A Pharmacokinetic Model of Topotecan Clearance from Plasma and Cerebrospinal Fluid

Cynthia Sung, Susan M. Blaney, Diane E. Cole, Frank M. Balis, Robert L. Dedrick

ABSTRACT

We present a physiological pharmacokinetic model that describes the plasma and cerebrospinal fluid (CSF) concentrations of topotecan [(S)-9-dimethylaminomethyl-10-hydroxycamptothecin hydrochloride; SK&F 104864-A; NSC 609699] following i.v. and intraventricular administrations in monkeys. The model consists of three physical spaces: the CSF, the plasma, and a body compartment. The model incorporates such processes as reversible conversion of topotecan lactone to an inactive hydroxy acid form, microvascular exchange between CSF and plasma, bulk CSF flow, exchange between plasma and body compartments, and elimination of drug from the plasma compartment. Several parameters in the model were obtained from published literature on the physiology of the monkey. The model was then fit to the plasma and CSF data to deduce the other parameters. Calculated clearances of topotecan lactone and total drug from the CSF after intraventricular injection were 3.9 and 2.2 ml/h, respectively. Clearances of topotecan lactone and total drug from the plasma following a 10-min infusion were 26.3 liters/h/m² and 17.8 liters/h/m², respectively. The calculated ratios of the area under the concentration curve in the CSF following i.v. infusion to the area under the concentration curve in plasma were 0.11 and 0.19 for topotecan and total drug, respectively, indicating significant CSF penetration. The volume of distribution was 0.77 liters/kg, which represents distribution in a volume approximating total body water. The forward and reverse rate constants for the lactone-to-hydroxy acid conversion were 1.0 and 0.29 h⁻¹, respectively. Comparison of the clearances (normalized to body surface area) with values reported for mice and humans shows reasonable similarity across species. This pharmacokinetic model may help guide future development and refinement of clinical protocols, especially in the treatment of diseases of the central nervous system.

INTRODUCTION

Topotecan [(S)-9-dimethylaminomethyl-10-hydroxycamptothecin hydrochloride; SK&F 104864-A; NSC 609699] is a topoisomerase I inhibitor that is currently under clinical evaluation in phase I and II trials for treatment of refractory cancer (1–5). Recent studies showing that topoisomerase I inhibitors are active against retroviruses in culture (6, 7), and in an animal model (8) may lead to clinical evaluation in the setting of retroviral disease, as well. Topotecan, a water-soluble analogue of camptothecin, is unstable in solution and undergoes spontaneous, reversible, pH-dependent hydrolysis that converts the active closed-ring lactone form to an inactive open-ring hydroxy acid species. The lactone form predominates in acidic conditions; at physiologic pH, however, the hydroxy acid is the major form (9). We recently performed detailed pharmacokinetic studies of topotecan in a nonhuman primate model (10) to assess the potential for application of topotecan in the treatment of CNS (3) disease. Plasma and CSF concentrations of topotecan lactone and total drug (lactone plus hydroxy acid forms) were followed after i.v. administration of a 10 mg/m² dose given as a 10-min infusion (11). The significant CSF penetration and the absence of neurotoxicity led to further evaluation of the pharmacology of topotecan administered directly into the CSF (3).

In this report, we present a physiologically based, compartmental pharmacokinetic model that describes the plasma and CSF clearances of the lactone and total drug after both i.v. and intraventricular administrations. Several parameters in the model were obtained from published literature on the physiology of the monkey. The model was then fit to plasma and CSF topotecan concentration data to deduce the other parameters. Analysis of the model includes comparison to reported studies in mice and humans.

MATERIALS AND METHODS

Drug. Topotecan (hydrochloride salt, in 0.9% saline solution adjusted to pH 3–4) was supplied by the Division of Cancer Treatment, National Cancer Institute (Bethesda, MD).

Pharmacokinetic Experiments and Sample Analysis. Nonhuman primates (n = 3; 6.9–8.7 kg) were given 10 mg/m² topotecan as a 10-min i.v. infusion, and blood and CSF samples were obtained over a period of 5.5 h after infusion was completed (11). When topotecan was given into the CSF, nonhuman primates (n = 3; 6.2–9.9 kg) received an intraventricular bolus dose of 0.1 mg topotecan as a 1.0-ml injection into an Ommaya reservoir that drained into the fourth ventricle. The reservoir was pumped 4–6 times to ensure adequate mixing with ventricular CSF. Samples were obtained over the following 9 h. Before and after each sampling of CSF, the reservoir was pumped 10 times. Plasma and CSF concentrations of topotecan and total drug were measured by high performance liquid chromatography, as described elsewhere (11).

