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Cerebrospinal fluid pharmacokinetics and penetration of continuous infusion topotecan in children with central nervous system tumors

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Abstract. The purpose of this study was to describe the cerebrospinal fluid (CSF) penetration of topotecan in humans, to generate a pharmacokinetic model to simultaneously describe topotecan lactone and total concentrations in the plasma and CSF, and to characterize the CSF and plasma pharmacokinetics of topotecan administered as a continuous infusion (CI). Plasma and CSF samples were collected from 17 patients receiving 5.5 or 7.5 mg/m^2 per day as a 24-h CI (5 patients, 7 courses), or 0.5 to 1.25 mg/m^2 per day as a 72-h CI (12 patients, 12 courses). CSF samples were obtained from either a ventricular reservoir (VR) or a lumbar puncture (LP). Topotecan lactone and total (lactone plus hydroxy acid) concentrations were determined by HPLC and fluorescence detection. Using MAP-Bayesian modelling, a three-compartment model was fitted simultaneously to topotecan lactone and total concentrations in the plasma and CSF. The penetration of topotecan into the CSF was determined from the ratio of the CSF to the plasma area under the concentration-time curve. The median CSF ventricular lactone concentrations, obtained prior to the end of infusion (EOI), were 0.86, 1.4, 0.73, 5.3, and 4.6 ng/ml for patients receiving 0.5, 1.0, 1.25, 5.5, and 7.5 mg/m^2 per day, respectively. EOI CSF lumbar lactone concentrations measured in three patients were 0.44, 1.1, and 1.7 ng/ml for topotecan doses of 1.0, 5.5, and 7.5 mg/m^2 per day, respectively. In two patients receiving 1.25 mg/m^2 per day, EOI CSF concentrations were obtained simultaneously from a VR and LP; the lumbar lactone concentrations were 30% and 49% lower than the ventricular concentrations. During a 24-h and a 72-h CI, the median CSF penetration of topotecan lactone was 0.29 (range 0.10 to 0.59) and 0.42 (range 0.11 to 0.86), respectively. A three-compartment model adequately described topotecan lactone and total concentrations in the plasma and CSF. Topotecan was therefore found to significantly penetrate into the CSF in humans. The pharmacokinetic model presented may be useful in the design of clinical studies of topotecan to treat CNS tumors.

Key words Topotecan · CSF penetration
CSF pharmacokinetics

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Introduction

Topotecan, a water-soluble, semisynthetic derivative of camptothecin, has shown excellent preclinical activity against a broad range of tumors [8, 9, 22, 27], with objective responses observed in both adult and pediatric tumors in phase I clinical trials [19, 20, 23, 24, 31]. Additionally, topotecan may possess activity in some childhood central nervous system (CNS) tumors: tumor regressions have been observed in ependymoma, medulloblastoma, and high-grade glioma xenografts following intraperitoneal administration of topotecan

[13]. The above suggests potential utility for this agent in CNS malignancies, and phase II clinical trials of topotecan in CNS tumors are currently in progress.

Despite numerous studies describing the plasma pharmacokinetics and pharmacodynamics of topotecan [2, 15, 16, 25, 28, 31, 32], the cerebrospinal fluid (CSF) pharmacokinetics and penetration of topotecan have not been described in humans. The degree of CSF penetration of an anticancer agent may be affected by its molecular weight, lipophilicity, and protein binding. Regardless of its in vitro activity, if a drug does not penetrate into the CSF, it is unlikely that it will be effective clinically against CNS tumors. Thus, we performed a pharmacokinetic study of continuous infusion topotecan in children with CNS tumors enrolled in phase I and phase II trials. The goals of this study were (a) to describe the CSF penetration of topotecan, (b) to generate a pharmacokinetic model that simultaneously describes both topotecan lactone and total concentrations in the CSF and plasma, and (c) to characterize the CSF and plasma pharmacokinetics of topotecan administered as a continuous infusion. As topotecan undergoes further phase II and phase III evaluation for the treatment of pediatric CNS tumors, such a pharmacokinetic model may be useful in prospectively designing topotecan dosing regimens capable of producing CSF levels which approach target cytotoxic concentrations.

