Population Pharmacokinetic Analysis of Topotecan in Pediatric Cancer Patients

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Abstract

Purpose: To characterize the population pharmacokinetics of topotecan lactone in children with cancer and identify covariates related to topotecan disposition.

Patients and Methods: The study population consisted of 162 children in seven clinical trials receiving single agent topotecan as a 30-min infusion. A population approach via nonlinear mixed effects modeling was used to conduct the analysis.

Results: A two-compartment model was fit to topotecan lactone plasma concentrations (n = 1874), and large pharmacokinetic variability was observed among studies, among individuals, and within individuals. We conducted a covariate analysis using demographics, biochemical data, trial effects, and concomitant drugs. The most significant covariate was body surface area, which explained 54% of the interindividual variability for topotecan systemic clearance. Interoccasion variability was considerable in both clearance and volume (20% and 22%, respectively), but was less than interindividual variability in both variables. Other covariates related to clearance were concomitant phenytoin, calculated glomerular filtration rate, and age (<0.5 years). Including them in the model reduced the interindividual variability for topotecan clearance by an additional 48% relative to the body surface area–normalized model. The full covariate model explained 76% and 50% of interindividual variability in topotecan clearance and volume, respectively.

Conclusions: We developed a descriptive and robust population pharmacokinetic model which identified patient covariates that account for topotecan disposition in pediatric patients. Additionally, dosing topotecan based on the covariate model led to a more accurate and precise estimation of topotecan systemic exposure compared with a fixed dosing approach, and could be a tool to assist clinicians to individualize topotecan dosing.

Topotecan, a topoisomerase I inhibitor, has shown promising antitumor activity in many pediatric neoplasms including neuroblastoma, medulloblastoma, rhabdomyosarcoma, and acute leukemias (1–6) when administered alone and in combination with cyclophosphamide and platinating agents (7, 8). Given this activity, topotecan has been used clinically in the treatment of many forms of pediatric cancers, although it is not Food and Drug Administration–approved for any pediatric indication. Topotecan is primarily cleared through renal excretion, with urinary recovery ranging from 60% to 70% (4, 9). The remainder of topotecan elimination occurs through nonrenal mechanisms, primarily biliary or hepatic.

In pediatric tumor xenografts, protracted scheduling of low-dose topotecan resulted in greater tumor regression and a higher rate of complete responses than did intermittent higher dose schedules (1). Moreover, antitumor effects were related to topotecan lactone systemic exposure, expressed as the area under the plasma concentration-time curve (AUC; ref. 10). The results from these preclinical studies suggested that the antitumor activity of topotecan follows a steep systemic exposure–antitumor response curve. For example, reduction of the topotecan plasma systemic exposure by as little as 50% led to complete loss of antitumor activity (10). In children, this has potential clinical relevance because of the marked interpatient variability in clearance (4, 9, 11), which translated into variability in topotecan systemic exposure.

Due to the inherent variability in topotecan disposition, pharmacokinetically guided dosing has been used to individualize topotecan dosage. We reported a promising response rate for patients receiving pharmacokinetically guided topotecan in two phase II clinical trials in medulloblastoma (6, 12) and neuroblastoma (6, 12). Although pharmacokinetically guided topotecan helps to achieve efficacious exposures and reduce...
variability in systemic exposure, it also has limitations and it will be important to simplify the current pharmacokinetic dosing approach.

Thus, the objectives of this study were to describe interindividual and intra-individual variability in topotecan pharmacokinetic parameters in a pediatric population, to examine the correlation among topotecan pharmacokinetic parameters and patient covariates, and to establish a model consisting of patient covariates to guide topotecan dosing in children with cancer.

**Patients and Methods**

**Patient population**

The population pharmacokinetic analysis included topotecan lactone plasma concentration-time data from 162 children that participated in four phase I and three phase II topotecan clinical trials. Clinical trial descriptions are provided in Table 1, and patient covariates are listed in Table 2. Eligibility criteria for the clinical trials precluded enrollment of children with liver dysfunction; however, trial no. 7 included children with decreased renal function secondary to nephrectomy as treatment for Wilms tumor. Informed written consent was obtained from the parent/guardian or patient, as appropriate, as approved by the St. Jude Children’s Research Hospital Institutional Review Board.

**Drug administration**

For i.v. administration, topotecan (Hycamtin; GlaxoSmithKline) was reconstituted with sterile water, USP. For two trials (trial nos. 3 and 5) an investigational form of the drug was used. Topotecan was administered via IVAC Controller (IVAC Corp.) over 30 min, either daily for 5 consecutive days (d5) or daily for 5 consecutive days for each of 2 consecutive weeks (d5 x 2) (see Table 1).

