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Pharmacokinetics and Optimal Dose Selection of Cefazolin for Surgical Prophylaxis of Pediatric Patients

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Abstract

Cefazolin is an antibiotic frequently used for perioperative prophylaxis. Data from healthy adults and pediatric surgery patients were pooled to refine a previously developed population pharmacokinetic (PK) model and to determine the optimal body weight cutoff for selecting fixed doses of either 1 or 2 g cefazolin to produce exposures in pediatric surgery patients similar to a single 2-g dose in adults. Regardless of dose used, cefazolin was well tolerated in pediatric patients. A total of 1102 plasma samples from 62 patients from 3 studies were available to assess the previous model. The pooled data set allowed for simplification of the model such that allometrically scaled clearance and volume parameters were found to provide a robust fit while removing unnecessary covariate relationships. Monte Carlo simulations using the final cefazolin population PK model suggested an optimal weight cutoff of 50 kg, in contrast to the previously suggested 60 kg for a single 2-g dose. Patients at or above this 50-kg cutoff would receive a 2-g dose of cefazolin, and those below 50 kg but ≥25 kg would receive a 1-g dose of cefazolin.

Keywords

cefazolin, model-based simulations, pharmacokinetics, surgical prophylaxis

Cefazolin is a first-generation cephalosporin antibiotic that has been in use for nearly 5 decades. It is indicated for a variety of infections as well as perioperative prophylaxis.[1,2] Cefazolin is the most commonly used antibiotic for perioperative prophylaxis because of its efficacy, low cost, duration of action, and spectrum of activity.[2–4] Although cefazolin is primarily active against gram-positive bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, it is also active against the gram-negative bacteria *Escherichia coli* and *Proteus mirabilis*.[1] Guidelines for perioperative prophylaxis with cefazolin rarely address dosing in pediatric patients. However, guidelines published in 2013 by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Surgical Infection Society recommend weight-based dosing at a dose of 30 mg/kg while acknowledging that data are limited and "nearly all pediatric recommendations are based on expert opinion."[2] Given the limited data available on the pharmacokinetics (PK) of cefazolin in pediatric surgical patients,[5–7] the studies reported here represent important information regarding appropriate cefazolin dosing in this population.

We have previously reported on the PK of cefazolin administered using fixed-dose, prefilled DUPLEX containers in healthy adults enrolled in a phase 1 study (n = 24[8]) and a small cohort of pediatric surgery patients aged 10 to 12 years (n = 12[9]).[5] Pharmacokinetic modeling and simulation using the adult and pediatric data from those 2 studies indicated that PK exposure to cefazolin was optimized if pediatric patients with a body weight below 60 kg (but at least 25 kg) received the 1-g fixed dose of cefazolin and those with a body weight of at least 60 kg received 2 g of cefazolin. The previous analysis was conducted specifically to inform a follow-on safety and PK study in a larger cohort of pediatric surgical patients,[10] the results of which are presented here. The objectives of these analyses were to evaluate and refine the previously developed population PK model for cefazolin[5] with the data from the additional

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pediatric study and to use the final model to update the cefazolin dose recommendations in pediatric surgery patients aged 10 to 17 years, as appropriate.

Methods

Study Design

Data from 3 studies were used to evaluate and refine the previously developed population PK model. The previous model, the development of which has been described in detail,[5] used data from 1 study conducted in healthy adults, study HC-G-H-0906, and 1 in children, study HC-G-H-1202. The current analyses pooled these 2 studies with an additional pediatric study, study HC-G-H-1601. All 3 studies were approved by the institutional review board (IRB) at each study site. Written informed consent was provided by the adult subjects and by the legally authorized representatives of the pediatric patients. In some cases, the pediatric patients themselves also gave assent depending on local IRB guidelines.

Study HC-G-H-0906 (study 0906) was a phase 1 open-label, multiple-dose, parallel, 2-arm study to evaluate the safety and pharmacokinetics of cefazolin in healthy adult subjects aged 18 to 70 years.[8] Twenty-four subjects were enrolled and randomized to 1 of 2 treatment groups: (1) 2 g intravenous cefazolin via the DUPLEX delivery system once on days 1 and 11 and 3 times daily on days 2 through 10 or (2) 1.5 g intravenous cefazolin for injection once on days 1 and 11 and 4 times daily on days 2 through 10. In both treatment groups, study drug was administered as a 15-minute infusion. Samples for PK analysis were collected at the following times on days 1 and 11: predose, 7.5 minutes (during infusion), 15, 20, 30, 40, and 50 minutes, and 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose. On days 2 through 10, samples were only drawn before the first dose.

Study HC-G-H-1202 (study 1202) was an open-label, single-dose study in children aged 10 to 12 years who received cefazolin as surgical prophylaxis.[9] Twelve children were enrolled and administered a weight-based dose of intravenous cefazolin infused over 30 minutes via the DUPLEX Drug Delivery System. Children weighing at least 25 kg but <50 kg were administered a single dose of 1 g cefazolin, and children weighing 50 kg or more were administered a single dose of 2 g cefazolin. All surgical procedures lasted less than 3 hours. Samples for PK analysis were collected at nine time points: pre-dose (within 15 minutes prior to infusion), at the end of infusion, and 15 minutes, 30 minutes, and 1, 2, 3, 6, and 8 hours after the end of infusion.

Study HC-G-H-1601 (study 1601) was a phase 4 open-label, single dose, parallel-group study to evaluate the safety of cefazolin in pediatric subjects aged 10 to 17 years scheduled for surgery.[10] A total of 61 patients were enrolled and assigned in a 1:1 ratio to one of 2 dose groups based on weight. Patients with a weight of at least 25 kg but <60 kg were to receive a single dose of 1 g of intravenous cefazolin. Patients with a weight of at least 60 kg were to receive a single dose of 2 g of intravenous cefazolin. Both doses were infused via the DUPLEX drug delivery system over 30 minutes starting 0.5 to 1 hour prior to surgery. PK samples were collected in a subset of 26 patients. A sparse sampling scheme was employed, with samples obtained at 0.5 to 1 hour and 2, 3, and 4 hours after the start of infusion. Surgeries were not expected to last longer than 3 hours. If a surgery did last longer, additional doses of study treatment were allowed. In these cases, efforts were made to obtain the 3-hour and possibly 4-hour PK samples prior to administration of the additional dose. PK samples were not collected after administration of the extra dose.