Materials and methods

Patients and treatment protocols

Simultaneous plasma and CSF pharmacokinetic studies were performed on 17 patients (19 courses) enrolled in phase I or phase II trials of topotecan as described in Table 1. Eligibility requirements for the clinical protocols included the following: (1) diagnosis of a previously treated malignant tumor refractory to conventional therapy, or, a newly diagnosed high-risk tumor for which no conventional treatment exists, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, or a Karnofsky performance score greater than 50 for patients more than 10 years of age, or a Lansky score greater than 50 for patients less than 10 years of age, (3) adequate renal (serum creatinine < 1.5 mg/dl), hepatic (total bilirubin < 1.5 mg/dl and SGPT less than or equal to twice normal), and bone marrow function (ANC > 1,000/μl, and platelet count > 100,000/μl), and (4) recovery from the toxic effects of all prior therapy. All patients or parents signed statements of informed consent, consistent with federal and local institutional guidelines, which noted the investigational nature of this study.

Topotecan was administered to patients via an outpatient portable infusion pump. Patients received topotecan as either a 24-h or a 72-h continuous infusion at the doses shown in Table 1. Topotecan was repeated every 21 days, or as soon as hematologic toxicities from the prior cycle had resolved. Intrapatient dosage escalations occurred only in patients receiving the 24-h continuous infusion; those patients tolerating the first cycle of topotecan at a dose of 5.5 mg/m^2 per day, without grade 4 hematologic toxicity and with at least stable disease, had an escalation to 7.5 mg/m^2 per day in subsequent cycles.

Toxicity was monitored with weekly laboratory studies which included complete blood counts and serum chemistries (e.g. creatinine, BUN, total bilirubin, AST, albumin). Toxicity was assessed using the NCI Common Toxicity Criteria.

Sample collection

Blood and CSF samples were collected at the sampling times shown in Table 1. Blood samples were drawn from a venous access site, separate from the site of topotecan infusion, and placed in heparinized tubes. CSF samples were obtained from either a ventricular reservoir (VR) in patients with a ventricular-peritoneal shunt (12 patients, 14 courses) or from a lumbar puncture (LP) (5 patients, 5 courses). Serial postinfusion samples were obtained from seven patients with a VR.

Table 1 Topotecan treatment protocols and sampling

	Protocol #1	Protocol #2	Protocol #3	Protocol #4
Description	Phase I trial in refractory solid tumors	Phase I-II Trial in pediatric CNS tumors	Phase II trial in recurrent CNS tumors	Phase I trial in refractory pediatric solid tumors
No. of patients studied	3	5	5	4
Drug dosage & administration	1.0 mg/m^2/day as a 72-h CI[1]	5.5 (3 patients, 4 courses) or 7.5 mg/m^2/day (3 patients) as a 24-h CI	1.0 mg/m^2/day (3 patients) or 1.25 mg/m^2/day (2 patients) as a 72-h CI	0.5 mg/m^2/day as a 72-h CI (In combination with Carboplatin, AUC = 6.5 mg-min/ml)
Sampling				
Plasma	24 h, 48 h, prior to EOI[2], and post 0.25, 0.5, 1, 2, 4, 8 h	3 h and prior to EOI, and post 0.25, 0.5, 1, 2, 4, 6 h	24 h and prior to EOI, and post 0.5, 1, 4 h	24 h and prior to EOI
CSF[3]	24 h and prior to EOI, and post 1, 4 h	3 h and prior to EOI, and post 0.25, 1, 4 h	24 h and prior to EOI, and post 1, 4 h	24 h and prior to EOI

[1]CI = continuous infusion
[2]EOI = end of infusion
[3]CSF samples obtained via a lumbar puncture or from a ventricular reservoir

Sample preparation and assay

Topotecan exists as a pentacyclic structure with a lactone moiety in the terminal or E ring. In aqueous solution, the lactone undergoes rapid and reversible pH-dependent hydrolysis to the hydroxy-acid, the predominant form at physiologic pH [12, 30]. Because the lactone rapidly hydrolyses, blood and CSF samples were immediately processed in the clinic or at the patient's bedside, and assayed by HPLC as described previously [28]. The accuracy of the HPLC assay at 0.3 ng/ml was 95%, and the lower limit of quantification was 0.25 ng/ml.

