

# A Pharmacokinetic Model of Topotecan Clearance from Plasma and Cerebrospinal Fluid

Cynthia Sung,<sup>1</sup> Susan M. Blaney, Diane E. Cole, Frank M. Balis, Robert L. Dedrick

Biomedical Engineering & Instrumentation Program, National Center for Research Resources, NIH; [C. S., R. L. D.]; Department of Pediatrics, Walter Reed Army Medical Center [S. M. B.]; and Pediatric Branch, National Cancer Institute, NIH [D. E. C., F. M. B.], Bethesda, Maryland 20892

## 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/m<sup>2</sup> and 17.8 liters/h/m<sup>2</sup>, 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<sup>-1</sup>, 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<sup>2</sup> 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/m<sup>2</sup> 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.<sup>3</sup> 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/m<sup>2</sup> 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  $k_{LH}$  and  $k_{HL}$ , 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,  $k_{el}$  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.  $C_{1,L}$ ,  $C_{2,L}$ , and  $C_{3,L}$  represent lactone concentrations in the CSF, plasma, and body compartments, respectively.  $C_{1,T}$ ,  $C_{2,T}$ , and  $C_{3,T}$  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

Received 11/8/93; accepted 8/5/94.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

<sup>1</sup> To whom requests for reprints should be addressed, at NIH, Building 13, Room 3N17, Bethesda, MD 20892.

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

<sup>3</sup> S. M. Blaney, D. E. Cole, K. Goodwin, C. Sung, D. G. Popluch, and F. M. Balis. Intrathecal administration of topotecan in nonhuman primates, submitted for publication.

dose of total drug and that the drug was instantaneously mixed in the CSF volume,  $V_1$ . The initial concentrations of topotecan lactone and total drug were set equal to the dose divided by  $V_1$  (equation G); the initial concentrations in the plasma and body compartments were set equal to zero (equation H). When topotecan was administered i.v., it was given as a 10-min 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,  $\dot{m}$ , 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,  $\dot{m}$  was set equal to zero.

Differential Equations

$$\frac{dC_{1,L}}{dt} = - \left( \frac{F+PA}{V_1} + k_{LH} + k_{HL} \right) \times C_{1,L} + (k_{HL}) \times C_{1,T} + \left( \frac{PA}{V_1} \right) \times C_{2,L} \quad (A)$$

$$\frac{dC_{1,T}}{dt} = - \left( \frac{F+PA}{V_1} \right) \times C_{1,T} + \left( \frac{PA}{V_1} \right) \times C_{2,T} \quad (B)$$

$$\frac{dC_{2,L}}{dt} = \left( \frac{F+PA}{V_2} \right) \times C_{1,L} - \left( \frac{PA+K}{V_2} + k_{LH} + k_{HL} + k_{el} \right) \times C_{2,L} + (k_{HL}) \times C_{2,T} + \left( \frac{K}{V_2} \right) \times C_{3,L} + \frac{\dot{m}}{V_2} \quad (C)$$

$$\frac{dC_{2,T}}{dt} = \left( \frac{F+PA}{V_2} \right) \times C_{1,T} - \left( \frac{PA+K}{V_2} + k_{el} \right) \times C_{2,T} + \left( \frac{K}{V_2} \right) \times C_{3,T} + \frac{\dot{m}}{V_2} \quad (D)$$

$$\frac{dC_{3,L}}{dt} = \left( \frac{K}{V_3} \right) \times C_{2,L} - \left( \frac{K}{V_3} + k_{LH} + k_{HL} \right) \times C_{3,L} + (k_{HL}) \times C_{3,T} \quad (E)$$

$$\frac{dC_{3,T}}{dt} = \left( \frac{K}{V_3} \right) \times C_{2,T} - \left( \frac{K}{V_3} \right) \times C_{3,T} \quad (F)$$

Initial Conditions for Intraventricular Dosing:

$$C_{1,L} = C_{1,T} = \text{Dose}/V_1 \quad (G)$$

$$C_{2,L} = C_{2,T} = C_{3,L} = C_{3,T} = 0 \quad (H)$$

Initial Conditions for i.v. Dosing:

$$C_{1,L} = C_{1,T} = C_{2,L} = C_{2,T} = C_{3,L} = C_{3,T} = 0 \quad (I)$$

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 inverse square of the residuals became weighting factors until convergence of 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,  $V_2$ , 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 reaction rates obtained in buffered solutions from pH 4–10. 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<sup>-1</sup> at 25°C. Hence, an initial estimate of the forward rate constant at pH 7.4 and 25°C is 0.50 h<sup>-1</sup>.