Safety Assessment

The results of the safety assessment for study 1202 have been reported in detail previously.[5] Cefazolin was generally well tolerated in that study. Six of the 12 patients reported adverse events (AEs), but most of them were mild to moderate in severity.

The safety assessments reported here were confined to study 1601. All patients who received study drug were included in the safety analysis population. Reporting of AEs began at the time informed consent was obtained (screening phase) and continued until exit from the study. The investigator was responsible for reporting all AEs. The nature of AEs and the date (and time, if known) of onset and duration of AEs were documented together with the investigator's assessment of the seriousness of the AE and the investigator's judgment regarding the causal relationship of an AE to the study drug and/or study procedure. Clinical laboratory assessments were performed by a central laboratory with the exception of screening laboratory tests and serum pregnancy tests, which were performed at local laboratories. Clinically significant abnormal results of tests of blood samples collected after dosing were recorded as AEs, and the patient was monitored until the test results had normalized or stabilized. Vital signs were measured and assessed at screening and on the day of surgery (30 minutes predose and postdose at 15 minutes, 0.5 to 1 hour, and 3 hours after the start of the drug infusion).

Drug Assay

Cefazolin concentrations were determined using a validated liquid-liquid extraction method and high-performance liquid chromatography. The details for study 1202 have been reported previously.[5] Briefly, the

assay used in study 1202 had a lower limit of quantitation of 0.78 μg/mL, interassay accuracy between −2.5% and 10.6%, and interassay precision between 2.6% and 4.4%. The assay used for study 0906 had a lower limit of quantitation of 0.781 μg/mL, with interassay accuracy between −1.9% and 1.0% and precision between 2.7% and 5.5%. The assay for study 1601 was performed at a different laboratory. For study 1601, the lower limit of quantitation was 2.00 μg/mL, with interassay accuracy between −0.584% and 4.22% and precision between 2.54% and 4.49%. Despite minor differences in assay performance metrics, all assays were conducted according to Good Laboratory Practices[11] and passed predefined criteria for performance.

Pharmacokinetic Analyses

The population PK analyses were conducted using NONMEM.[12] Model criteria used to assess the population PK model included:

- Evaluation of individual and population mean PK parameter estimates and their precision as measured by the percent relative standard error (%RSE);
- Graphical examination of standard diagnostic and population analysis goodness-of-fit plots and normalized prediction distribution errors (NPDEs);
- Graphical examination of the agreement between the observed and individual post hoc predicted concentration-time data;
- Reduction in both residual variability and interindividual variability;
- Comparison of the minimum value of the objective function (MVOF) for nested models or Akaike's information criterion (AIC) for nonnested models[13]; and
- Physiologic plausibility of the parameter estimates.

Using data pooled from studies HC-G-H-1202 and HC-G-H-0906, the previous model had been determined to be a 2-compartment model with linear elimination and zero-order drug administration in the central compartment.[5] As a first step in the refinement of this previous model, the structural model was assessed by pooling data from all 3 studies and reestimating PK parameters and their associated interindividual variability (IIV) values. The determination for both structural and covariate model refinement was made on evaluation of model fit, with visual inspection of univariate screening plots of relevant PK parameters against the covariates previously mentioned. Given the limited covariate information and prior knowledge of influential predictors from the previous analysis,[5] a formal stepwise covariate modeling exercise was eschewed in favor of an abbreviated approach scrutinizing previously incorporated covariate and random effects. If the resultant covariate model was able to capture the observed cefazolin plasma PK data with minimal bias and sufficient precision, it was declared the final population PK model.

The model was then qualified internally by computation of parameter uncertainty via sampling-importance-resampling (SIR) and construction of prediction-corrected visual predictive checks (PC-VPC).[14–16] The SIR procedure provides important information on the precision of the model parameters in the context of the relatively unreliable asymptotic standard errors that are provided from the fit of the model. The evaluation of the PC-VPC plots serves to confirm the suitability of the final model for use in performing Monte Carlo simulations by comparing model-based simulations with the observed data.

The individual Bayesian post hoc PK parameter estimates obtained from the fit of the final cefazolin population PK model were used to generate predicted concentration-time profiles for each subject included in the PK data set. Predicted maximum and minimum plasma concentrations (C_{max} and C_{min}, respectively) on day 1 of dosing were determined directly from the profiles and the area under the plasma concentration-time curve from time zero to 8 hours ($AUC_{0\text{-}8}$). The $AUC_{0\text{-}8}$ was calculated via integration of the simulated concentration-time curves. To account for a multiphase disposition observed in the raw data, α- and β-elimination half-lives were derived by the method of Gibaldi and Perrier.[17] Descriptive statistics for the key PK parameters were then reported.

Model-Based Simulations

A simulated database of 6000 pediatric patients was then created, with 3000 patients aged 10 to 12 years and 3000 patients aged 13 to 17 years; 50% of subjects were assigned as male sex and 50% as female. Hypothetical patients were assigned height and weight appropriate for their age and sex using the Centers for Disease Control and Prevention growth chart data files and assigning individual Z scores to each patient to allow for random variability in height and weight,[18] and all were assumed to have normal renal function.

The demographic characteristics of this simulated patient population were then used as the basis for simulating cefazolin concentration-time profiles for each hypothetical patient following receipt of a single intravenous dose of cefazolin of either 1 or 2 g. Two dosing strategies were evaluated: one in which subjects with a body weight below 50 kg received a 1-g dose and those with a body weight at or above 50 kg received a 2-g dose (ie, weight cutoff at 50 kg) and a second strategy in which subjects with a body weight below 60 kg received a 1-g dose and those with a body weight at or above 60 kg received a 2-g dose.