Pharmacokinetic analysis

A three-compartment model (Fig. 1) was fitted simultaneously to topotecan lactone and hydroxy-acid concentrations in the plasma and CSF. The model, consisting of a compartment representing the CSF, plasma, and tissue, is structurally similar to one previously published that describes the CSF pharmacokinetics of topotecan in nonhuman primates [29]. Removal of drug from the CSF was parameterized as a clearance (CL_{CSF}). Before modeling, simplifying assumptions included: (a) infused drug was all in the lactone form, although it has been reported to vary from 84% to 94% in one study [15], (b) volume of distribution, exchange rate constants between compartments, and elimination from the plasma compartment were the same for the lactone and hydroxy-acid, consistent with the parallel disposition and elimination of topotecan lactone and total observed in a previous study of continuous infusion topotecan [28], and (c) the rate of conversion between the lactone and hydroxy-acid was the same in the three compartments; only small differences in these conversion rates have been observed in aqueous solutions and lipid bilayers [7].

The three-compartment model used included nine parameters: volume of the plasma or central compartment (V_c), volume of the CSF (V_{csf}), clearance of drug from the CSF (CL_{CSF}), intercompartmental exchange rate constants (K_{12}, K_{13}, K_{31}), forward and reverse rate constants for the lactone-to-hydroxy-acid conversion (K_{LH}, K_{HL}), and elimination rate constant from the central compartment (K_e). The volume of the CSF (V_{csf}) was set to 140 ml, a previously described value for an average patient of 11 years, 35 kg, and 0.96 m^2 [5]; the other eight parameters (V_c, CL_{CSF}, K_{12}, K_{13}, K_{31}, K_{LH}, K_{HL}, and K_e,) were estimated.

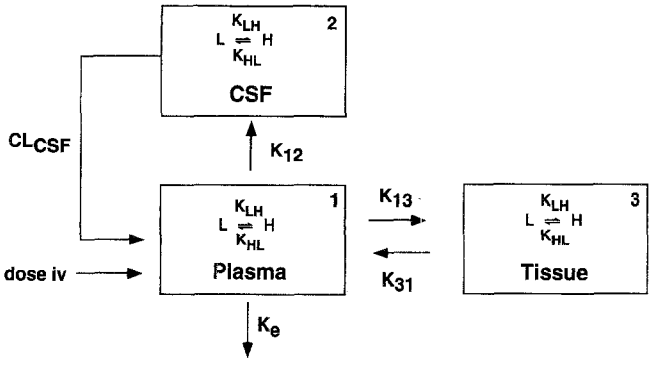

Fig. 1 Three-compartment model for topotecan lactone and total concentrations in the plasma and CSF (CL_{CSF}, clearance of drug from the cerebrospinal fluid (CSF), K_{12} exchange rate constant from the plasma to the CSF compartment, K_{13} and K_{31} exchange rate constants between the plasma and tissue compartment, K_{LH} and K_{HL} the forward and reverse rate constants for the lactone-to-hydroxy-acid conversion; K_e the elimination rate constant from the plasma or central compartment)

Pharmacokinetic parameters were estimated using MAP-Bayesian modelling as implemented in ADAPT II [11]. First, Bayesian priors for V_c, K_{13}, K_{31}, K_e, K_{LH}, and K_{HL}, were estimated by fitting a two-compartment model simultaneously to plasma topotecan lactone and total concentrations from 17 other patients receiving a 72-h continuous infusion [28], using maximum likelihood estimation (ADAPT II). Next, Bayesian priors for K_{12} and CL_{CSF} were established by fitting the three-compartment model simultaneously to topotecan lactone and total concentrations in plasma and CSF from six patients (with 18 to 24 observations per patient), using maximum likelihood estimation. Three of the six patients received a 24-h continuous infusion, and three received a 72-h continuous infusion. Finally, to estimate pharmacokinetic parameters for all patients, including those with fewer observations (4 to 16), the three-compartment model was fitted simultaneously to topotecan lactone and total concentrations in plasma and CSF from all courses (17 patients, 19 courses), using a MAP-Bayesian algorithm.