The fits were performed in a stepwise manner. First, CSF data from intraventricular dosing were fit to a truncated set of equations to obtain estimates of  $PA$ ,  $V_1$ , ( $k_{LH} + k_{HL}$ ), and  $k_{LH}/k_{HL}$ . The truncated equations were simplified forms of equations A and B in which the backflux of drug from the plasma compartment was ignored. This treatment was justified by the experimental observation that the concentration of drug in the plasma after intraventricular dosing is more than 10,000 times lower than the CSF concentration. Therefore, the contribution to CSF concentration from backflux from the plasma compartment is expected to be insignificant. With  $V_1$  set equal to the value obtained from the first fit, CSF and plasma data from i.v. dosing were fit to the full model to obtain values for  $V_3$ ,  $PA$ ,  $K$ , ( $k_{LH} + k_{HL}$ ),  $k_{LH}/k_{HL}$ , and  $k_{el}$ . Finally, parameter values obtained from this fit were used as initial estimates in a global fit, in which all data from both intraventricular and i.v. dosings were fit simultaneously to the full model to obtain  $V_3$ ,  $PA$ ,  $K$ , ( $k_{LH} + k_{HL}$ ),  $k_{LH}/k_{HL}$ , and  $k_{el}$ .

The AUC for topotecan and total drug from the beginning of infusion were calculated by the trapezoidal method on numerical solutions to equations A–F. Clearances were calculated by dividing the dose by the AUC and then were normalized to the average body surface area of these monkeys, 0.4 m<sup>2</sup>. The volume of distribution of the total drug after i.v. administration is equal to the sum of  $V_1$ ,  $V_2$  and  $V_3$ .

RESULTS

We have attempted to construct a pharmacokinetic model with a minimal number of parameters that would be consistent with the physiology of the monkey and still reasonably fit the experimental data. By applying the three-compartment model shown in Fig. 1 to the data from both the intraventricular and i.v. experiments, we obtained the parameter values listed in Table 1. Fig. 2 illustrates the experimental data and the corresponding model-predicted curves.

When topotecan was given as a bolus injection into the CSF, the concentration of total drug followed a nearly monoexponential decrease for 6 h (Fig. 2A). The pharmacokinetic model implies that the total drug concentration decays monoexponentially with a decay constant equal to  $(F + PA)/V_1$  (equation B) and that the Y-intercept is the dose divided by  $V_1$  (equation G). After 6 h, the predicted curve for total drug deviates from the experimental data; however, this deviation has a relatively small effect on the calculation of AUC.

The concentration of topotecan lactone after intraventricular injection exhibits a biexponential decrease (Fig. 2A). According to the model, clearance during the early phase occurs from chemical conversion to the hydroxy acid form as well as from the physical processes of bulk CSF flow and microvascular exchange (equation A). As

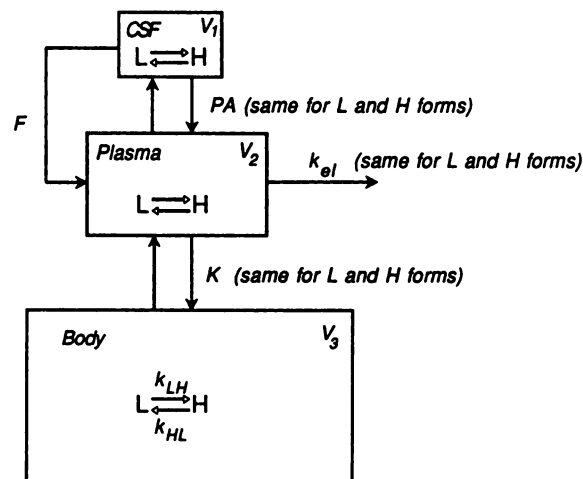


Fig. 1. A schematic representation of the physiological pharmacokinetic model for topotecan.

