Therapeutic Drug Monitoring

Impact of Disease on Amikacin Pharmacokinetics and Dosing in Children

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Abstract:	<p>Background: Amikacin is widely used to treat severe Gram-negative bacterial infections. Its peak concentration in plasma is associated with treatment efficacy. Amikacin pharmacokinetics (PK) is influenced by disease conditions, in addition to other patient characteristics. In this retrospective study, we evaluated the impact of clinical characteristics and disease condition on amikacin PK in children with burn injuries and those with cancer.</p> <p>Methods: Amikacin PK data from 66 children with burn injuries and 112 children with cancer were analyzed. A population PK model was developed using the non-linear mixed effects modeling approach. Models were developed using NONMEM 7.3. Data processing and visualization was performed using R packages.</p> <p>Results: The amikacin PK data was best described by a 2-comp model. The parameters were estimated with mean (95% confidence intervals) as follows: central volume of distribution (V1), 5.70 L (4.64 – 6.76 L); central clearance (CL), 2.12 L/h (1.79 – 2.46 L); peripheral volume of distribution (V2), 4.79 L (2.36 – 7.22 L); distribution clearance (Q), 0.71 L/h (0.25 – 1.16 L/h). The final model identified the disease condition as a significant covariate, and indicated 55% (28% - 82%) higher CL and 17% (1% - 34%) higher V1 in burn patients compared with cancer patients.</p>

	<p>Volume of distribution was significantly influenced by age and body weight. Clearance was significantly influenced by age, body weight and creatinine clearance. Using the final PK model, we developed a workflow for selecting optimal dosing strategies for three representative pediatric patient profiles.</p> <p>Conclusion: Disease condition was significant in influencing amikacin PK in children. To reach the same target concentrations (64 mg/L peak concentration) with a daily dose plan, burn patients need higher doses than cancer patients. Future investigations are needed to explore the impact of other diseases on amikacin disposition in children, and to prospectively validate the proposed dosing strategy.</p>
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Reviewer #2: Minor Comment:

Suggest removing the following statement from the results section: "Concentrations below LLOQ were replaced by the value of LLOQ/2 (0.4 mg/L)." [pg 7]

Rationale: duplicate information provided in methods section

Response: *Thank you for noticing this. The sentence has been removed.*

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Abstract

Background: Amikacin is widely used to treat severe Gram-negative bacterial infections. Its peak concentration in plasma is associated with treatment efficacy. Amikacin pharmacokinetics (PK) is influenced by disease conditions, in addition to other patient characteristics. In this retrospective study, we evaluated the impact of clinical characteristics and disease condition on amikacin PK in children with burn injuries and those with cancer.

Methods: Amikacin PK data from 66 children with burn injuries and 112 children with cancer were analyzed. A population PK model was developed using the non-linear mixed effects modeling approach. Models were developed using NONMEM 7.3. Data processing and visualization was performed using R packages.

Results: The amikacin PK data was best described by a 2-comp model. The parameters were estimated with mean (95% confidence intervals) as follows: central volume of distribution (V1), 5.70 L (4.64 – 6.76 L); central clearance (CL), 2.12 L/h (1.79 – 2.46 L); peripheral volume of distribution (V2), 4.79 L (2.36 – 7.22 L); distribution clearance (Q), 0.71 L/h (0.25 – 1.16 L/h). The final model identified the disease condition as a significant covariate, and indicated 55% (28% - 82%) higher CL and 17% (1% - 34%) higher V1 in burn patients compared with cancer patients. Volume of distribution was significantly influenced by age and body weight. Clearance was significantly influenced by age, body weight and creatinine clearance. Using the final PK model, we developed a workflow for selecting optimal dosing strategies for three representative pediatric patient profiles.

Conclusion: Disease condition was significant in influencing amikacin PK in children. To reach the same target concentrations (64 mg/L peak concentration) with a daily dose plan, burn patients need higher doses than cancer patients. Future investigations are needed to explore the impact of other diseases on amikacin disposition in children, and to prospectively validate the proposed dosing strategy.

Keywords:

Amikacin, burn injury, cancer, pediatrics, population pharmacokinetics.

