio software version 3.1 (<http://www.r-project.org/>) was used for data exploration and visualization. Clinical relevance plots to show the covariate effect sizes on each parameter were generated using a "PostFREM" feature in PsN.

(vi) Pharmacokinetic simulations. To explore gentamicin target attainment at different drug doses, 1,000 simulations were performed to create a population of 1,000 oncology and 1,000 nononcology subjects with demographic and clinical features reflective of the original study population. Demographic and clinical features of oncology and nononcology subjects were generated as follows: (i) covariate values from the original data set (TBW, FFM, PMA, and SCR) were log transformed to ensure a normal distribution, (ii) a full omega matrix between the covariates was calculated to account for correlation between the variables, and (iii) 1,000 new covariate vectors were generated following a normal distribution based on the typical covariate value and calculated distribution. Doses evaluated in this study were once-daily dosing of 7.5 mg/kg, 9 mg/kg, 10 mg/kg, and 12 mg/kg. Typical population and random-effect values for oncology and nononcology patients obtained from the final mechanistic-based covariate model were used for the simulations. Local clinical exposure targets (31) of a C_{max} of ≥ 25 mg/liter at 0.5 h postdose after the end of the infusion and an AUC_{24} of ≥ 70 mg · h/liter at 24 h postdose were considered when examining the different drug doses. Doses examined in this study were assessed according to their efficacy, which was determined based on the highest number of subjects achieving the exposure targets (31). Simulations were performed using the RxODE package in R Studio software (version 3.1; <http://www.r-project.org/>). Data generation and graphical analysis were performed using the MASS, corpcor, and ggplot2 packages in R Studio software (version 3.1; <http://www.r-project.org/>).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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