### Pharmacokinetic sampling and topotecan analytic assay

Both intensive and limited sampling schemes were used in the clinical trials included in this population analysis (see Table 1 for sampling strategy for each clinical trial). Several clinical trials (both phases I and II) used a pharmacokinetically guided approach to dosing topotecan. A total of 1,862 observed topotecan concentrations were used in the population analysis (see Table 1). At each sample time point, whole blood was collected and processed to analyze topotecan lactone as previously described (9, 13). The lower limit of quantitation of the high-performance liquid chromatography method for topotecan lactone in plasma was 0.25 ng/mL, and for the pharmacokinetic analysis, only those samples with concentrations greater than the lower limit of quantitation were included.

**Nonlinear mixed effects modeling analysis**

Nonlinear mixed effects modeling analysis was done with NONMEM (version V, double precision, level 1.1) using the first-order conditional estimation method with INTERACTION (14). Additionally, nonlinear mixed effects modeling analysis was also done using the Monte Carlo parametric expectation maximization (MC-PEM) algorithm as implemented in S-ADAPT (15). Diagnostic graphs and additional statistical analyses were completed using R-project (version 2.1.1).

The development of the population pharmacokinetic model for topotecan in children occurred as follows:

**Step 1: Development of the base model (covariate-free model).** We used a two-compartment pharmacokinetic model with first-order elimination (ADVAN 3 subroutine in NONMEM) as the base model. We chose the two-compartment model based on our previous experience with topotecan (9, 11) and visual inspection of the current data set. The pharmacokinetic parameters estimated with the model included systemic clearance (CL), volume of the central compartment (V1), and intercompartmental rate constants (k12, k21). The analysis allowed for both covariance between CL and V1 (NONMEM) along with covariance between all four parameters (MC-PEM; the full covariance matrix between all four parameters was not used in NONMEM due to convergence issues). The distribution of the parameters was assumed to be log-normal. Thus, interindividual (IIV) and interoccasion (IOV) variability in parameters were modeled as exponential terms (Eq. A):

\[
\theta_i = \theta_0 + \sum_{j=1}^{n} \eta_{ij}
\]

where \( \theta_i \) represents the estimated pharmacokinetic parameter (CL, V1, k12, k21) for a given individual i, \( \theta_0 \) is the population parameter estimate, \( \eta_{ij} \) describes the variation of individual i from the population estimate (i.e., IV), and when the drug was administered on multiple occasions per individual, \( \sum_{j=1}^{n} \eta_{ij} \) represents the variability of occasion j from individual i average value (IOV). In all cases, \( \eta \) was assumed

<table>
<thead>
<tr>
<th>Trial no.</th>
<th>No. of pharmacokinetic studies/observations</th>
<th>Trial type and indication</th>
<th>Topotecan dosage and schedule</th>
<th>Sampling scheme</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82/395</td>
<td>Phase I recurrent solid tumors</td>
<td>Target AUC = 120-180 ng•h/mL (d x 5) x 2, q24-28 d</td>
<td>Pre-, and at 0.5, 1, 3, and 6 h after EOI</td>
<td>(5)</td>
</tr>
<tr>
<td>2</td>
<td>28/140</td>
<td>Phase I recurrent acute leukemia</td>
<td>Fixed dosage = 2.4 mg/m² (d x 5)</td>
<td>Pre-, and 0.25, 0.5, 1, 3, and 6 h after EOI, and pre-day 2</td>
<td>(13)</td>
</tr>
<tr>
<td>3</td>
<td>52/230</td>
<td>Phase I recurrent solid tumors*</td>
<td>0.8 and 1.1 mg/m²</td>
<td>Pre-, and 0.5, 1, 3, and 24 h after EOI</td>
<td>(6)</td>
</tr>
<tr>
<td>4</td>
<td>49/227</td>
<td>Phase II newly diagnosed medulloblastoma</td>
<td>Target AUC = 120-160 ng•h/mL (d x 5)</td>
<td>Pre, and 0.25, 0.5, 1, 3, and 6 h after EOI</td>
<td>(11)</td>
</tr>
<tr>
<td>5</td>
<td>39/105</td>
<td>Phase I recurrent solid tumors</td>
<td>Target AUC = 120-160 ng•h/mL (d x 5)</td>
<td>Pre-, 0.5, 3, and 23.5 h after EOI</td>
<td>(12)</td>
</tr>
<tr>
<td>6</td>
<td>207/639</td>
<td>Phase II newly diagnosed high-risk neuroblastoma</td>
<td>Target AUC = 80-120 ng•h/mL (d x 5) x 2</td>
<td>Pre-, 0.25, 1, and 6 h after EOI</td>
<td>(26)</td>
</tr>
<tr>
<td>7</td>
<td>42/126</td>
<td>Phase II recurrent Wilms tumor</td>
<td>Target AUC = 70-90 ng•h/mL (d x 5) x 2</td>
<td>Pre-, 5 min, 2, and 3 h after EOI</td>
<td>(26)</td>
</tr>
</tbody>
</table>

Abbreviations: EOI, end of infusion; (d x 5), daily dose for the first 5 d of the cycle; (d x 5) x 2, daily dose for 5 d per week for 2 wk.