INTRODUCTION

Seventy years after its discovery, amikacin is still one of the most frequently used aminoglycosides in intensive care units (ICUs) to treat severe Gram-negative bacterial infections in children and adults.^{1,2} As a hydrophilic compound, amikacin is well distributed throughout the body after intravenous administration, and eliminated through glomerular filtration.³ The efficacy of amikacin generally exhibits a concentration-dependent pattern.^{4,5} The plasma peak concentration over minimal inhibitory concentration ratio ($C_{\max}/\text{MIC}$) is correlated to efficacy, while the trough concentration ($C_{\min}$) is associated with renal and tubular toxicity.^{4,6} Available amikacin dosing regimens for children are highly variable.⁷ Physiological factors (such as body weight, age and kidney function) influence amikacin distribution and/or clearance, and result in large inter- and intra-individual PK variability. Even after considering these physiological covariates, there is still significant variability in amikacin disposition.⁸⁻¹⁰

Disease conditions may also be relevant to amikacin PK, especially in children with high-risk conditions (e.g. burn injuries, febrile neutropenia and malignancies). These need to be considered when designing dosing strategies.^{8,11-14} Increased amikacin volume of distribution and clearance have been documented in children with burn injuries^{13,14}, probably related to fluid infusions and increased kidney blood flow.^{15,16} Higher amikacin doses may be required to achieve the target peak concentrations reaching at least a $C_{\max}/\text{MIC}$ ratio of 8-10 for a specific pathogen.^{13,14} Therefore, when the MIC is 8 mg/L, a plasma peak concentration of 64 mg/L should be aimed to achieve sufficient efficacy. Elevated aminoglycoside distribution and clearance have been noted in adults with solid and hematologic malignancies.¹⁷⁻¹⁹ In adults with febrile neutropenia due to hematological malignancies, higher amikacin doses also were suggested for patients with myeloblastic leukemia and hypoalbuminemia.^{20,21} In children with malignancies, however, the PK data of amikacin are limited.²²⁻²⁴

The aim of this pooled analysis was to study the impact of disease conditions on the amikacin PK through a population modeling approach in children. We aimed to explore the influence of disease conditions (burn

vs. cancer), among other maturational covariates, on amikacin disposition in children. In addition, we aimed to provide amikacin dosing guidance for these specific populations.

METHODS

Study populations

Two cohorts of pediatric patients were included in the study. Cohort 1 contained data from a previously published study on children with burn injuries.¹⁴ These patients were admitted to the Shriners Hospitals for Children, Ohio, and received amikacin for the treatment of (suspected) Gram-negative burn wound sepsis based on clinical criteria. Cohort 2 included patients admitted to the pediatric oncology department of the University Hospitals Leuven, Belgium, between January 2010 and June 2013 with oncology diagnoses. These patients received amikacin as part of their first course of empirical treatment for febrile neutropenia. Both studies were approved by the university ethical boards of the contributing centers.

Routine amikacin therapeutic drug monitoring (TDM) data and patient characteristics were retrospectively collected from patient medical records. Clinical characteristics included age (years), weight (kg), height (cm), sex, and diagnosis (burn vs. cancer). Laboratory results included serum creatinine (mg/dL) and serum albumin (g/L). For the children with cancer, the first trough (measured prior to the second dose) and first peak amikacin levels (1 hour after the second dose) were available for analysis. For the children with burn injuries, blood amikacin levels were sampled around 1, 6, 8, 12 and 24 hours since infusion. In both cohorts, amikacin was infused intravenously over 30 minutes, with 10-20 mg/kg/day dosage (divided in 2-4 doses) in children with burn injuries and 20 mg/kg dosage once daily in children with oncologic diagnosis.