Table 1. Summary Statistics of Baseline Subject Demographics for the PK Analysis Population

Variable	Study 0906 n = 24	Study 1202 n = 12	Study 1601 n = 26	Total n = 62
Age, y, median (min-max)	39.5 (24.0-53.0)	11.0 (10.0-12.0)	15.0 (11.0-17.0)	16.0 (10.0-53.0)
Height, cm, median (min-max)	178 (160-195)	146 (130-170)	168 (149-184)	168 (130-195)
Weight, kg, median (min-max)	81.5 (64.2-102)	42.8 (27.4-67.9)	61.9 (35.6-115)	66.2 (27.4-115)
BSA, m^2, median (min-max)	1.99 (1.68-2.35)	1.35 (1.02-1.79)	1.72 (1.23-2.37)	1.76 (1.02-2.37)
CLCRN, mL/minute/1.73 m^2, median (min-max)	89.5 (68.3-142)	117 (86.1-165)	109 (83.1-248)	102 (68.3-248)
Sex, n (%)				
Male	21 (87.5)	7 (58.3)	15 (57.7)	43 (69.4)
Female	3 (12.5)	5 (41.7)	11 (42.3)	19 (30.6)
Race, n (%)				
White	9 (37.5)	10 (83.3)	17 (65.4)	36 (58.1)
Black	15 (62.5)	1 (8.33)	6 (23.1)	22 (35.5)
Asian	0 (0)	0 (0)	1 (3.85)	1 (1.61)
Other/unspecified	0 (0)	1 (8.33)	2 (7.69)	3 (4.84)

BSA, body surface area; CLCRN, normalized creatinine clearance; cm, centimeter; kg, kilogram; m, meter; max, maximum; mL, milliliter; min, minimum; n, number of subjects/patients; PK, pharmacokinetic; y, years.

Results

Subject Demographics and Baseline Characteristics

The analysis population consisted of the population reported previously (24 healthy adults from study 0906 and 12 pediatric surgical patients from study 1202[5]) and 61 pediatric surgical patients who had been enrolled in study 1601. Summary statistics of baseline demographics for the PK analysis population stratified by study population as well as overall are provided in Table 1. Age ranged from 24 to 53 years in healthy adults and from 10 to 17 years in pediatric surgery patients; total body weight ranged from 64.2 to 102 kg and from 27.4 to 115 kg, respectively. Creatinine clearance ranged from 68.3 to 142 mL/min/1.73 m^2 in adults and from 83.0 to 248 mL/min/1.73 m^2 in children. Both populations were predominantly male (87.5% of adults; 57.9% of children). Healthy adults from study 0906 were predominantly black (62.5%), whereas pediatric surgery patients were predominantly white (71.1%).

Safety Assessment

During study 1601, 27 of the 61 patients in the safety population reported a total of 61 AEs; 13 of 33 subjects (39.4%) reported treatment-emergent AEs (TEAEs) after cefazolin 1 g, and 14 of 28 subjects (50.0%) reported TEAEs after cefazolin 2 g. The majority of subjects reported TEAEs considered unrelated to the study drug (24 subjects [39.3%]) overall; only 3 subjects (4.9%) reported TEAEs considered possibly related to the study drug (nasal pruritus [cefazolin 1 g] and pruritus and hypotension [both cefazolin 2 g]). All TEAEs were considered mild in severity.

Pharmacokinetic Analyses

The pooled data set contained a total of 1102 plasma samples from 62 subjects. Although no samples were determined to be outliers, 28 samples were found to be below the limit of quantitation (BLQ). All BLQ samples were from study 0906. BLQ samples were flagged and excluded from the analysis, leaving the final data set to be 1074 samples from 62 individuals. In study 1601, the majority of patients provided 4 cefazolin plasma PK samples. The typical concentration-time profiles for these samples appeared consistent when compared with healthy adult PK data from study 0906. However, cefazolin concentrations over time were higher in patients from study 1202 (Figure 1A), indicating disparity between the 2 pediatric studies. If the pediatric surgery patients from studies 1601 and 1202 were considered as a single population, the cefazolin data became consistent with that seen in healthy adults but with more variability (Figure 1B).

Because of the between-study differences in pediatric cefazolin concentration-time data, the pooled PK data set was used to assess the previously developed population PK model as a base model. Although basic goodness of fit was achieved, NPDEs suggested a trend away from the assumption of normality, and PC-VPCs stratified by population and study indicated problems in accommodating data from both healthy adult and pediatric surgery patients. The previously developed model was therefore updated to improve its ability to characterize cefazolin concentrations across populations. As the intended use of cefazolin in this context is as single-dose surgical prophylaxis, this decision was made to remove all concentrations drawn after the first 24 hours in study 0906 to focus on first dose in both healthy adults and pediatric patients. All