In the case of trial no. 2, we only used data obtained after i.v. topotecan administration.

*Oral bioavailability study that consisted of intravenous and oral topotecan doses. Only the pharmacokinetic data from the intravenous doses were used in the population analysis.
Thirteen covariates were considered in theokinetic parameters. GFR was calculated by the following equation (17):

\[ \text{GFR} = \sum_{\text{covariates}, \text{p}} \frac{\text{covariate}_p \times \theta_p}{\text{max}} \]  

An initial screening of the model covariates was done using two methods. First, a univariate analysis of each covariate was done in NONMEM to determine its significance independent of other covariates. A covariate was considered significant in the univariate analysis if the addition of the covariate to the model reduced the objective function value (OFV) at least 3.84 units \((P < 0.05, \text{ based on the } \chi^2 \text{ test for the difference in the -2 log-likelihood between two hierarchical models that differ by 1 degrees of freedom}), \) and \( \theta_p \) was significantly different than zero \([P < 0.05, \text{ i.e., } 1.96 \text{SE (} \theta_p \text{)}] \).

Second, a screening was done on the individual estimates of CL and \( \text{V}_1 \) as determined using the POSTHOC (Bayesian) estimates of these variables generated from NONMEM. Specifically, relationships among the covariates and the pharmacokinetic parameters along with correlations among the covariates were studied. This was done both graphically and by linear mixed-effects modeling. Linear mixed-effects models were used to determine which covariates (and combinations of covariates) were significantly related to CL or \( \text{V}_1 \). At each step, individual covariates were added (forward stepwise) or removed (backward deletion) from the regression model using the Akaike information criterion via the “stepAIC” function in the R package “MASS” (R-project, version 2.1.1).

After the initial screening of covariates, we built the final covariate model using a forward stepwise approach followed by a backwards deletion strategy using nonlinear mixed effects modeling via NONMEM. With the present approach, each covariate was independently removed from the full model to confirm its relevance by the backwards deletion strategy. An increase in the objective function value of >10.9 units \((P < 0.001) \) was required to confirm the significance of the covariate and for inclusion in the final model. The BSA-normalized model with IOV and the final covariate model were also run using the MC-PEM approach for comparison purposes (i.e., to test sensitivity to the numerical method used). This is particularly important with this data set because many of the occasions had sparse sampling.

The robustness of the final model was evaluated by the bootstrap procedure. For this purpose, individual patients were randomly sampled with replacement from the original data set to obtain new data sets that contained the same number of patients as the original sample size. Each new data set was fit to the final covariate model and the population variables were estimated.

### Step 3: Model prediction.
An objective of this study was to establish a model consisting of patient covariates, which could be used to individualize topotecan dosing in children with cancer. This predictive model could be used by clinicians to adjust topotecan dosing in a patient to achieve a desired topotecan systemic exposure (i.e., AUC value). When we did this analysis, we did not include covariates that were not available prospectively (e.g., study effect or investigational drug formulation), even if they were significantly related to topotecan clearance in the population pharmacokinetic model.

We assessed if the predictive model could target a topotecan lactone AUC value of 100 \( \text{ng} \cdot \text{h/mL} \) with better precision and accuracy than using a fixed conventional topotecan dosage. To estimate the model-predicted AUC in each patient, we calculated the dosage necessary to attain an AUC of 100 \( \text{ng} \cdot \text{h/mL} \) using the predicted clearance calculated from the predictive model. Then, using the actual clearance (from the POSTHOC estimate) we determined the model-predicted AUC obtained from this calculated dosage. The estimated AUC from the

### Table 2. Patient demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>( n )</th>
<th>Mean</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>162</td>
<td>9.1</td>
<td>8.0 (0.04-22.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>162</td>
<td>33.9</td>
<td>24.9 (3.7-102.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162</td>
<td>129.0</td>
<td>126.9 (49.0-184.2)</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>162</td>
<td>1.09</td>
<td>0.96 (0.23-2.29)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan investigational formulation</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole*</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>119</td>
<td>0.59</td>
<td>0.50 (0.20-3.70)</td>
</tr>
<tr>
<td>Technetium CL renal (mL/min)</td>
<td>45</td>
<td>69.7</td>
<td>65.0 (10.0-135.0)</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>119</td>
<td>75.0</td>
<td>63.9 (8.1-183.7)</td>
</tr>
</tbody>
</table>