Analytical methods

Amikacin concentrations were measured with fluorescence polarization immunoassay (Abbott TDx, Abbott Park, IL, USA) for children with burn injuries. The assay was linear from 0.8 to 50.0 mg/L with intra-day and inter-day variability less than 7.6%.¹³ The same analytical method was used for children with oncology

diagnosis until 31 May 2012, after which a kinetic interaction of microparticles in solution (KIMS) immunoassay (Roche/Hitachi Cobas c systems, Roche Diagnostics GmbH, Mannheim, Germany) was used for amikacin quantification with a coefficient of variation less than 5%. For both assays, the lower limit of quantification (LLOQ) was 0.8 mg/L. Concentrations below LLOQ were replaced by the value of LLOQ/2 (0.4 mg/L).²⁵

Pharmacokinetic analysis

The pharmacokinetic data of amikacin were analyzed using the non-linear mixed effects modeling approach. Population models were developed using NONMEM 7.3 (ICON plc). Pharmacokinetic parameters were estimated using first-order conditional estimation method with eta-epsilon interaction (FOCEI). Perl-speaks-NONMEM (PsN) 4.4.0 and Pirana 2.9.6a were used to facilitate the model building and conduct bootstrap and visual predictive check (VPC) analyses. R packages (3.4.3) were used to construct customized codes for plotting results.

Data from burn and cancer patients were initially modeled separately to explore potential differences in PK parameters. The data were subsequently pooled to fit in a single unified base model. Both one- and two-compartment model structures were examined and the two-compartment structure was selected for optimal model fitting. The model was parameterized with clearance (CL), distribution clearance (Q), central volume of distribution (V1) and peripheral volume of distribution (V2). Between-subject variability (BSV) was investigated for all PK parameters assuming an exponential error model structure:

$$\theta_i = \theta_{pop} \times e^{\eta_i}$$

In this equation, θ_i is the individual parameter for the i th subject. θ_{pop} is the population mean of this parameter. η_i is the individual deviation from the population mean in the i th subject. Normal distribution of η was assumed with mean of zero and variance of ω^2 .

Residual variability was separately assessed in an additive, proportional and additive/proportional combined error model structure. The combined error model structure was constructed as below:

$$C_{ij} = Y_{ij} \times (1 + \varepsilon_1) + \varepsilon_2$$

In this equation, C_{ij} is the measured amikacin concentration for the i th subject at time j ; Y_{ij} is the model predicted concentration; ε_1 is the proportional residual error; ε_2 is the additive residual error. Normal distribution of ε_1 and ε_2 was assumed with mean of zero and variance of σ_1^2 and σ_2^2 , respectively.

Patient characteristics including disease condition (burn vs. cancer), age, body weight, sex, height, and creatinine clearance (calculated using the Schwartz equation²⁶) were evaluated as potential covariates for PK parameters. Stepwise covariate screening with forward addition (χ^2 , $p < 0.05$) and backward elimination (χ^2 , $p < 0.01$) was performed to select covariates that significantly improve the model fitting. Selected covariates were included in the final model. A power relationship was assumed for continuous covariates (age, body weight, height, creatinine clearance), and linear relationship was assumed for categorical covariates (disease condition and sex). The construction of an individual parameter is as below:

$$\theta_i = \theta_{pop}^* \times \left(\frac{Cov}{Median} \right)^{\beta_{co}} \times (1 + \beta_{ca}) \times e^{\eta_i}$$

In this equation, θ_i is the individual parameter for the i th subject. θ_{pop}^* is the covariate-adjusted population mean of this parameter. η_i is the individual deviation from the population mean in the i th subject. Cov is the continuous covariate value of the i th subject; $Median$ is the median value of the continuous covariate in the dataset. β_{co} is the estimated exponential term for the corresponding continuous covariate. β_{ca} is the estimated value assigned to the alternative level of a categorical covariate (e.g. burn compared with cancer). The final covariate model was used to describe the observed amikacin concentrations in the studied patients.

Optimal dose simulation

Based on the final PK model, steady-state peak (ssC_{max}) and trough (ssC_{min}) amikacin concentrations were simulated for three representative patient profiles (1, 5 and 14 years old, Table 3). Constant rate IV infusions over 30 min with different doses (10 mg/kg/day to 100 mg/kg/day) were used with an interval of 24 hours. The Monte Carlo approach (n=5000) was applied in the simulations. The dosing targets were to reach a ssC_{max} of 64 mg/L or higher, using an EUCAST MIC clinical breakpoint of 8 mg/L, and to maintain a ssC_{min} of 2 mg/L or lower.^{2,27} For each dose amount, the percentage of patients that reached those targets were calculated.