The Model. A physiologically based, compartmental pharmacokinetic model was formulated to describe data from both intraventricular and i.v. administrations of topotecan in monkeys. The model consists of three compartments: CSF, plasma, and a body compartment (Fig. 1). Clearance of drug from the CSF occurs by bulk flow, F, and by microvascular exchange, PA, with the plasma compartment. The plasma compartment communicates with the body compartment by an intercompartmental transport parameter, K, which is a function of plasma flow rate and capillary exchange properties. Within each of these compartments, the lactone form of topotecan interconverts with the hydroxy acid form. The forward and reverse rate constants for lactone to hydroxy acid conversion are designated kₐ and k₈, respectively. We have assumed that topotecan, in either the lactone or hydroxy acid form, is eliminated from the plasma compartment with the same characteristic rate constant, k₈, and that the microvascular exchange rate constant between the plasma and ventricular CSF is the same for both lactone and hydroxy acid forms of the drug. It has been reported that approximately 40% of topotecan is excreted unmetabolized in the urine by 24 h (1, 2). Our model assumes that elimination occurs only from the plasma compartment, which is appropriate for kidney filtration and secretion, but which may not be accurate if significant metabolism of the drug occurs in the body's tissues.

The concentrations of topotecan lactone and total drug in each of the three compartments are represented by the set of ordinary differential equations, equations A–F. C₁, C₂, C₃, C₄, C₅, and C₆ represent lactone concentrations in the CSF plasma, and body compartments, respectively. C₄, C₅, and C₆ represent total drug concentrations in those compartments, respectively. When topotecan was administered into the CSF, it was injected as a bolus of pure lactone drug. To simulate this delivery, we assumed that the dose of lactone was equal to the

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2 The abbreviations used are: CNS, central nervous system; CSF, cerebrospinal fluid; AUC, area under the curve.

Our initial estimates of the kinetics and equilibrium of lactone-hydroxy acid interconversion were based on the work of Underberg et al. (9), who reported that topotecan was administered i.v., it was given as a 10-mm constant infusion of essentially pure lactone drug (>97% lactone by high-performance liquid chromatographic analysis of the infusate). This mode of delivery was simulated by an infusion of pure lactone drug into the plasma compartment (equations C and D) at a rate, \( m \), equal to the dose divided by 10 min. Initial concentrations of topotecan lactone and total drug in all compartments were set equal to zero (equation I). At the end of the 10-min infusion period, \( m \) was set equal to zero.

### Differential Equations

\[
\begin{align*}
\frac{dC_{1LT}}{dt} &= -\left(\frac{F + PA}{V_1} + k_{LH} + k_{HL}\right)C_{1L} + (k_{HL})C_{1T} + \left(\frac{PA}{V_1}\right)C_{3L} \\
\frac{dC_{2LT}}{dt} &= -\left(\frac{F + PA}{V_2} + k_{2L} + k_{LH}\right)C_{2L} + (k_{LH})C_{2T} + \left(\frac{PA}{V_2}\right)C_{3L} \\
\frac{dC_{3LT}}{dt} &= \left(\frac{F + PA}{V_1} + k_{LH} + k_{HL}\right)C_{1L} + \left(\frac{PA}{V_1}\right)C_{3L} \\
\frac{dC_{3LT}}{dt} &= \left(\frac{F + PA}{V_2} + k_{LH} + k_{HL}\right)C_{2L} + \left(\frac{PA}{V_2}\right)C_{3L} \\
\frac{dC_{4LT}}{dt} &= \left(\frac{K}{V_3}\right)C_{3L} - \left(\frac{F + PA}{V_3}\right)C_{3T} \\
\frac{dC_{5LT}}{dt} &= \left(\frac{K}{V_3}\right)C_{3T} - \left(\frac{F + PA}{V_3}\right)C_{3L} \\
\end{align*}
\]

**Initial Conditions for Intraventricular Dosing:**

- \( C_{1LT} = C_{1T} = \text{Dose}/V_1 \)  
- \( C_{2LT} = C_{2T} = C_{3LT} = C_{3T} = 0 \)
- \( C_{4LT} = C_{4T} = C_{5LT} = C_{5T} = 0 \)