**NOTE:** Units are presented in parentheses. \( n \) = number of patients. *Administered as a combination of sulfamethoxazole and trimethoprim.

normally distributed with a mean of zero and variance of \( \Omega \). The intraindividual variability (residual error) was modeled using a mixed proportional and additive error model (Eq B): \( C_{pa} = \bar{C}_{pa} (1 + \varepsilon_{pa}^a + \varepsilon_{pa}^b) \) (B)

\[ \text{C}_{pa} = \bar{C}_{pa} (1 + \varepsilon_{pa}^a + \varepsilon_{pa}^b) \]  

where \( C_{pa} \) and \( \bar{C}_{pa} \) represent the \text{th} actual and predicted topotecan plasma concentration in individual \( i \), respectively. The error terms \( \varepsilon_{pa}^a \) and \( \varepsilon_{pa}^b \) are the components of the proportional (relative error) and additive error (absolute error), respectively. Both are assumed to have a mean of zero and variance of \( \sigma \).

#### Step 2: Identification of significant covariates related to the pharmacokinetic parameters.
Thirteen covariates were considered in the analysis (Table 2). Both continuous [glomerular filtration rate (GFR), body surface area (BSA), weight (WT), height (HT), technetium-99 m diethyleneetriaminopentacetic acid (TECH), serum creatinine (SCR), and age] and categorical variables [sex, race, investigational drug formulation (INV), study effect, concomitant administration of dexamethasone, sulfamethoxazole/trimethoprim, or phenytoin] were included. For two trials (trial nos. 3 and 5), an investigational formulation of topotecan was used. Because previously published data indicated that this dosage formulation differed from the commercial formulation, we included dosage formulation as a possible covariate in the model (16). GFR was calculated by the following equation (17):

\[ \text{GFR (mL/min)} = k \sqrt{\text{age(months)} + 6} \times \frac{\text{WT}}{\text{SCR}} \]  

where \( k = 1.05 \) for males and 0.95 for females, weight (WT) is in kilograms and serum creatinine (SCR) is expressed milligrams per deciliter. Afterwards, the GFR was normalized to the patient’s BSA.

The relationships between the pharmacokinetic parameters (CL or \( \text{V}_1 \)) and categorical or continuous covariates were described using the following model (18, 19):

\[ \theta = \bar{\theta} + \sum_{p=1}^{m} \text{covariate}_p \times \theta_p \]  

where \( \bar{\theta} \) was the population estimate, \( \hat{\theta} \) was the population estimate with none of the covariates included, and \( \theta_p \) was the effect of covariate \( p \) on the model. When a categorical variable was considered, the presence of a covariate was coded as covariate \( \text{p} = 1 \) and its absence as covariate \( \text{p} = 0 \). In the case of missing data, the above equation had the form (19):

\[ \theta = \bar{\theta} + \left\{ \sum_{p=1}^{m} \text{covariate}_p \times \theta_p \text{ if covariate } p \text{ exists for individual } i \right\} \]  

(Topotecan Population Pharmacokinetics in Children)
conventional 2.7 mg/m² dosage (the BSA-normalized dosage that would be given to yield an AUC of 100 ng·h/mL in a patient with a population average clearance) was determined using the actual clearance of each pharmacokinetic study. The comparison between the predictive model and conventional dosing approaches was done using the median percentage bias calculated as the percentage median value of the ratio of observed to predicted and the precision calculated as the root mean squared prediction error as previously reported by Sheiner and Beal (20).

Results

Patients. Between 1996 and 2003, 162 patients were enrolled in seven clinical trials. The demographic and clinical characteristics of the patient population included in the pharmacokinetic analysis are summarized in Table 2.

Population pharmacokinetic analysis: covariate-free model. Based on visual inspection of the current data set and previous experience with topotecan, we used a two-compartment model with first-order elimination to fit the data. As depicted in Fig. 1, most samples were drawn before 8 h postinfusion with only 4% of the samples collected after 8 h. Because the inflection in the concavity of the data occurs between 6 and 24 h, the interindividual variability could not be estimated by NONMEM for the intercompartmental rate constants ($k_{12}$ and $k_{21}$). Thus, we empirically fixed this variability at 25% (CV%). However, this approximation was not necessary in the analysis using MC-PEM, and $k_{12}$ and $k_{21}$ estimated interindividual variability were 39% and 18%, respectively. This was similar to the empirically fixed value used in the NONMEM analysis.

The population pharmacokinetic parameters obtained for the base model included clearance, volume, $k_{12}$ and $k_{21}$, which were 27.1 L/h, 37.3 L, 0.335 h⁻¹, and 0.587 h⁻¹ respectively. We found substantial variability in the parameter estimates of the base model with an interindividual variability for topotecan CL and $V_1$ of 57% and 43%, respectively. The proportional component of the residual variability was 21%, whereas the additive error was fixed considering the limit of quantitation of the assay (Supplementary Table S1).