RESULTS

Descriptive statistics / Study population

Data of 73 children with burn injuries and 118 children with oncologic diagnosis were available for analysis. Data with missing covariate records, missing sampling/dosing time records, or incorrect units were excluded from analysis. 66 and 112 patients, respectively, were included in final analysis. Table 1 summarizes the clinical characteristics of both cohorts. 412 plasma amikacin concentration records (189 from burn patients, 223 from cancer patients) were included in the final analysis. 16.7% of them were LLOQ data.

Population pharmacokinetic models

Amikacin pharmacokinetic data from burn and cancer patients were first separately explored for the best model structures for data description. For both patient cohorts, a two-compartment model with first-order elimination best described the amikacin pharmacokinetics (data not shown). The data were subsequently pooled to develop a unified base model. Both one- and two- compartmental structures were explored. The two-compartment model with proportional residual error was found to describe the data the best (Table 2). Stepwise covariate search demonstrated significant improvement of model fitting by incorporating disease

condition, weight, age and creatinine clearance. Therefore, these covariates were included in the final model (Table 2).

Model evaluation

Both base and final models were evaluated using diagnostics including observed concentrations vs. population predicted values, observed concentrations vs. individual predicted values, conditional weighted residuals vs. time after first dose, and conditional weighted residuals vs. population predicted values (Figure 1 and 2). Significant improvement of model fitting was observed after including selected covariates.

For the final model, a bootstrap analysis with 1000 replications was conducted and finished with 99.3% success rate. The bootstrap returned the mean and 95% confidence intervals of parameter estimates in close agreement with values derived from the final model (Table 2). A visual predictive check (VPC) analysis was performed (n=500) and the simulation result is overlaid with observed amikacin concentrations (Figure 3). More specifically, the prediction-corrected version of VPC was applied to control misrepresentation of data trend caused by variability in dose and/or influential covariates.²⁸ 94.4% of observed data fell in the 95% predictive interval, demonstrating the model stability and sufficiency to describe the observed amikacin concentrations.

Amikacin dosing optimization

The results of the dosing simulations were plotted (Figure 4). For each patient profile, the percentage of patients (y-axis) that reaches the target concentrations can be read from the plots corresponding to each dose (x-axis). The reference lines for 70% of patients reaching targets were plotted as illustration. For example, consider dosing cancer patients with profile 2 (a child of 5 years old, 18 kg weight and with creatinine clearance of 170 mL/min/1.73m²). A daily dose of 33 mg/kg is expected to reach at least 64 mg/L plasma peak concentration in 70% of patients, while about 75% patients are expected to have trough concentrations lower than 2 mg/L. For burn patients with the same profile, a daily dose of 44 mg/kg is

expected to reach the same peak target in 70% of patients, while more than 90% patients are expected to have trough concentrations lower than 2 mg/L.

DISCUSSION

In this study, we explored the impact of disease condition on the amikacin pharmacokinetics between children with burn injuries and those with cancer. A population 2-compartmental model was developed to describe the amikacin PK in both subpopulations simultaneously. Burn patients had 55% (95% CI: 28% - 82%) higher CL and 17% (95% CI: 1% - 34%) higher V1 than patients with cancer. Using this model, we proposed an optimal dosing strategy to reach target amikacin concentrations based on specific patient characteristics and disease conditions.

In our final PK model, several physiological parameters were included as covariates (Table 2). This is in line with historical efforts in characterizing amikacin PK using the population modeling approach.^{8-14,29,30} A recent review summarizes the modeling attempts of amikacin in critically ill adult patients.³¹ Both 1-compartmental and 2-compartmental models have been reported as the optimal structure describing the amikacin data. Studied populations included healthy adults, and patients with pneumonia, sepsis, trauma, and liver cirrhosis. Besides specific disease status or diagnosis, creatinine clearance and total body weight have consistently appeared in the final covariate lists. Although these findings in adults should not readily be assumed the same in children, they do indicate the general PK behavior of this drug in correspondence to its physiochemical properties. In children, the amikacin PK is less studied. There have been limited attempts in modeling amikacin PK in children, especially exploring the impact of disease condition. A report by Lanao *et al.* indicated the amikacin PK was best described by a two-compartment model with clearance in linear correlation with creatinine clearance in children with either normal or impaired renal function.³² However, the ‘micro’ parameterization was applied in this study. A rough conversion to ‘macro’ parameterization returned the average PK parameter values of a 20kg child as follow: 3.7 L/h of CL, 2.3 L of V1, 2.2 L/h of Q, and 1.8L of V2. In a recent report by Alhadab *et al.*, a two-compartment model was