Calculated pharmacokinetic parameters include systemic clearance (CL_{sys}), the apparent half-life in plasma ($t_{1/2,\,plasma}$), and the apparent half-life in CSF ($t_{1/2,\,CSF}$) [14]. Values for area under the concentration-time curve (AUC) were numerically calculated from the final estimated parameters. Since the AUC from time 24 h postinfusion to infinity was less than 1% of the total in both the plasma and CSF, we report the AUC from time 0 to 24 h postinfusion (i.e. 48 or 96 h). Topotecan CSF penetration was defined as the CSF to plasma AUC ratio.

Statistical analysis

Pharmacokinetic parameters were summarized using descriptive statistics including median and range. The nonparametric Mann-Whitney test was used to compare (a) pharmacokinetic parameters and CSF penetration between patients receiving either the 24-h or the 72-h continuous infusion, and (b) pharmacokinetic parameters and CSF penetration between patients with CSF samples obtained from either a VR or a LP.

Results

Patient characteristics

The characteristics of the 17 patients studied are listed in Table 2. Although all patients had received prior chemotherapy, the study population was not heavily pretreated compared with our experience from other phase I studies. All patients had normal age-adjusted serum creatinine (median 0.5 mg/dl; range 0.3 to 0.9 mg/dl), total bilirubin (median 0.4 mg/dl; range 0.2 to 0.7 mg/dl), and serum albumin (median 4.2 g/l; range 3.5 to 4.8 g/dl).

Plasma and CSF pharmacokinetics

Topotecan lactone and total concentrations achieved in the CSF and plasma during the 24-h and the 72-h continuous infusion are listed in Tables 3 and 4. During both the 24-h and 72-h continuous infusion, the lowest CSF concentrations observed were in those patients

where the CSF was obtained from a LP. In two patients receiving 1.25 mg/m^2 per day topotecan, CSF samples were obtained simultaneously from both a VR and a LP, prior to the end of infusion. The ventricular and lumbar concentrations were 0.57 and 0.29 ng/ml, respectively, in one patient, and 1.77 and 1.23 ng/ml, respectively, in the other patient. Of note, the only patient studied to achieve a partial response received a 24-h continuous infusion. This patient had the highest ventricular CSF total concentration (21.0 and 21.7 ng/ml), and the second highest ventricular CSF lactone concentration (4.1 and 5.3 ng/ml) measured during the patient's first and second course. The presence of diffuse ventricular leptomeningeal tumor may have increased the degree of CSF penetration (0.54 and 0.59) observed in this patient.

Representative concentration-time profiles of topotecan lactone and total in the CSF and plasma during the 24-h and the 72-h continuous infusion are shown in Figs. 2 and 3, respectively. The relationship between the CSF and plasma concentrations predicted by our pharmacokinetic model, and the observed concentrations in the CSF and plasma are shown in Fig. 4. Of the predicted CSF lactone and total concentrations, 75% were within ± 20% of the observed concentrations; 89% of the predicted plasma lactone and total concentrations were within ± 20% of the observed concentrations. Thus, the pharmacokinetic model adequately described topotecan concentrations in the CSF and plasma.

Table 2 Patient characteristics

Boy/girls	9/8
Age, years Median (range)	12(1 to 16)
Weight, kg Median (range)	32.1 (8.1 to 80.4)
BSA, m^2 Median (range)	1.2 (0.5 to 2.0)
Prior treatment	
Surgery	10
Radiotherapy	15
Chemotherapy	9
Median no. of regimens (range)	1 (1 to 2)
Median no. of agents (range)	3 (2 to 5)
Autologous bone marrow transplants	2
Diagnoses	
Astrocytoma	4
Brain stem glioma	1
Ependymoma	2
Malignant glioma	6
Medulloblastoma	4

Table 4 Topotecan lactone (LAC) and total (TOT) concentrations in plasma during a 24-h and 72-h continuous infusion (CI)