The data were fit to the pharmacokinetic equations by a nonlinear, least squares method using the Marquardt-Levenberg algorithm in the software program MLAB (Civilized Software, Bethesda, MD). An initial fit was performed using estimated variances obtained by the function EWT in MLAB as weighting factors. An iterative process was then carried out in which the parameter values was obtained. Several parameters in the pharmacokinetic model were constrained or set equal to values consistent with the physiology of the monkey. The bulk CSF flow rate, \( F \), is 1.8 ml/h, in monkeys (12), and the plasma volume, \( V_p \), is 420 ml (13); an upper limit on the value of the transport parameter, \( K \), is the cardiac output of plasma, which is approximately 48 liters/h (13). The i.v. infusion rate was set equal to the average in the three animals (8517 nmol/10 min). The intraventricular dose was 0.1 mg or 218 nmol.

Our initial estimates of the kinetics and equilibrium of lactone-hydroxy acid interconversion were based on the work of Underberg et al. (9), who reported that the rate constants increased with temperature, but the equilibrium constant was unchanged by temperature. A linear interpolation of the log of the equilibrium constant \( (k_{LH}/k_{HL}) \) versus pH between pH 7 and 8 gave an estimate of 4.2 at physiological pH 7.4. The reverse rate constant did not change over the range of pH 7–8 and was 0.12 h\(^{-1}\) at 25°C. Hence, an initial estimate of the forward rate constant at pH 7.4 and 25°C is 0.50 h\(^{-1}\).
### Pharmacokinetic Model for Topotecan

<table>
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</tr>
<tr>
<td>$k_{e1}$</td>
<td>16.6</td>
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</tr>
</tbody>
</table>

* $F$ and $V_1$ were set to values in accordance with the physiology of the monkey. Other parameter values were obtained from fits of the experimental data to the model.

### CSF Concentrations After Intraventricular Injection

**Fig. 2A.** Concentrations of topotecan and total drug in the CSF following intravenous infusion. **B.** Concentrations of topotecan and total drug in the plasma following a 10-min i.v. infusion. **C.** Concentrations of topotecan and total drug in the CSF following a 10-min i.v. infusion. The dashed line and the solid line represent concentrations of total drug and topotecan lactone, respectively. The model-fitted value of $K$ was 9.8 liter/h or ~20% of the cardiac output, in good agreement with literature values of capillary permeability of low-molecular-weight, hydrophilic drugs.

### PLasma Concentrations After Intravenous Infusion

From the global fit of the data to the model, we found that $PA$, the microvascular exchange rate between plasma and CSF, is 0.41 ml/h. $V_1$ and $V_3$ are 2.6 ml and 5630 ml, respectively. Hence, the apparent volume of distribution ($V_1 + V_2 + V_3$) is 6.05 liters or, expressed on a body-weight basis, 0.77 liter/kg. This volume indicates that topotecan distributes in a volume approximating total body water. The rate constants for interconversion of lactone and hydroxy acid, $k_{LH}$ and $k_{HL}$, are 1.00 and 0.29 h$^{-1}$, respectively, yielding an equilibrium ratio of 3.4. The rate constant for elimination of topotecan from the plasma compartment, $k_{e1}$, is 16.6 h$^{-1}$.

...
Based on these parameter values, the calculated plasma clearances of topotecan lactone and total drug are 10.5 and 7.0 liters/h, respectively. Normalized to the average body surface area (0.4 m²), the clearances are 26.3 liters/h/m² and 17.8 liters/h/m², respectively. CSF clearances of topotecan lactone and total drug after intraventricular dosing are calculated to be 3.9 and 2.2 ml/h, respectively.

**DISCUSSION**

Topotecan was administered to monkeys by two routes, i.v. and intraventricularly. To model the data, we have formulated a physiologically based pharmacokinetic model that consists of three physical compartments (the CSF, the plasma, and the body) and identified a set of parameter values that fits the data from both experiments (Table 1; Fig. 2). These parameter values are consistent with the physiology of the monkey and with the kinetics and equilibrium of topotecan lactone conversion to hydroxy acid.

The model predicts the volume of the CSF compartment to be 2.6 ml. This parameter was determined from intraventricular dosing experiments and thus suggests that the drug is initially distributed in the ventricular CSF volume. Approximately 46% of the clearance of topotecan lactone from the CSF after intraventricular administration occurs by bulk CSF flow, 44% by conversion to the inactive hydroxy acid form, and 10% by microvascular exchange.