also used to describe the amikacin PK in children with cancer.³³ Allometric scaling was *a priori* applied (not tested) and no other covariates were identified. According to the modeling results of this publication, the average PK parameter values of a 20 kg child are: 4.3 L/h of CL, 8.6 L of V1, 1.7 L/h of Q, and 4.3 L of V2. While the numbers are not exactly the same as our results, they are very close to our PK parameter estimates of children with cancer. In addition, previous studies and ours presented a relatively small distribution clearance value (Q), indicating a slow distribution from central to peripheral tissues. Treluyer *et al.* applied a one-compartment model and reported that in children with suspected infections, the inclusion of postnatal age and body weight reduced the variability in amikacin volume of distribution, while the inclusion of plasma creatinine levels reduced the variability of clearance.³⁴ According to this report, the CL of a typical 20kg child is 2.46 L/h and the V is 6.74 L. This is very close to the central clearance and volume estimates of cancer patients from our study. Due to difference in sample size, patient population, parameterization, covariate inclusion and choice of model structures, all studies so far deviated moderately between each other in specific PK parameter estimates. However, PK parameter estimates from our model are consistent with literature values in general.

In this study, we presented an innovative model that identified the impact of disease condition on amikacin PK. Examining disease condition as a categorical parameter allowed the PK comparison with statistical confidence. We demonstrated that if other covariates remain the same, children with burn injuries exhibited 17% higher central volume and 55% higher clearance compared with children with cancer. Both burn injuries and malignancy have been associated with increased volume and clearance of amikacin in adults and children.^{20,35,36} These observations might be related to fluid boluses, increased cardiac output and renal perfusion as documented in adult burn cases.^{15,16,37,38} To the best of our knowledge, we hereby provide the first report that in children, burn injury has more exaggerated effects in increasing amikacin volume of distribution and clearance compared with oncologic conditions. In clinical practice, this means that the amikacin dose administered needs to be higher (mg/kg) for children with burns compared to those with cancer, to achieve optimal efficacy.

We provided a dosing proposal according to specific patient characteristics and disease conditions, using simulations of three representative patient profiles. First, in line with our conclusions based on the PK analysis, the simulations indicated that burn patients require higher doses compared with cancer patients, to reach the same target peak concentration. This was consistently observed throughout all examined age groups and dosing intervals. Second, for a given patient profile, an optimal dose range can be identified that balances the chances of reaching target peak concentrations and maintaining relatively low trough concentrations. For example, for cancer patients with profile 3 (Figure 5), a dose range of 25 - 30 mg/kg/day is expected to reach beyond 64 mg/L peak concentration and maintain below 2 mg/L trough concentrations in at least 70% of patients. A dose lower than 25 mg/kg/day would reduce percentage of patients reaching target peak concentrations. A dose higher than 30 mg/kg/day would increase percentage of patients exceeding target trough concentrations. This range can be defined by locating the intercept of green horizontal lines with the solid peak curve and dashed trough curves (Figure 5A). The range will change if the percentage of patients reaching peak and/or trough targets is set differently (Figure 5A). It is worth noting that it may not be feasible to reach certain patient percentage targets for both peak and trough concentrations. For example in Figure 5A for cancer patients, no range can be defined if aiming to achieve both target peak and trough concentrations in more than 80% of the patients. The range will shrink as the percentage target (green line) moves up, and reduce to zero if target goes beyond where solid and dashed black lines intercept. Finally, the optimal dose range will change with different target concentrations. For example, *Pseudomonas aeruginosa* infections are commonly associated with high MIC values (4 – 16 mg/L).