Infusion length	Dose (mg/m^2/day)	Plasma LAC (ng/ml) Median (range)	Plasma TOT (ng/ml) Median (range)
24-h CI[a]			
	5.5	13.9 (10.2–16.3)	30.7 (26.6–31.1)
	7.5	16.9 (14.8–22.5)	37.4 (34.3–47.0)
72-hour CI[b]			
24-h sample	0.5	1.1 (0.70–1.1)	2.3 (1.4–2.6)
	1.0	2.2 (1.5–5.3)	4.6 (2.9–12.2)
	1.25	2.9 (2.6–3.2)	5.3 (4.5–6.2)
72-h sample	0.5	0.97 (0.74–1.1)	1.9 (1.4–2.6)
	1.0	1.8 (1.6–2.1)	3.9 (3.2–4.3)
	1.25	3.2 (3.0–3.4)	5.1 (5.10–5.12)

[a]Data represent samples obtained at 24 h (prior to the end of infusion) from 5 patients (7 courses)
[b]Data represent samples obtained at 24 h and/or 72 h (prior to the end of infusion) from 12 patients. Paired 24-h and 72-h samples were obtained from 8 of the 12 patients

Table 3 Topotecan lactone (LAC) and total (TOT) concentrations in cerebrospinal fluid (CSF) during a 24-h and 72-h continuous infusion

Infusion Length	Dose (mg/m^2/day)	CSF LAC (ng/ml) Median (range)		CSF TOT (ng/ml) Median (range)	
		VR[a]	LP[b]	VR	LP
24-h CI[c]					
	5.5	5.3 (4.1–7.4)	1.1	21.0 (14.7–21.7)	4.2
	7.5	4.6 (3.3–5.9)	1.7	11.9 (10.3–13.4)	6.3
72-h CI[d]					
24-h sample	0.5	0.81 (0.57–1.1)	–	1.2 (0.84–1.7)	–
	1.0	0.68 (0.40–0.95)	0.25 (0.24–0.61)	1.1 (0.95–1.2)	1.1 (1.02–2.2)
	1.25	0.41 (0.38–0.44)	–	1.4 (1.3–1.4)	–
72-h sample	0.5	0.86 (0.30–1.3)	–	1.3 (0.84–1.8)	–
	1.0	1.4 (0.78–1.7)	0.44	2.4 (2.2 –3.2)	1.9
	1.25	0.73 (0.57–0.88)	–	2.1 (1.8–2.5)	–

[a]CSF samples obtained from a ventricular reservoir
[b]CSF samples obtained from a lumbar puncture
[c]Data represents samples obtained at 24 h (prior to the end of the infusion) from 5 patients (7 courses)
[d]Data represents samples obtained at 24 h and/or 72 h (prior to the end of infusion) from 12 patients. Paired 24-h and 72-h samples were obtained from 8 of 12 patients

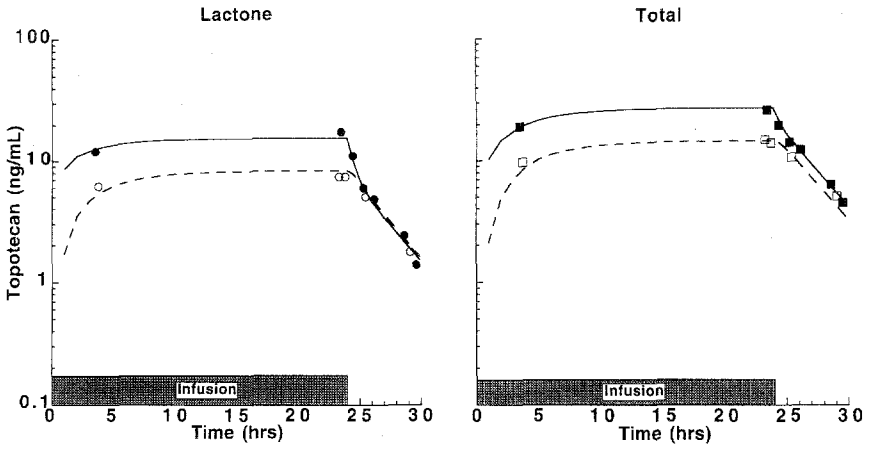

Fig. 2 Concentration versus time plot for a representative patient receiving a 24-h continuous infusion. The *solid and open symbols* represent topotecan concentrations in the plasma and CSF, respectively. The lines represent the best-fit curves using model fit parameters