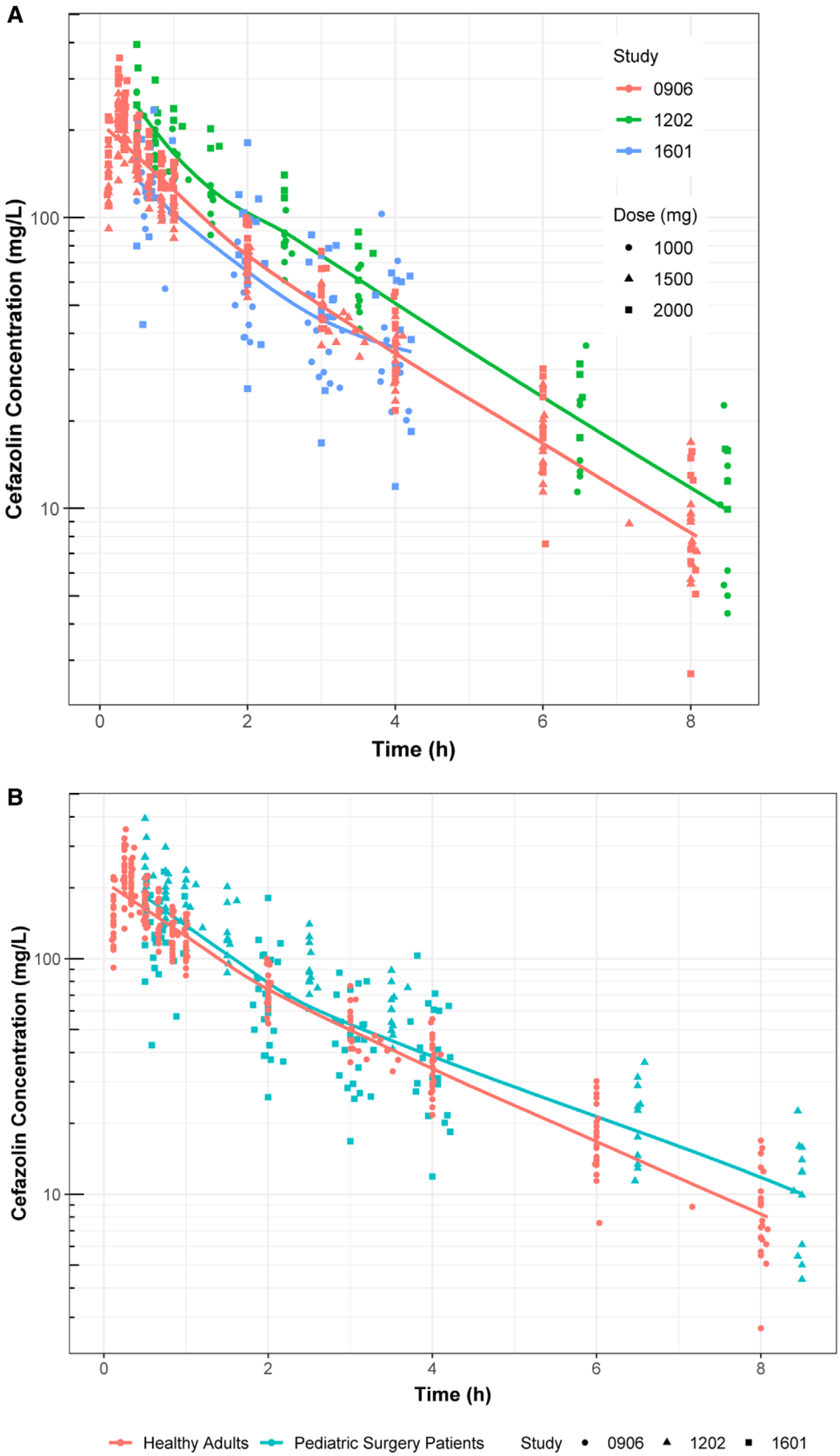

Figure 1. Cefazolin plasma concentration versus time through the first 8 hours, stratified by study and dose (A) or by population and study (B). h, hour; L, liter, mg, milligram. Solid lines represent loess smoothers through the data.

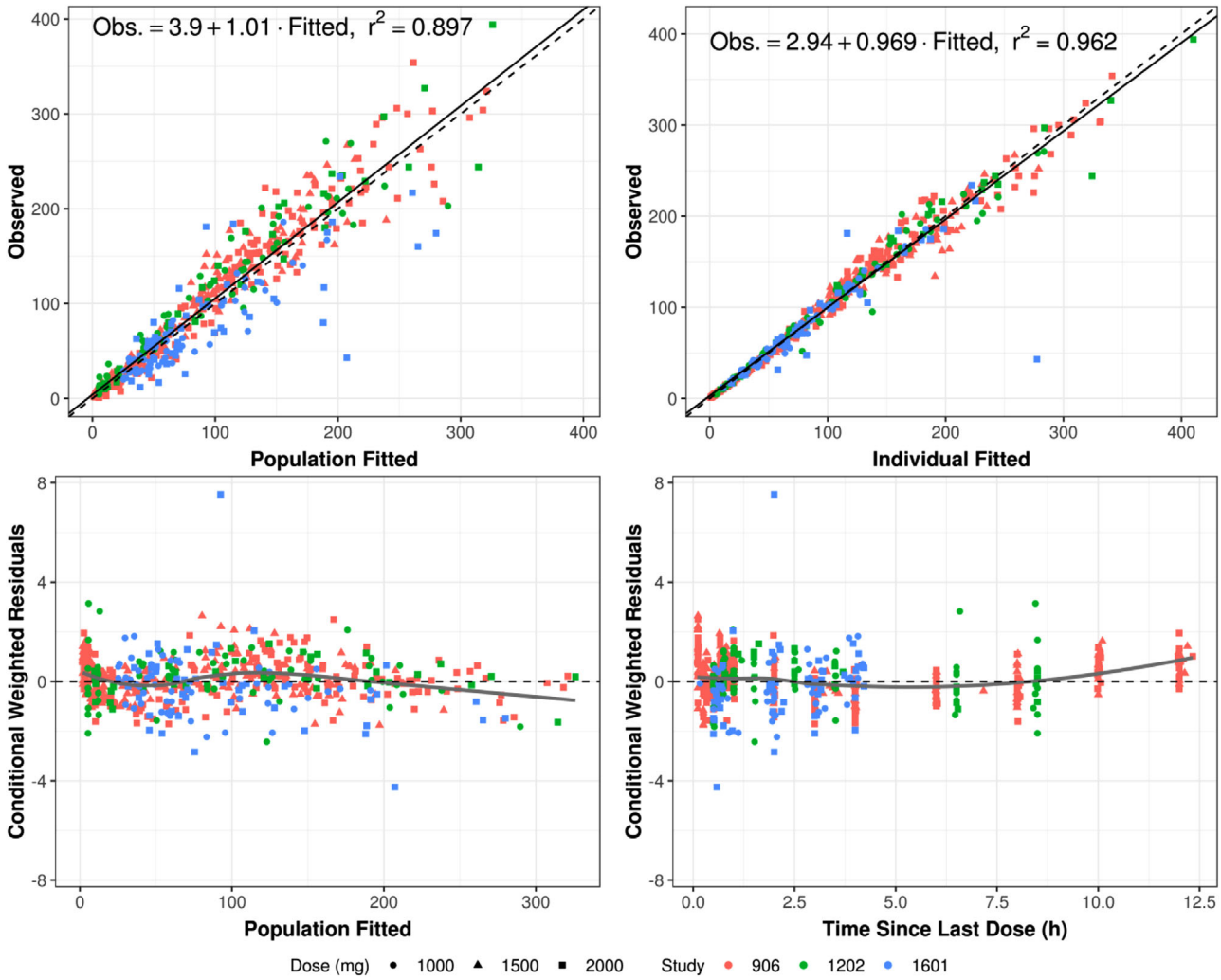

Figure 2. Goodness-of-fit plots for the final cefazolin population PK model. Two conditional weighted residual (CWRES) values eclipsed the threshold value of ±4 but were ultimately retained secondary to their inability to influence either population- or individual-level fitting. Dashed lines represent reference lines (line of identity, top; zero-residual line, bottom); solid lines represent lines of best fit (top) or loess smoothers through the data (bottom). h, hour; mg, milligram.

the 24-hour samples, which were drawn immediately prior to the first dose on day 2, were BLQ. Use of this reduced data set allowed for the resolution of bias in NPDEs and reduced the complexity of the model, as did the removal of a proportional shift in CL for pediatric surgery patients. Note that the influence of body weight on cefazolin CL was added to the model at this time, consistent with the established concept of allometric scaling.[19] A significant reduction in the MVOF (ΔOFV = −34.7 units) as well as a lowering of AIC resulted when the covariance between CL and V_c was introduced. Because of the very small amount of BLQ data (with none of the BLQ data points in pediatric surgery patients), precise estimation of the additive residual variability component was difficult, ultimately leading to the parameter being fixed to 0.5 μg/mL, a plausible value below the lower limit of quantification.