Size-based covariates. We considered BSA and weight as possible size-based covariates. BSA was found as a significant determinant of topotecan clearance and volume explaining 54% and 43% of the interindividual variability, respectively ($\Delta$OFV = -56, $P < 0.0001$). Weight was also found to be a significant determinant of topotecan clearance and volume ($\Delta$OFV = -52, $P < 0.0001$). However, this change in the objective function was smaller than that observed when comparing the base model to the BSA-normalized data (Supplementary Table S1). Moreover, considering weight as a covariate explained 40% and 44% of the interindividual variability in topotecan clearance and volume, respectively, which although significant was not as much of an effect as BSA. Finally, no significant improvement, relative to the BSA-normalized data, was found in the diagnostic plots when considering weight normalization as a covariate. Thus, BSA normalization was incorporated in the base model and remained in all subsequent analysis of the population model.

Interoccasion variability. Substantial variability was found among topotecan lactone pharmacokinetic parameters for patients studied on different occasions. An occasion was defined as the set of concentrations obtained after any single topotecan dose. The variability among occasions (IOV) was 20% and 22% (CV%) for clearance and volume, respectively (Supplementary Table S2). With the inclusion of IOV, the residual error (e.g., error attributable to sample handling, processing, assay), was reduced from 21% to 8.5% (CV%), which is consistent with the expected assay error of ~10% (9, 13).

Moreover, using the MC-PEM method, which included the full covariance matrix, the variable estimates obtained (data not shown) were in good agreement with those reported in Supplementary Table S2 for the BSA-normalized model taking into account IOV. Thus, for all further analyses, the model parameters clearance and volume were normalized to BSA and IOV was included in the model.

Univariate analysis and forward stepwise regression. Results of the univariate analysis using NONMEM were in agreement with those obtained from linear mixed-effects models for most of the covariates. In the case of the univariate analysis via NONMEM, a rank was established to decide the order each covariate would be incorporated into the model, based on the change of the objective function (and the associated $P$ value) with respect to the BSA-normalized model with IOV. Significant covariates that explained IV in clearance identified in the univariate analysis using NONMEM and the linear-mixed effect model ($P < 0.05$) included GFR, phenytoin administration, age, investigational drug, trial nos. 1 and 4, SCR, and dexamethasone coadministration. For volume, covariates that explained IV included age, coadministration of phenytoin, and trial nos. 1 and 4. Additionally, the linear mixed effects model analysis identified TECH as explaining IV in CL, and sulfamethoxazole/trimethoprim administration and GFR explaining the IV in volume.

The most significant covariate for topotecan clearance obtained in the univariate analysis was GFR ($\Delta$OFV = -34.4; $P < 0.0001$; Supplementary Table S2). This was expected because topotecan undergoes significant renal elimination. The linear relationship between topotecan clearance and GFR was found to significantly improve the model, accounting for 14% of the interindividual variability in clearance compared to the
BSA-normalized model with IOV. From the scatterplot of clearance versus GFR (Fig. 2A), a nonlinear relationship may be argued and hence this covariate was screened using an exponential as opposed to a linear relation. However, this did not further improve the model. Thus, the linear function for GFR was incorporated into the model to relate it to clearance.

Other covariates that related topotecan clearance with renal function were evaluated. In the case of TECH, it was not a significant covariate when considering the univariate analysis using NONMEM, possibly due to the paucity of TECH-related data points (missing in 55% of the observations). In addition, we observed that patients with higher than normal serum creatinine (i.e., SCR > 1.25 mg/dL) had a significant decrease in topotecan clearance explaining 15% of the IIV in CI in the univariate analysis with NONMEM ($P < 0.001$). However, considering that GFR and SCR are highly intercorrelated, only GFR was included in the model.

Next, we considered the variability in the pharmacokinetic parameters among studies. As shown in Fig. 2B, the clearance for patients enrolled in trial nos. 1 and 4 were higher compared with all other studies. In addition, the volume was also higher for patients enrolled in those studies (data not shown). When considering these trials as covariates, we observed a significant drop in the objective function relative to the BSA-normalized model that considered IOV and GFR ($\Delta$OFV = -42.4, $P < 0.0001$; Supplementary Table S2) and it accounted for 26% and 24% of the IIV variability in clearance and volume, respectively.

Moreover, patients from trial nos. 3 and 5 (which used the investigational formulation of the drug in contrast to the commercial formulation in the rest of the trials) showed a lower topotecan clearance than the rest of the population analyzed. Therefore, adding investigational drug formulation as a covariate on clearance explained an additional 2% of the IIV relative to the BSA-normalized model with IOV, GFR, and study effect ($\Delta$OFV = -17.2, $P < 0.001$; Supplementary Table S2).