³⁹ If a high peak target of 64 mg/L in combination with a low trough threshold (2 mg/L) is desired, it may be hard to attain this target in a very high percentage of patients (e.g. more than 70%). Practically, the treatment may be effective enough with a lower peak concentration (pathogen and MIC dependent) and well tolerated with a slightly higher trough concentration.² As illustrated in Figure 5B, with a new target trough concentration of 5 mg/L or lower, it is possible to find a dose range that will reach both targets in at least 90% of both patient groups. This can be practically useful when different microbial species infection is being treated or a higher tolerance level is expected.

It is of note that the specific C_{max}/MIC ratios adapted under clinical settings may refer to unbound amikacin concentrations. In our current study, the unbound ratio of amikacin was not quantified. Therefore, all the PK parameter estimates refer to the total drug properties. When applied in actual clinical settings, one may convert the target unbound C_{max} and C_{min} to total concentrations accordingly, before applying the dose optimization using on the current model. Nonetheless, since amikacin exhibit low plasma protein binding (<5%)⁴⁰, findings from this study are still informative for guiding amikacin dosing in clinic.

Although our study is based on large patient cohorts, there are some limitations. First, in the children with cancer, the available amikacin TDM data were limited to early amikacin exposure. This relates to the retrospective data collection. Second, among all age groups in children, neonates are relatively more often studied for amikacin PK.^{41 42-45} However, our data didn't include those from neonates since both burns as well as oncological diagnoses are very rare in this age group.

In conclusion, we have shown that disease condition exhibits significant impact on amikacin pharmacokinetics in children. Patients with burn injuries had higher amikacin clearance (55%) and volume of distribution (17%) compared to those with cancer. Based on these findings, an optimal dosing regimen was proposed to adjust dosing to patient characteristics as well as disease condition. Future investigations are needed to evaluate the impact of other diseases on amikacin PK in children and to prospectively validate the proposed dosing in a clinical setting.

Conclusion

The present study suggests several factors that influence amikacin PK in children. Volume of distribution was significantly influenced by age and body weight. Clearance was significantly influenced by age, body weight and creatinine clearance. Using a population PK model, we developed a workflow for selecting optimal dosing strategies for three representative pediatric patient profiles. To reach the same target concentrations (64 mg/L peak concentration) with a daily dose plan, burn patients need higher doses than

cancer patients. Future investigations are needed to explore the impact of other diseases on amikacin disposition in children, and to prospectively validate the proposed dosing strategy.

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FIGURE LEGENDS

Figure 1. Base model diagnostics. Diagnostic plots of the base model (burn and cancer patients) are presented. A) Observations vs. population predictions. B) observations vs. individual predictions. C) conditional weighted residuals vs. population predictions. D) conditional weighted residuals vs. time. Red line: loess regression line.

Figure 2. Final model diagnostics. Diagnostic plots of the unified final covariate model (burn and cancer patients) are presented. A) Observations vs. population predictions. B) observations vs. individual predictions. C) conditional weighted residuals vs. population predictions. D) conditional weighted residuals vs. time. Red line: loess regression line.

Figure 3. Visual predictive check plots for final covariate model. Amikacin plasma concentrations (mg/L) vs. time after last dose (hour) is plotted with semi-logarithmic scale. Circles, observations. Dashed lines: 2.5th and 97.5th quantiles of observations. Solid lines: 50th quantile of observations. Blue shaded areas: 2.5th and 97.5th quantiles of simulation. Orange shaded areas: 50th quantiles of simulation. Upper and lower bounds of shaded areas indicate 95% confidence interval of corresponding simulation quantiles.

Figure 4. Dosing optimization plots. Percentage of patients reaching target steady-state peak (higher than 64 mg/L) and trough (lower than 2 mg/L) concentrations vs. corresponding amikacin dose (mg/kg/day) based on simulation results. A) Patient profile 1. B) Patient profile 2. C) Patient profile 3. Black: patients with cancer. Red: patients with burn injuries. Horizontal line: exemplified 70% threshold.