Evaluation of the covariate relationships in the model resulted in the removal of the renal clearance-normalized creatinine clearance covariate relationship, as its removal resulted in a nonsignificant increase in the MVOF (ΔOFV = +3.9 units) and resulted in a parsimonious model deemed capable of characterizing cefazolin disposition in healthy adults and pediatric surgery patients. No additional covariate influences were found after assessing continuous and categorical screening plots using both the base and final models.

Cefazolin observations were well predicted at both the population and individual levels (coefficient of determination [r^2] = 0.897 and 0.962, respectively), without evidence of systematic bias in basic goodness-of-fit plots (Figure 2) or NPDEs (data not shown). Parameter estimates and associated precision from the SIR procedure are provided in Table 2. The PC-VPCs derived from the final cefazolin population PK model

Table 2. Population PK Parameter Estimates for the Final Cefazolin Population PK Model and Summary Statistics of Resampled Population PK Parameters

	Final Model		Resample Statistics (n = 1000)			
Parameter[a,b,c]	Final Estimate	%RSE	Mean	Median	%RSE	95%CI
CL_R (L/h)	3.43	3.7	3.42	3.42	3.6	3.22-3.63
CL_{NR} (L/h)	0.153	FIXED				
V_C (L)	5.38	6.0	5.38	5.37	5.4	4.94-5.87
CL_D (L/h)	8.04	9.6	8.10	8.08	8.1	7.03-9.23
V_P (L)	3.84	3.2	3.84	3.84	2.7	3.66-4.01
IIV-CL	0.0734	27.9	0.0748	0.0732	18.7	0.055-0.0992
IIV-CL-V_C[d]	0.0741	30.0	0.0744	0.0721	22.1	0.0508-0.104
IIV-V_C	0.132	21.0	0.135	0.132	22.5	0.0924-0.185
$RV_{proportional}$	0.0123	32.0	0.0126	0.0125	7.7	0.0110-0.0142

CI, confidence interval; CL_D, distributional clearance; CL_{NR}, nonrenal clearance; CL_R, renal clearance; h, hour; IIV, interindividual variability; L, liter; n, number of subjects/patients; PK, pharmacokinetic; RSE, relative standard error; RV, residual variability; V_C, central volume of distribution; V_P, volume of distribution for the peripheral compartment; WTKG, weight in kilograms.

[a] Cefazolin total clearance is calculated as $CL = [0.153 + 3.43] \cdot \left(\frac{WTKG}{70}\right)^{0.75} \times \exp(\text{IIV})$.

[b] Cefazolin V_C and V_P coefficients are multiplied by $(WTKG/70)^1$.

[c] Cefazolin CL_D coefficient is multiplied by $(WTKG/70)^{0.75}$.

[d] Covariance in IIV of CL and Vc.

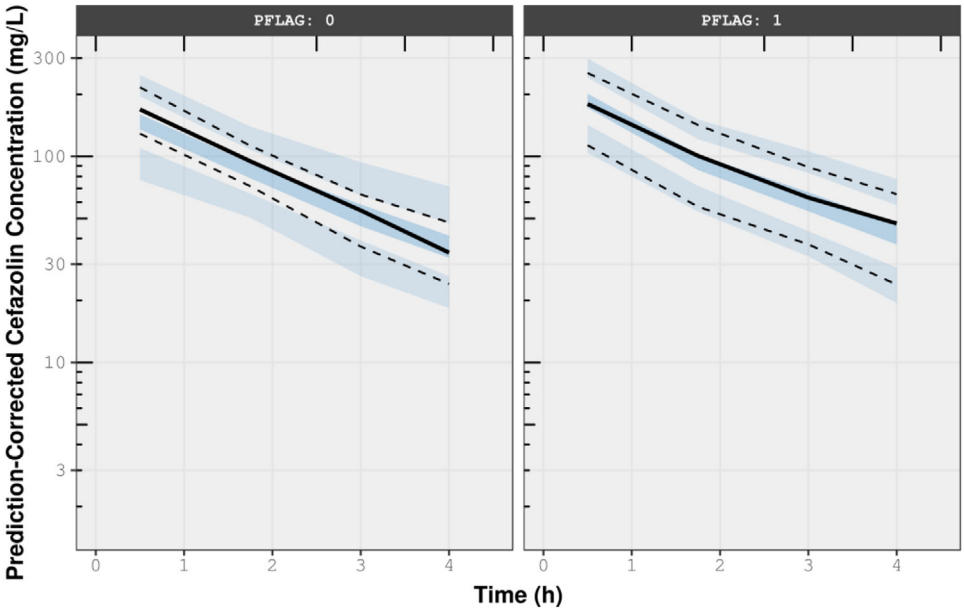

Figure 3. Prediction-corrected visual predictive checks using the final cefazolin population PK model, stratified by patient population. PFLAG represents flag variable for denoting whether the population is healthy adults (PFLAG = 0) or pediatric patients (PFLAG = 1). Black lines represent 50th (solid) and 5th/95th percentiles (dashed) of the observed data; dark blue shaded region represents the 90% prediction interval around the 50th percentile of predictions; light blue-shaded regions represent 90% prediction intervals around the 5th (lower) and 95th (upper) percentiles of predictions. h, hour; L, liter; mg, milligram.

stratified by population and study are provided in Figure 3. These model-based simulations indicate that the population PK model was able to robustly capture both the central tendency and extent of variability in cefazolin concentrations over time in the 2 populations. Thus, the final model was considered fit for purpose in generating cefazolin exposure metrics and for use in Monte Carlo simulations.