Because we studied children ranging in age from 0.04 to 22 years, we evaluated age as a potential covariate. When evaluated as a linear continuous variable, age was not a significant covariate ($P > 0.1$; Fig. 2C). However, when age was considered as a categorical variable (i.e., age <0.5 years and age >0.5 years), BSA-normalized topotecan clearance and volume were 30% and 42% of the mean population parameters for ages >0.5 years old, respectively. Thus, we included age as a categorical variable in the model, and it accounted for 2.5% and 1.5% of the IIV on clearance and volume, respectively ($P < 0.001$).

The potential effects of the coadministration of phenytoin, dexamethasone, and sulfamethaxazole/trimethoprim were evaluated. As depicted in Fig. 2D, we found that topotecan clearance was significantly higher after coadministration with...
phenytoin, as had been previously reported in a single case study (21). Specifically, when phenytoin was incorporated in the model, it explained an additional 8.5% of the IIV in CL relative to the BSA-normalized model that considered all the previous significant covariates (ΔOFV = -12, P < 0.001; Supplementary Table S2). The other two concomitant drugs evaluated, dexamethasone and sulfamethoxazole/trimethoprim, did not significantly contribute to the population model (P > 0.1). Therefore, they were not included in further analyses.

Sex, race, and the other covariates evaluated were not significant in the present population analysis.

**Final model.** After the backwards deletion analysis, the model which included BSA normalization, IOV, GFR, age (as a categorical variable, for patients less than 0.5 years old), phenytoin coadministration, investigational drug, and trial nos. 1 and 4, reduced the interindividual variability of topotecan clearance and volume with respect to the base model by 76% and 50%, respectively. Parameter estimates of the final model are presented in Table 3. The model-predicted and individual-predicted concentrations versus observed topotecan concentrations using the final model are represented as scatterplots in Fig. 3. Considering that the model predictions were symmetrically distributed around the line of identity, we conclude that the model adequately describes topotecan disposition.

The robustness of the final model was assessed with the bootstrap procedure. The parameters (SE) obtained from the

### Table 3. Final estimates of population pharmacokinetic parameters obtained using NONMEM, MC-PEM, and bootstrap analysis of the final model

<table>
<thead>
<tr>
<th>Model</th>
<th>Mean (SE)</th>
<th>IIV (SE)</th>
<th>IOV (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final model* (NONMEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (L/h/m²)</td>
<td>27.7 (4.7)</td>
<td>0.079 (0.015)</td>
<td>0.038 (0.006)</td>
</tr>
<tr>
<td>V₁ (L/m²)</td>
<td>32.7 (1.1)</td>
<td>0.091 (0.018)</td>
<td>0.049 (0.007)</td>
</tr>
<tr>
<td>k₁₂ (h⁻¹)</td>
<td>0.430 (0.033)</td>
<td>0.0625 (fixed)</td>
<td></td>
</tr>
<tr>
<td>k₂₁ (h⁻¹)</td>
<td>0.756 (0.044)</td>
<td>0.0625 (fixed)</td>
<td></td>
</tr>
<tr>
<td>Residual variability</td>
<td>εₚᵦₚᵦ</td>
<td>0.007 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Final model † (MC-PEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (L/h/m²)</td>
<td>27.6 (3.6)</td>
<td>0.088 (0.014)</td>
<td>0.040 (0.005)</td>
</tr>
<tr>
<td>V₁ (L/m²)</td>
<td>32.2 (3.2)</td>
<td>0.087 (0.018)</td>
<td>0.048 (0.020)</td>
</tr>
<tr>
<td>k₁₂ (h⁻¹)</td>
<td>0.404 (0.091)</td>
<td>0.143 (0.187)</td>
<td></td>
</tr>
<tr>
<td>k₂₁ (h⁻¹)</td>
<td>0.724 (0.119)</td>
<td>0.033 (0.010)</td>
<td></td>
</tr>
<tr>
<td>Residual variability</td>
<td>εₚᵦₚᵦ</td>
<td>0.007 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Bootstrap</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (L/h/m²)</td>
<td>27.7 (0.33)</td>
<td>0.076 (0.001)</td>
<td>0.038 (0.0004)</td>
</tr>
<tr>
<td>V₁ (L/m²)</td>
<td>32.7 (0.09)</td>
<td>0.087 (0.001)</td>
<td>0.048 (0.0005)</td>
</tr>
<tr>
<td>k₁₂ (h⁻¹)</td>
<td>0.434 (0.03)</td>
<td>0.0625 (fixed)</td>
<td></td>
</tr>
<tr>
<td>k₂₁ (h⁻¹)</td>
<td>0.754 (0.005)</td>
<td>0.0625 (fixed)</td>
<td></td>
</tr>
<tr>
<td>Residual variability</td>
<td>εₚᵦₚᵦ</td>
<td>0.007 (0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Note that the population estimate for CL is based on the median GFR (63.9) and all the discrete covariates are set to 0. The population estimate for V₁ is based on all the discrete covariates set to 0.