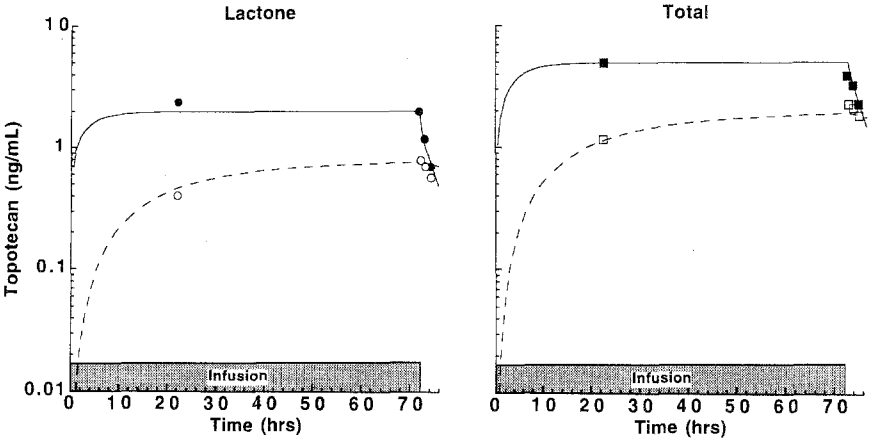

Fig. 3 Concentration versus time plot for a representative patient receiving a 72-h continuous infusion. The *solid and open symbols* represent topotecan concentrations in the plasma and CSF, respectively. The lines represent the best-fit curves using model fit parameters

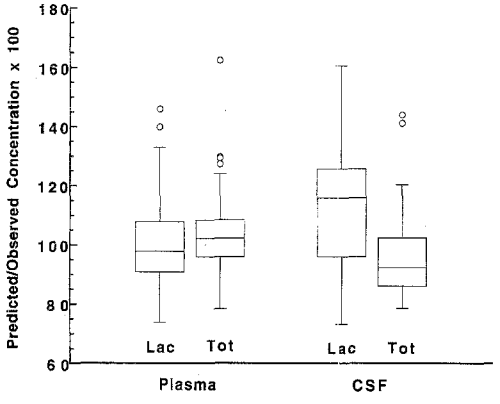

Fig. 4 Box plot for the relationship between model-predicted concentrations and observed concentrations expressed as a percent of observed concentration. The box defines the upper quartile and lower quartile, and encloses 50% of the data. The median is depicted as a line within the box. The lines extending from the top and bottom of each box mark the minimum and maximum. Outliers are depicted as individual circles

Table 5 Topotecan pharmacokinetic parameters from simultaneous modeling of the lactone and hydroxy-acid form

	CSF samples from a ventricular reservoir		CSF samples from a lumbar puncture	
Parameter	Median	Range	Median	Range
V_c (l/m^2)	16.8	11.1 to 19.6	11.7	5.5 to 16.9
CL_{CSF} (ml/h/m^2)	26.2	6.7 to 165.0	6.5	3.1 to 43.4
K_{12} (h^{-1})	0.0008	0.0002 to 0.01	0.0002	0.00009 to 0.0005
K_{13} (h^{-1})	0.39	0.30 to 1.40	0.33	0.30 to 0.65
K_{31} (h^{-1})	0.68	0.26 to 0.97	0.77	0.67 to 1.6
K_e (h^{-1})	1.3	0.66 to 1.8	1.5	1.1 to 1.9
K_{LH} (h^{-1})	1.7	0.72 to 3.3	2.8	1.5 to 4.4
K_{HL} (h^{-1})	1.5	0.88 to 2.7	1.7	1.0 to 3.0
Cl_{sys} (l/h/m^2)	19.8	12.1 to 30.4	21.9	6.2 to 28.6
$t1/2_{plasma}$ (h)	2.6	1.5 to 8.3	2.2	1.7 to 3.2
$t1/2_{CSF}$ (h)	4.8	1.8 to 73.0	13.5	4.5 to 37.6