Summary statistics of pertinent PK exposure metrics and key secondary PK parameters from the final cefazolin population PK model stratified by both study and population as well as overall are provided in Table 3. Cefazolin exposures were similar between healthy adults and pediatric surgery patients, although the pediatric population had greater variability. The pediatric population also did not have any major

Table 3. Summary Statistics (Geometric Mean [CV%]) for Individual, Model-Derived Cefazolin Plasma Exposure and Secondary PK Parameters, Stratified by Study and by Population, for Individuals Included in the PK Population

Parameter	Study 0906/Healthy Adults (n = 12[a])	Study 1202 (n = 12)	Study 1601 (n = 26)	Pediatric Surgery Patients (n = 38)
$AUC_{0\text{-}8}$ (mg·h/L)	476 (16.7)	559 (23.1)	366 (40.0)	418 (40.4)
C_{max} (mg/L)	293 (14.2)	266 (21.6)	164 (36.8)	191 (39.7)
CL (L/h)	3.99 (18.4)	2.12 (26.8)	3.82 (38.4)	3.17 (44.5)
V_C (L)	5.30 (16.4)	3.01 (30.1)	6.12 (45.7)	4.89 (52.9)
V_{SS} (L)	9.64 (13.3)	5.48 (24.2)	9.80 (35.7)	8.16 (42.3)
$t_{1/2\alpha}$ (h)	0.170 (7.08)	0.150 (13.4)	0.188 (16.7)	0.175 (18.9)
$t_{1/2\beta}$ (h)	1.85 (16.5)	1.94 (12.5)	1.91 (14.3)	1.92 (13.6)

PK, pharmacokinetic; $AUC_{0\text{-}8}$, area under the curve from time 0 to 8 hours; CL, clearance; C_{max}, maximum concentration; CV%, percent coefficient of variation; h, hour; L, liter; mg, milligram; n, number of subjects/patients; PK, pharmacokinetic; $t_{1/2\alpha}$, alpha half-life; $t_{1/2\beta}$, beta half-life; V_C, volume of distribution in central compartment; V_{SS}, volume of distribution in steady state.

Note: In study 0906, cefazolin was administered as a 0.25-hour infusion, whereas in studies 1202 and 1601 infusion was over 0.5 hours.

[a]Subjects randomized to 2 g intravenous cefazolin via the DUPLEX delivery system only.

underlying conditions that would be expected to alter PK parameters. When viewed by study, study 1202 $AUC_{0\text{-}8}$ estimates were on average 30% higher than those in healthy adults, and study 1601 values were ≈15% lower, which is consistent with the observed concentration-time profiles (Figure 1A).

Model-Based Simulations

Comparisons of the distributions of cefazolin exposure in simulated subjects by age are provided in Figure 4. Contrary to prior conclusions,[5] a 50-kg minimal weight cutoff for administering a 2-g cefazolin dose appeared to normalize pediatric AUC from time zero to infinity ($AUC_{0\text{-}\infty}$) to a comparable range and central tendency as seen in healthy adults, with the 10- to 12-year-old population manifesting slightly lower exposures and the 13- to 17-year-old population manifesting slightly higher exposures. Use of a 60-kg minimal cutoff for the provision of a 2-g cefazolin dose resulted in median predicted exposures that were consistently below the geometric mean of healthy adults. If the simulated population was considered a single clinical entity rather than being stratified by age, the resulting $AUC_{0\text{-}\infty}$ distribution was highly concordant with the healthy adult geometric mean and its 80% to 125% interval (Figure 5). In this circumstance, a 60-kg minimal cutoff resulted in $AUC_{0\text{-}\infty}$ predictions in which 45.2% of pediatric surgery patients would fall below 80% of the healthy adult geometric mean.

Discussion

The analyses reported here build on previous analyses and provide important new information regarding the PK of cefazolin in pediatric surgical patients. The inclusion of 26 pediatric surgical patients from a recently completed safety study allowed for the refinement of the previous population PK model while providing more clarity around the optimal body weight cutoff for a 1- or 2-g dose in pediatric surgery patients. Pharmacokinetic simulations using the refined population PK model indicated that a fixed dose of 1 g cefazolin is appropriate in pediatric surgical patients aged 10 to 17 years who have a body weight below 50 kg. A fixed dose of 2 g is appropriate in pediatric surgical patients aged 10 to 17 years who have a body weight of at least 50 kg.

Reevaluation of the population PK model was necessary after disparities were seen between the observed PK data from the 2 pediatric studies pooled for these analyses: studies 1601 and 1202. This resulted in substantial changes to the relationships defining those patient factors that are associated with the interindividual variability in cefazolin PK. Specifically, the previous model included 2 covariate relationships that were no longer appropriate when using the larger, pooled data set: (1) the proportional shift in CL for pediatric surgical patients and (2) the inclusion of a correlation between renal function and cefazolin clearance. The resultant model is much simpler in that it only includes terms relating cefazolin PK parameters with body weight, using fixed exponential terms consistent with the concept of allometric scaling (ie, CL terms have a fixed exponent of 0.75, whereas the volume terms have a fixed exponent of 1.0[19]).

The removal of the proportional shift in CL for pediatric surgery patients is highly desirable given that the empirical introduction of that relationship lacked a strong physiologic basis and simply served to adjust for the higher than expected concentrations in a small cohort of patients (n = 12 in study 1202). When evaluated by study, clear differences were seen in the PK of cefazolin in the 2 pediatric studies, with those from study 1202 appearing systematically higher than those from study 1601. This phenomenon was not attributable to the slight imbalance in age between the studies (21 of 26 study 1601 patients were at least 13 years old), as the