This pharmacokinetic model allows us to estimate the plasma concentrations during the period of i.v. infusion. These estimates are important for determining the AUC, and hence the clearances, because a significant fraction of the total AUC may occur during the infusion period. For example, we calculate that 50% of the AUC of topotecan lactone and 35% of the AUC of total drug in the plasma occur during the infusion period. Thus, plasma sampling during the infusion period would have been very useful in obtaining a more accurate estimate of topotecan clearance. By including the estimated infusion-period area of the AUC in our calculations, we determined that the clearance of total drug is 116 ml/min. This clearance is substantially greater than the estimated monkey glomerular filtration rate of 24 ml/min (15), suggesting that, in addition to kidney filtration, kidney secretion or other metabolic processes contribute to elimination of the drug. The difference between the clearance of topotecan lactone and that of total drug is the presumed nonenzymatic conversion to the inactive hydroxy acid form. Approximately one-third of the topotecan lactone clearance is attributable to this conversion. Following i.v. infusion, significant penetration of drug into the CSF occurs (Fig. 2C). The calculated ratio of AUC in the CSF to AUC in the plasma is 0.11 for topotecan lactone and is 0.19 for total drug.

The forward and reverse rate constants that we derived from modeling the in vivo experiments (37°C) are −2.0 and 2.4 times higher, respectively, than values inferred from the experiments done at 25°C by Underberg et al. (see above; Ref. 9). The higher rates are likely the effect of higher temperature. Underberg et al. (9) also noted an increase in forward and reverse rate constants with temperature, although the magnitude of the increase was not given.

Our interest in evaluating topotecan as a potential treatment of CNS cancer motivated the measurements of CSF concentrations after i.v. as well as intraventricular dosing. Hence, the pharmacokinetic model explicitly includes a CSF compartment. The model, in many other respects, is similar to one of the models proposed by Grochow et al. (16) because it uses the assumptions that the lactone and hydroxy acid forms of the drug have equal volumes of distribution and rates of intercompartmental exchange and elimination and that topotecan is given in the pure lactone form. Grochow et al. (16) found that these constraints led to an unsatisfactory description of their experimental data and, therefore, developed a more complex model. In our experiments, however, these assumptions were supported by the nearly parallel decreases in topotecan lactone and total drug in the terminal periods of observation and by the assay measurements of the infused drug solutions showing a composition of >97% lactone. Our simpler model, which incorporated these assumptions, was thus sufficient to simulate our data. Refinedness in the model may become necessary as more is learned about other processes, if they exist to any significant extent, such as metabolism, plasma protein binding, and differential transport and elimination rates of the two forms of the drug.

We calculated that the plasma clearance of topotecan lactone in the monkey is 26.3 liter/h/m². Because the model permits estimation of the AUC during the infusion period, we arrived at a clearance lower than that obtained from a model-independent analysis of these data (11). This clearance is in good agreement with those reported by Wall et al. (Ref. 2; 25.7 liter/h/m²), following a 30-min infusion in adult humans, and by Blaney et al. (Ref. 5; 28.3 liter/h/m²), following a 24-h infusion in a pediatric population. However, the clearance of topotecan lactone reported by Grochow and Rowinsky (1, 16) in adult humans who received a 30-min infusion was 73.2 liter/h/m², substantially higher than the clearance in our findings. Their calculations appropriately included the infusion period AUC; therefore, it is not apparent what other factors might explain the difference.

The clearance of total drug from the plasma, interestingly, appears to scale reasonably well across species. In mice, the reported clearance is 19.8 liter/h/m² (16) and 20 liter/h/m² (3). In monkeys, we measured a total-drug plasma clearance of 17.8 liter/h/m². In a pediatric population, the total-drug clearance was 9.8 liter/h/m² (5), and in adult humans, it was 8.0 liter/h/m² (2). The volume of distribution, when expressed on a body-weight basis rather than on a surface-area basis, also shows similarity across species. In monkeys, we measured a volume of distribution of 0.77 liters/kg; in humans, it is approximately 1.1 liters/kg (2).

Clinical evaluation of topotecan continues, spurred on by objective tumor responses to doses that are well tolerated by patients (17). The pharmacokinetic data and model presented here provide a basis for developing and refining clinical protocols, especially in the treatment of CNS disease.

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**REFERENCES**


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