Abbreviations: MISSGFR, missing data for GFR; ST1/4, trial nos. 1 and 4, respectively; INV, investigational drug formulation; AGE, age <0.5 y; phenytoin:phenytoin coadministration.

*The final model estimated by NONMEM corresponds to: CL (L/h/m²) = 15.9 (4.62) + 0.184 (0.061) × GFR + 13.5 (4.2) × MISSGFR + 13.5 (3.0) × ST4 - 6.49 (1.17) × INV - 7.2 (1.9) × AGE + 9.9 (2.8) phenytoin; V₁ (L/m²) = 32.7 (1.15) + 6.0 (1.9) × ST1 + 15.3 (4.94) × ST4.

†The final model estimated by MC-PEM corresponds to: CL (L/h/m²) = 19.6 (3.51) + 0.125 (0.049) × GFR + 10.1 (3.54) × MISSGFR + 14.8 (3.8) × ST4 - 6.68 (1.38) × INV - 4.6 (3.8) × AGE + 10.3 (3.3) phenytoin; V₁ (L/m²) = 32.2 (3.20) + 7.2 (2.1) × ST1 + 17.0 (3.9) × ST4.
bootstrap replications were very similar to the NONMEM estimates as shown in Table 3. Additionally, the estimates obtained by the MC-PEM method (Table 3), which included the full covariance matrix, were also in agreement with the results obtained by NONMEM.

Model prediction. Once we obtained a descriptive and robust covariate model, we evaluated the model performance by means of the prediction analysis. Although the covariates study effect and investigational drug formulation explained a significant amount of the variability in topotecan clearance, they were not available prospectively. Therefore, they were not considered in the predictive model. Thus, the relationship between clearance and covariates for the predictive model was \( CL = 15.9 + 0.184 \times \text{GFR} + 13.5 \times \text{BSA} - 7.2 \times \text{AGE} + 9.9 \times \text{phenytoin} \).

To compare the predictive model and conventional dosing approaches, data were used from 409 pharmacokinetic studies in 94 patients that received the commercial drug formulation. The median percent bias (minimum, maximum) of achieving the desired target AUC in the fixed conventional dosage group was -7.2% (-71%, 366%). In contrast, when using the predictive model the median percent bias was -3.4% (-56%, 162%). The results showed that the predictive model significantly reduced the range of estimated AUC to half of that obtained using a conventional dosage. Moreover, the precision expressed as the root mean squared prediction error associated with the model performance.

Discussion

Although children with cancer have been treated with topotecan for 15 years, this work represents the first population pharmacokinetic analysis of topotecan lactone in this population. The final covariate model that considered BSA, interoccasion variability, GFR, age of phenytoin usage, trial nos. 1 and 4, and investigational drug formulation reduced the interindividual variability of topotecan clearance and volume relative to the base model by 76% and 50%, respectively. Interindividual variability for the final covariate model (\( \text{IIV}_C = 28\% \), \( \text{IIV}_{V1} = 30\% \)) was greater than the interoccasion variability (\( \text{IIV}_C = 20\% \), \( \text{IIV}_{V1} = 22\% \)), providing support for a pharmacokinetically guided topotecan dosing approach. Specifically, we showed that if the present population model was used to individualize the topotecan dosage then the range of the AUC around the target would be significantly smaller than with a fixed-dosage approach, presumably by accounting for patients with larger or smaller than average topotecan clearance values.

Not only is this the first population pharmacokinetic analysis of topotecan in children, it is the only population pharmacokinetic analysis of topotecan lactone of which we are aware. At least five population pharmacokinetic studies have been published in adults, but all measured total topotecan, which consists of both lactone and carboxylic acid forms (16, 22–25). In those studies, the population average for total topotecan clearance ranged from 15 to 32 L/h. Overall, the results from the previous studies are similar to those reported in the present study, with the exception that we found BSA as a significant covariate, whereas none of the adult studies did. The measures of interindividual and interoccasion variability and residual error for our model are in the same range as published in the adult studies (16, 23).

The population mean values for clearance (27.1 L/h) and volume (37.3 L) obtained with NONMEM are consistent with what we have previously published (3, 6, 26). Moreover, these values were in good agreement with results obtained using MC-PEM analysis.