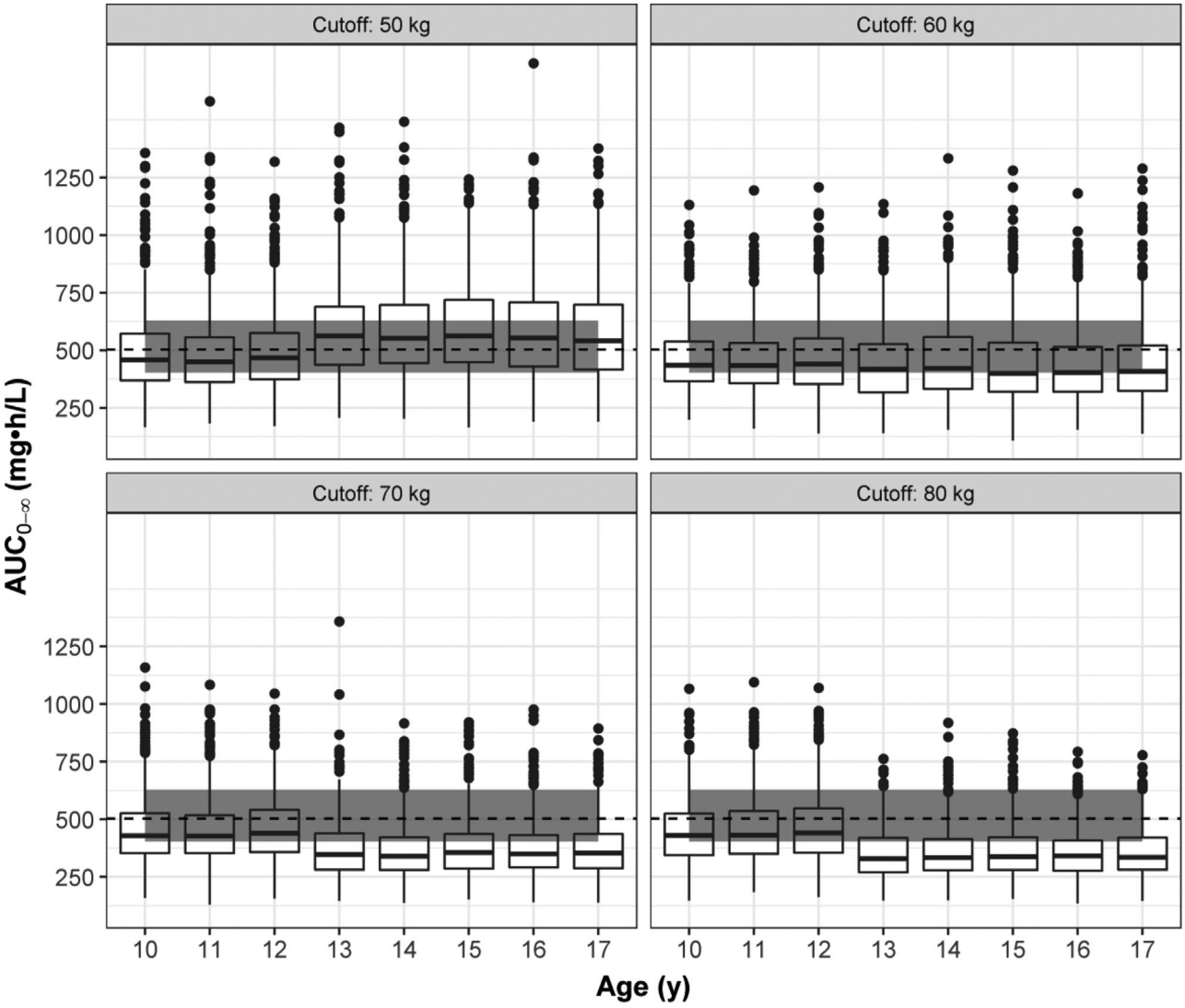

Figure 4. Box-and-whisker plots of simulated $AUC_{0-\infty}$ by age in virtual pediatric populations aged 10 to 17 years, stratified by minimal weight cutoff for the administration of a 2-g cefazolin dose. Dashed horizontal line is geometric mean for adults; band represents 80% to 125% of geometric mean. Line in middle of the box is the median; upper and lower limits of the box represent the 75th and 25th percentiles, respectively. $AUC_{0-\infty}$, estimated area under the curve from time zero to infinity; h, hour; kg, kilogram; L, liter; mg, milligram; y, years.

five 10- to 12-year-old patients enrolled in study 1601 consistently experienced lower cefazolin concentrations than those observed in similarly aged patients from study 1202. No other differences were apparent in the 2 study populations that might explain the differences between the 2 studies. Lacking a physiologic explanation, the differences in PK between patients enrolled in study 1202 and patients enrolled in study 1601 are most likely a manifestation of the increased variability in cefazolin PK in these pediatric patients, with the small sample sizes in the 2 studies providing a false signal for systematic differences between study populations. Ultimately, the final population PK model indicates that the PK of cefazolin in surgical patients aged 10 to 17 years, although somewhat variable, is consistent with that in healthy adults once the differences in body size are accounted for using allometric scaling.

The removal of the relationship between renal function and cefazolin CL was somewhat unexpected given that cefazolin is predominantly cleared via the kidneys.[20] However, the lack of a statistically significant relationship is likely a consequence of the respective study populations being composed of individuals with approximately normal renal function. Importantly, the dosing recommendations derived from these analyses would not be appropriate for pediatric patients with renal impairment.

In contrast to prior conclusions,[5] the refined population PK model suggests a 50-kg minimum weight cutoff for selecting the fixed dose of cefazolin in this