Figure 5. Examples to define optimal dose ranges. A) Target steady-state peak (higher than 64 mg/L) and trough (lower than 2 mg/L) concentrations. B) Target steady-state peak (higher than 64 mg/L) and trough (lower than 5 mg/L) concentrations. Black: patients with cancer. Red: patients with burn injuries. Green horizontal lines: exemplified threshold with certain percentage patients reaching targets. Blue horizontal lines: optimal dose range that both peak and trough targets are reached.

Figure 1

Figure 2

Figure 3

Amikacin plasma concentrations vs. TAD

Figure 4 A

Figure 4 B

Figure 4 C

Figure 5A

Figure 5B

Table 1. Clinical characteristics. Sex distribution is presented as male numbers (percentage). Other demographics are presented as median (5th – 95th percentiles). CrCL, creatinine clearance.

Characteristics	Burn (N=66)	Cancer (N=112)	Pooled (N=178)
Age (years)	5.0 (1.0 – 15.0)	6.3 (0.9 – 17.3)	6.2 (0.9 – 16.3)
Sex (Male)	43 (65.2%)	63 (56.3%)	106 (59.6%)
Weight (kg)	20.5 (10.1 – 79.0)	20.6 (8.8 – 62.2)	20.6 (9.5 – 64.7)
Height (cm)	114.6 (75.7 – 177.0)	117.8 (71.6– 175.0)	116.6 (72.0 – 177.0)
Serum Creatinine (mg/dL)	0.4 (0.2 – 1.2)	0.33 (0.16 - 0.71)	0.35 (0.17 - 0.85)
CrCL (mL/min/1.73m ²)	164.8 (55.9 – 312.1)	194.2 (127.5 – 336.7)	188.2 (98.2 – 328.9)

Table 2. PK parameter estimates. CL, clearance. V1, central volume of distribution. Q, distribution clearance. V2, peripheral volume of distribution. The covariate and PK parameter relationship is indicated as parameter-covariate. BSV, between-subject variability. ω^2 , variance of corresponding BSV. σ^2 , variance of residual variability. RSE%, percentage relative standard error. CI, confidence interval. Onc: oncology diagnosis. Burn: burn injury diagnosis.

Parameters	Base	Final		Bootstrap	
	Value (RSE%)	Value	95% CI	Mean	95% CI
CL (L/h)	2.73 (6.4%)	2.12	1.79 – 2.46	2.10	1.76 – 2.48
V1 (L)	1.66 (14.6%)	5.70	4.64 – 6.76	5.71	4.47 – 6.73
Q (L/h)	1.29 (10.0%)	0.71	0.25 – 1.16	0.72	0.27 – 1.11
V2 (L)	8.53 (10.5%)	4.79	2.36 – 7.22	4.97	3.09 – 8.84
CL – CRCL	–	0.21	0.04 – 0.37	0.21	0.06 – 0.39
CL – WT	–	0.70	0.62 – 0.79	0.69	0.60 – 0.77
V1 – WT	–	0.87	0.76 – 0.99	0.88	0.75 – 1.01
V2 – AGE	–	0.26	0.08 – 0.44	0.27	0.10 – 0.65
CL – TYPE:	Cancer	0	–	0	–
	Burn	0.55	0.28 – 0.82	0.58	0.29 – 0.87
V1 – TYPE:	Cancer	0	–	0	–
	Burn	0.17	0.01 - 0.34	0.18	0.01 - 0.40
BSV	Value (RSE%)	Value	RSE%	Mean	RSE%
ω^2_{CL}	0.18 (14.9%)	0.06	20.0%	0.06	18.5%
ω^2_{V1}	–	0.04	41.5%	0.04	44.5%
ω^2_Q	0.08 (54.3%)	–	–	–	–
Residual error	Value (RSE%)	Value	RSE%	Mean	RSE%
σ^2 (proportional)	0.10 (12.2%)	0.06	15.8%	0.06	15.8%

Table 3. Simulation patient profiles. CrCL, creatinine clearance.

Profile	Age (year)	Weight (kg)	CrCL (mL/min/1.73m ²)	Dosing Frequency
1	1	10	170	q.d.
2	5	18	170	q.d.
3	14	50	170	q.d.

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