Although our analysis includes children from 0.04 to 22.0 years, we noted no continuous relation with age and topotecan clearance, most likely due to the high correlation between age and BSA. We have previously done a retrospective evaluation of topotecan disposition in infants, which suggested that topotecan clearance was lower in infants (<2 years) compared with older patients (27). However, the results of this larger study would indicate that unless a child is in the first months of life (<6 months of age), the topotecan clearance would be similar to older patients. We speculate that maturation of renal function during the first weeks of life, leading to a change in GFR, produces this observed change in topotecan clearance with age.

One clinical trial in our analysis had significantly higher topotecan clearances (trial no. 4), which we initially thought resulted from phenytoin use in children with brain tumors (although phenytoin was also used in patients in other trials). In such populations, phenytoin is often used to treat seizures secondary to tumor mass effect. Despite accounting for phenytoin use in these patients, topotecan clearance still remained significantly higher. Notably, these patients had topotecan pharmacokinetic studies within 1 month of major brain surgery, thus we speculate that this may have played a role in the increased topotecan clearance. This finding suggests that topotecan disposition might be altered in pediatric patients who were recently subjected to traumatic events or surgery.

During the model-building process, accounting for the two studies that received only the investigational formulation of topotecan (INV) explained a significant portion of the IIV variability in clearance. We noted that the clearance of these patients was lower than observed in the other four clinical trials. However, another group previously reported an increase in total topotecan pharmacokinetic parameters in patients receiving the investigational formulation of topotecan. To account for the administration of this formulation, those investigators introduced a bioavailability factor in their model (16). In both studies, the administration of investigational drug formulation affected the estimates of topotecan pharmacokinetic parameters. Thus, this covariate must be considered in the model-building process.

We have shown in early phase I studies that 40% to 70% of topotecan elimination is by renal mechanisms, and that probenecid could inhibit topotecan renal clearance in preclinical murine models (28). Furthermore, as mentioned above, results of population pharmacokinetic studies in adults have shown that measures of renal function are important covariates of topotecan clearance. Thus, it is not surprising that our analysis showed that calculated GFR was a significant covariate because it gives insight into renal function. In the subset of patients with technetium clearance values, we found a significant positive relation with the calculated GFR. However, technetium was not a significant covariate most likely because
those values were not available in most patients, whereas the calculated GFR was available in all patients with serum creatinine values. Finally, although renal function was significantly related to topotecan clearance in our population model, its contribution was not as significant as we had expected, possibly due to the fact that the renal function for the majority of patients was within the reference range.

The results of our population pharmacokinetic analysis suggested that topotecan is an appropriate candidate for a pharmacokinetically guided dosing approach because in the final model, the interoccasion variability for clearance (20% CV) was less than the interindividual variability (28% CV). The results of several studies where investigators have successfully used the pharmacokinetically guided approach offer further support for this dosing strategy (5, 6, 12). In these studies, investigators determined a target topotecan systemic exposure (i.e., AUC) based on preclinical studies, and then used an empirically defined range about that target (e.g., target AUC of 100 ng·h/mL with a range of 80-120 ng·h/mL). The IOV results of our population analysis suggest that we can successfully target (obtain an AUC within 20% of the targeted value) in ~67% of the attempts because 1 SD or 67% of the normal distribution falls within 20% of the mean clearance. Interestingly, this prediction is close to the 70% targeting success rate we have previously reported (12). Moreover, this finding has importance to clinicians as they design clinical trials of targeted topotecan and determine an appropriate range for the topotecan target.

A primary objective of this study was to establish a model consisting of patient covariates to guide topotecan dosing in children with cancer. Results of prior clinical trials of topotecan in children have shown that myelosuppression was the primary toxicity, and that topotecan lactone clearance varies widely among individuals (5, 11, 12). It is not surprising that the fixed conventional dosing approach evaluated in the present study led to a wide range in bias and precision of topotecan lactone AUC values. The model consisting of patient covariates improved the bias and precision of topotecan AUC values by reducing the number of outliers that would receive extreme exposures due to either very small or large pharmacokinetic parameters. Thus, the predictive model developed in the present study presents a lower variability in the attained topotecan lactone target exposure than that observed with the fixed dosage approach.

In summary, we have developed a population pharmacokinetic model of topotecan lactone in pediatric patients with different tumor types. We analyzed for the effects of covariates on topotecan pharmacokinetics using a nonlinear mixed effect approach. In the present analysis, we identified several significant covariates (BSA, GFR, age, and concomitant administration of phenytoin) that can be used prospectively in a model to predict topotecan clearance. Interindividual variability for the final covariate model was greater than the interoccasion variability, which provided support for a pharmacokinetically guided topotecan dosing approach. Finally, when used to individualize a patient’s topotecan AUC value, the model that relates the covariates that could be used to prospectively guide topotecan administration to topotecan pharmacokinetic parameters had better performance characteristics (bias and precision) than a fixed dosage approach, suggesting that the covariate model should be evaluated in a clinical setting.

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