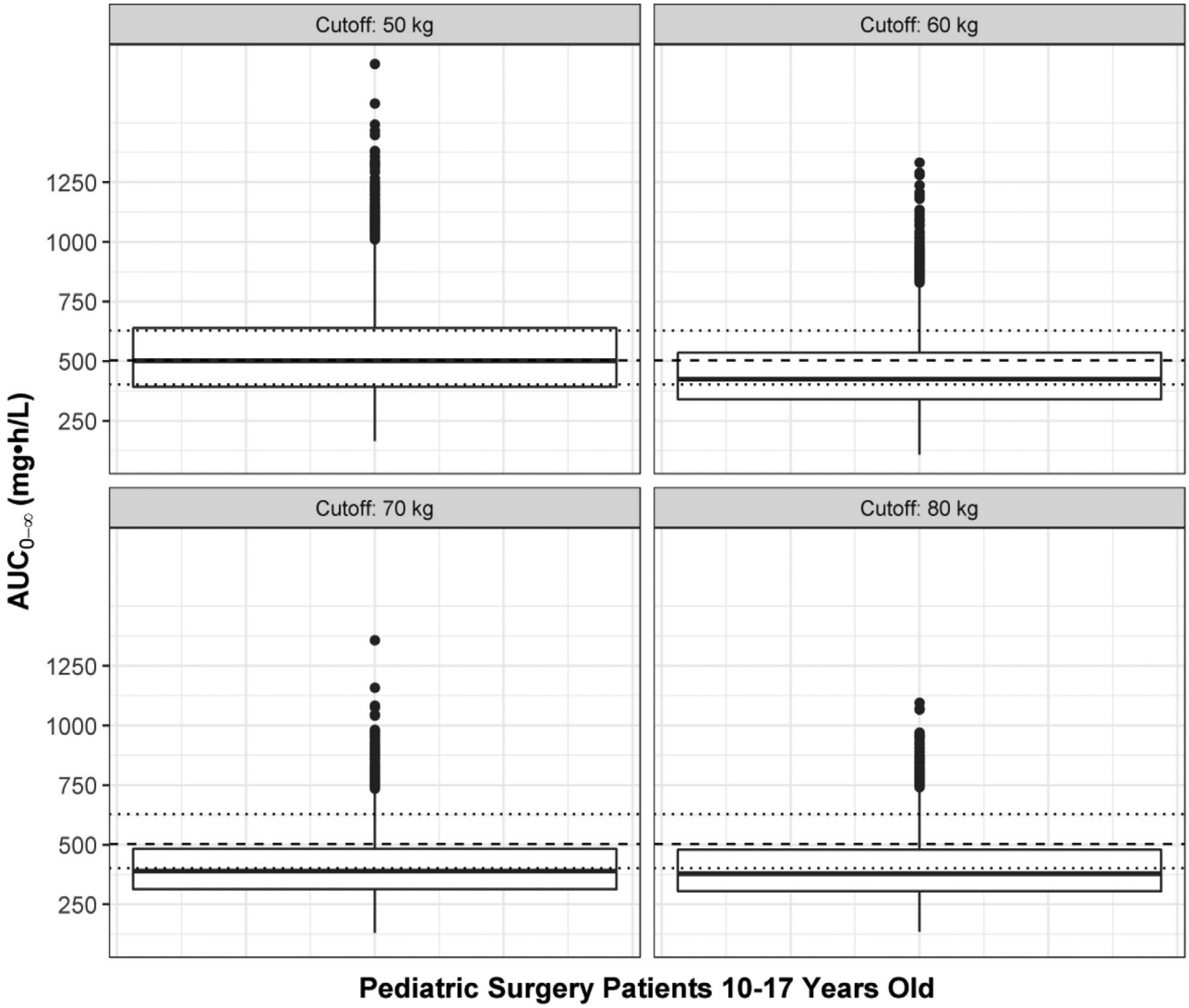

Figure 5. Box-and-whisker plots of simulated $AUC_{0\text{-}\infty}$ in a singular virtual pediatric population aged 10 to 17 years, stratified by minimal weight cutoff for the administration of a 2-g cefazolin dose. Dashed horizontal line is geometric mean for adults; dotted top and bottom lines represents 80% to 125% of geometric mean. Line in middle of the box is the median, upper and lower limits of the box represent the 75th and 25th percentiles, respectively. $AUC_{0\text{-}\infty}$, estimated area under the curve from time zero to infinity; h, hour; kg, kilogram; L, liter; mg, milligram.

population as opposed to the previously identified cutoff of 60 kg. Patients aged 10 to 17 years with body weight of at least 50 kg should receive a 2-g dose of cefazolin, and those below 50 kg should receive a 1-g dose of cefazolin. With the removal of the proportional shift in CL and acknowledgement of the consistency in PK described above, Monte Carlo simulations showed that the 60-kg cutoff would result in consistently lower cefazolin $AUC_{0\text{-}\infty}$ in pediatric surgery patients aged 10 to 17 years compared with that of healthy adults. Using a cutoff of 50 kg, better alignment with adult exposures was realized, with patients aged 10 to 12 years producing slightly lower $AUC_{0\text{-}\infty}$ values and patients aged 13 to 17 years producing slightly higher $AUC_{0\text{-}\infty}$ values. When considered as a homogeneous population, however, use of a 50-kg minimum weight cutoff in pediatric surgery patients aged 10 to 17 years produced virtually identical measures of $AUC_{0\text{-}\infty}$ central tendency and variability compared with healthy adults, whereas use of a 60-kg minimum cutoff resulted in 45.2% of pediatric exposures falling below 80% of the healthy adult geometric mean.

Despite the robustness of the population PK model and increased confidence in the optimal weight cutoff for fixed dosing of cefazolin, there are some limitations. First, it is important to note that the pediatric studies only included generally healthy patients undergoing general surgical procedures planned to last less than 3 hours. Thus, although the expectation would be that redosing with the same cefazolin dose as was given

prior to surgery is appropriate, the current data were limited to single-dose administration prior to surgery and therefore did not inform the impact of additional doses after the start of surgery. Second, the patients in this study did not undergo cardiopulmonary bypass. Given the potential for such patients to exhibit altered cefazolin PK,[7] the use of a fixed dose of cefazolin in patients undergoing cardiopulmonary bypass would require further study.

Conclusions

The previously developed cefazolin population PK model was revised using pooled data from healthy adults and pediatric surgery patients aged 10 to 17 years, suggesting allometric scaling is adequate to describe cefazolin disposition across the age range studied. Monte Carlo simulations indicate that a minimal weight cutoff of 50 kg for the administration of a 2-g cefazolin dose will provide drug exposures in pediatric surgery patients aged 10 to 17 years approximately equivalent to those observed in healthy adults.

Conflicts of Interest

Diana Valencia Martinez, Diane Licursi, Angela Karpf, and Wes Cetnarowski are employees of B. Braun Medical Inc. Michael Schmitz was a principal investigator for Studies HC-G-H-0906 and HC-G-H-1601, and his institution was paid by B. Braun for that participation. At the time this study was conducted, Christopher Rubino and Nikolas Onufrak were employees of Institute for Clinical Pharmacodynamics, Inc. which received consulting fees from B. Braun Medical Inc.

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Data Availability Statement

Qualified researchers may request access to patient-level data and related analysis information (eg, model/simulation code). Patient-level data will be anonymized and analysis information will be redacted to protect the privacy of trial participants and any proprietary methods. Requests should be made to the corresponding author and will require the approval of the sponsor, B. Braun Medical, Inc.

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