Table 1 Pharmacokinetic model parameters<sup>a</sup>

Parameter	Value	Units
$F$	1.8	ml/h
$PA$	0.41	ml/h
$K$	9,800	ml/h
$V_1$	2.6	ml
$V_2$	420	ml
$V_3$	5630	ml
$k_{LH}$	1.00	$h^{-1}$
$k_{HL}$	0.29	$h^{-1}$
$k_{el}$	16.6	$h^{-1}$

<sup>a</sup>  $F$  and  $V_2$  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.

equilibrium between lactone and hydroxy acid is achieved, the slope becomes shallower, representing clearance by physical processes only. The difference between the rate constant for total drug concentration curve and the rate constant for the early phase of topotecan clearance is  $k_{LH}$  (equations A and B). The predicted curve for topotecan clearance in Fig. 2A shows systematic overestimation of the experimental data between 1 and 4 h. Attempts to adjust the parameter values to achieve a better fit to these data led to unsatisfactory fits to the data from the i.v. experiments (Fig. 2B and C), possibly indicating that the kinetics of the lactone-to-hydroxy acid conversion may be slightly different in CSF and in plasma. Calculations of the AUC for topotecan following intraventricular injection based on the parameters in Table 1 predict an AUC approximately 15% higher than that obtained from a model-independent analysis.<sup>3</sup>

Fig. 2B illustrates the clearance of topotecan (lactone and total drug) from the plasma after i.v. infusion of the drug in three monkeys. Clearance of total drug following infusion exhibits a nearly monoexponential decrease, with a characteristic half-time of 1.0 h. The monoexponential behavior indicates that exchange between the plasma and the rest of the body occurs on a relatively rapid time scale compared to the sampling schedule. We supposed, at first, that the monoexponential decrease would permit us to model the plasma and body compartments as a single compartment. However, the necessity of treating the plasma and body compartments separately became evident after unsuccessful attempts to fit the CSF data (Fig. 2C) when  $V_2$  and  $V_3$  were lumped together. In such a model, the topotecan dose would be diluted immediately in a volume equal to  $V_2 + V_3$ . As a result, the concentration gradient between the CSF and the lumped compartment (which serves as the driving force for transport into the CSF compartment) would be too low to account for the observed concentrations in the CSF. Separation of  $V_2$  and  $V_3$  results in a brief period (for these parameter values, approximately the duration of the infusion) during which the concentration difference between plasma and CSF is sufficiently high so that predicted CSF concentrations attain values close to those measured experimentally. A physiological argument can be made for separating  $V_2$  and  $V_3$ , because hydrophilic agents the size of topotecan tend to be limited in their movement into peripheral tissues by both plasma flow and capillary permeability. The extraction of sucrose in muscle, for example, has been reported in the range from 0.1 to 0.3 (14). In addition, an arterial first-pass effect exists in which an i.v. administered drug experiences limited dispersion during transit through the lung. One would, therefore, expect a few passes through the vascular system to be necessary before a steady-state can be attained between the plasma and peripheral tissues. 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.

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,  $k_{el}$  is 16.6  $h^{-1}$ .

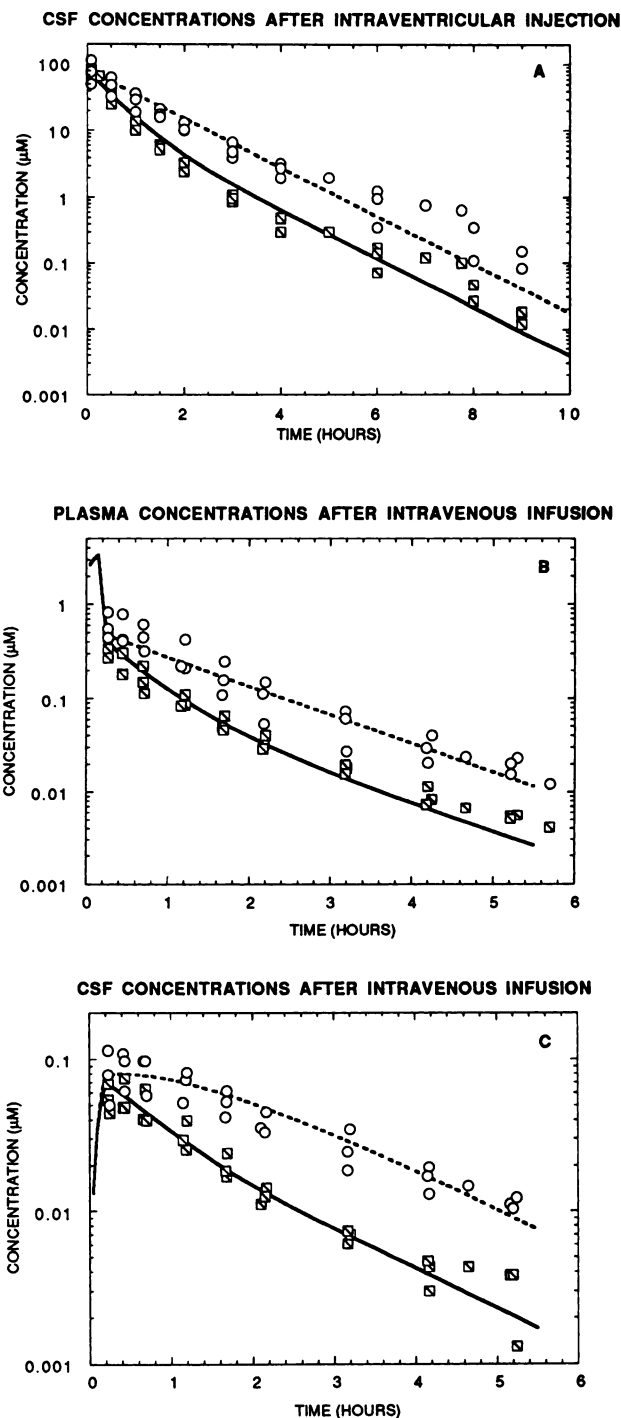


Fig. 2. A, concentrations of topotecan and total drug in the CSF following intraventricular injection. B, concentrations of topotecan and total drug in the plasma following a 10-min i.v. infusion. C, concentrations of topotecan and total drug in the CSF following a 10-min i.v. infusion.  $\circ$  and  $\square$ , experimentally measured concentrations of total drug and topotecan lactone, respectively. The dashed line and the solid line represent concentrations of total drug and topotecan lactone, respectively, predicted from the pharmacokinetic model using the parameter values in Table 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 ( $0.4 \text{ m}^2$ ), the clearances are  $26.3 \text{ liters/h/m}^2$  and  $17.8 \text{ liters/h/m}^2$ , 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 ( $37^\circ\text{C}$ ) are  $\sim 2.0$  and  $2.4$  times higher, respectively, than values inferred from the experiments done at  $25^\circ\text{C}$  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. Refinements 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  $26.3 \text{ liter/h/m}^2$ . 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;  $25.7 \text{ liter/h/m}^2$ ), following a 30-min infusion in adult humans, and by Blaney *et al.* (Ref. 5;  $28.3 \text{ liter/h/m}^2$ ), 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  $73.2 \text{ liter/h/m}^2$ , 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  $19.8 \text{ liter/h/m}^2$  (16) and  $20 \text{ liter/h/m}^2$  (3). In monkeys, we measured a total-drug plasma clearance of  $17.8 \text{ liter/h/m}^2$ . In a pediatric population, the total-drug clearance was  $9.8 \text{ liters/h/m}^2$  (5), and in adult humans, it was  $8.0 \text{ liters/h/m}^2$  (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  $0.77 \text{ liters/kg}$ ; in humans, it is approximately  $1.1 \text{ liters/kg}$  (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.

## ACKNOWLEDGMENTS

We gratefully acknowledge Marc Lewis and Barry Bunow for assistance with MLAB. We also thank Seth Steinberg and David Venzon for advice on analysis of the data and Barry Bowman and Peter Bungay for editing the manuscript.

## REFERENCES

- Rowinsky, E. K., Grochow, L. B., Hendricks, C. B., Ettinger, D. S., Forastiere, A. A., Hurowitz, L. A., McGuire, W. P., Sartorius, S. E., Lubejko, B. G., Kaufmann, S. H., and Donehower, R. C. Phase I and pharmacologic study of topotecan: a novel topoisomerase inhibitor. *J. Clin. Oncol.*, *10*: 647-656, 1992.
- Wall, J. G., Burris, H. A., III, Von Hoff, D. D., Rodriguez, G., Kneuper-Hall, R., Shaffer, D., O'Rourke, T., Brown, T., Weiss, G., Clark, G., McVea, S., Brown, J., Johnson, R., Friedman, C., Smith, B., Mann, W. S., and Kuhn, J. A phase I clinical and pharmacokinetic study of the topoisomerase I inhibitor topotecan (SK&F 104864) given as an intravenous bolus every 21 days. *Anti-Cancer Drugs*, *3*: 337-345, 1992.
- Houghton, P. J., Cheshire, P. J., Myers, L., Stewart, C. F., Synold, T. W., and Houghton, J. A. Evaluation of 9-dimethyl aminomethyl-10-hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. *Cancer Chemother. Pharmacol.*, *31*: 229-239, 1992.
- Kantarjian, H. M., Beran, M., Ellis, A., Zwelling, L., O'Brien, S., Cazenave, L., Koller, C., Rios, M. B., Plunkett, W., Keating, M. J., and Estey, E. H. Phase I study of topotecan, a new topoisomerase I inhibitor in patients with refractory or relapsed acute leukemia. *Blood*, *81*: 1146-1151, 1993.
- Blaney, S. M., Balis, F. M., Cole, D. E., Craig, C., Reid, J. M., Ames, M. M., Krailo, M., Reaman, G., Hammond, D., and Poplack, D. G. Pediatric phase I trial and pharmacokinetic study of topotecan administered as a 24-h continuous infusion. *Cancer Res.*, *53*: 1032-1036, 1993.

6. Priel, E., Showalter, S. D., and Blair, D. G. Inhibition of human immunodeficiency virus (HIV-1) replication *in vitro* by noncytotoxic doses of camptothecin, a topoisomerase I inhibitor. *AIDS Res. Hum. Retroviruses*, **7**: 65–72, 1991.
7. Li, C. J., Zhang, L. J., Dezube, B. J., Crumpacker, C. S., and Pardee, A. B. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc. Natl. Acad. Sci. USA*, **90**: 1839–1842, 1993.
8. Priel, E., Aflalo, E., Chechelnitsky, G., Benharroch, D., Aboud, M., and Segal, S. Inhibition of retrovirus-induced disease in mice by camptothecin. *J. Virol.*, **67**: 3624–9, 1993.
9. Underberg, W. J. M., Goossen, R. M. J., Smith, B. R., and Beijnen, J. H. Equilibrium kinetics of the new experimental anti-tumour compound SK&F 104864-A in aqueous solution. *J. Pharm. Biomed. Anal.*, **8**: 681–683, 1990.
10. McCully, C., Balis, F., Bacher, J., Phillips, J., and Poplack, D. A rhesus monkey model for continuous infusion of drugs into cerebrospinal fluid. *Lab. Anim. Sci.*, **40**: 520–525, 1990.
11. Blaney, S. M., Cole, D. E., Balis, F. M., Godwin, K., and Poplack, D. G. Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. *Cancer Res.*, **53**: 725–727, 1993.
12. Curran, R., Mosher, M., Owens, E., and Fenstermacher, J. Cerebrospinal fluid production rates determined by simultaneous albumin and inulin perfusion. *Exp. Neurol.*, **29**: 546–553, 1970.
13. Forsyth, R., Nies, A., Wyler, F., Neutze, J., and Melmon, K. Normal distribution of cardiac output in the unanesthetized, restrained rhesus monkey. *J. Appl. Physiol.*, **25**: 736–741, 1968.
14. Crone, C., and Christensen, O. Cardiovascular physiology III. *In*: A. Guyton and D. Young (ed.), *Internal Review Physiology*, pp. 149–213. Baltimore: University Park Press, 1979.
15. Calder, W. A., III, and Braun, E. J. Scaling of osmotic regulation in mammals and birds. *Am. J. Physiol.*, **244**: R601–R606, 1983.
16. Grochow, L. B., Rowinsky, E. K., Johnson, R., Ludeman, S., Kaufmann, S. H., McCabe, F. L., Smith, B. R., Hurowitz, L., DeLisa, A., Donehower, R. C., and Noe, D. A. Pharmacokinetics and pharmacodynamics of topotecan in patients with advanced cancer. *Drug Metab. and Dispos.*, **20**: 706–713, 1992.
17. Slichenmyer, W., Rowinsky, E., Donehower, R., and Kaufmann, S. The current status of camptothecin analogues as antitumor agents. *J. Natl. Cancer Inst.*, **85**: 271–291, 1993.