The CSF and plasma pharmacokinetic parameters for all patients receiving continuous infusion topotecan are listed in Table 5. The final pharmacokinetic estimates obtained from MAP-Bayesian modelling for all patients, including those with fewer (4 to 16) observations, were similar to the pharmacokinetic estimates obtained using maximum likelihood estimation for those patients with 24 or more observations (data not shown). Pharmacokinetic parameters were compared between patients with CSF samples obtained from a VR, and patients with samples obtained from a LP for the following reasons: (a) CSF concentrations

obtained from a LP were overall lower than those obtained from a VR, and (b) patients with CSF samples obtained from a VR had ventricular-peritoneal shunts, which can alter normal physiological CSF flow. Comparison of pharmacokinetic parameters between these two patient populations showed a significant difference for V_c ($P = 0.04$), K_{12} ($P = 0.004$), and K_{LH} ($P = 0.03$). Comparison of pharmacokinetic parameters between patients receiving the 24-h continuous infusion and those receiving the 72-h continuous infusion did not reveal any significant differences. Two patients were less than 3 years old, and possibly had smaller V_{CSF} than the other patients; however, the pharmacokinetic parameter estimates for these patients were similar to the median value for all other patients. Four patients received a carboplatin infusion prior to the topotecan continuous infusion; systemic clearances for these patients were similar to those of the other 11 patients receiving continuous infusion topotecan (17.3, 21.1, 30.4, and 19.1 l/h per m^2).

The penetration of topotecan into the CSF during continuous infusion administration is shown in Fig. 5. For the 24-h continuous infusion, the median CSF penetration of topotecan lactone and total was 0.29 (range 0.10 to 0.59). For the 72-h continuous infusion, the median CSF penetration of topotecan lactone and total was 0.42 (range 0.11 to 0.97). CSF penetration between the 24-h and the 72-h continuous infusion was not significantly different ($P = 0.2$). As shown in Fig 5. (open symbols), the CSF penetration of topotecan into the lumbar space was lower than that into the ventricular space; this difference was statistically significant ($P = 0.02$). The median ratio of lactone AUC to total AUC in plasma for all patients was 0.42 (range 0.36 to 0.77); the median ratio in CSF was 0.42 (range 0.35 to 0.68).

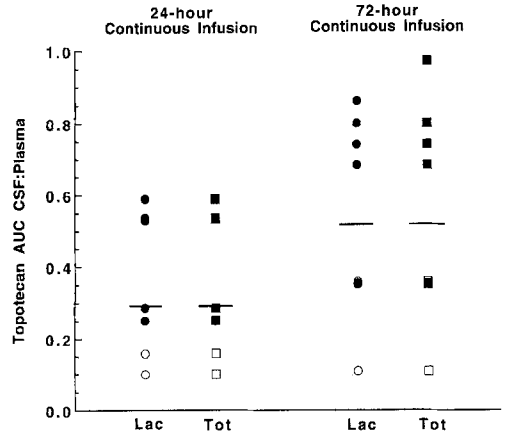

Fig. 5 Penetration of topotecan in the CSF during continuous infusion. Topotecan CSF penetration is described as the ratio of the topotecan lactone or total AUC in CSF to that in plasma. *Closed and open symbols* represent samples obtained from a ventricular reservoir or a lumbar puncture, respectively. The horizontal lines represent median values. (In the 72-h continuous infusion group, three patients overlap at 0.35)

Discussion

Although the plasma pharmacokinetics of topotecan have been previously described [2, 15, 16, 25, 28, 31, 32], this is the first report to document the CSF pharmacokinetics and penetration of topotecan in humans. The potential clinical importance of these data is underscored by the observation that this agent possesses significant activity against primary CNS tumors in preclinical studies [13], and responses have been noted in phase I trials [19, 20, 23, 24, 31].

The CSF penetration of topotecan reported in this study (Fig. 5) is significantly greater than other anticancer agents. With the exception of excellent CSF penetration of thiotepa [18], it is uncommon to find a CSF to plasma ratio greater than 0.2 for most anticancer agents. For example, the CSF to plasma ratio for the active metabolite of cyclophosphamide is 0.17 [1], etoposide has a ratio of less than 0.1 [17], and most nucleosides, such as cytarabine, rarely have a CSF to plasma ratio greater than 0.2 at conventional doses [33]. Although topotecan is a water-soluble agent, and the least lipophilic of the camptothecins [7], the significant CSF penetration of topotecan may be attributed to its low molecular weight (421 g/mol), and low protein binding ($< 20\%$), two features which are associated with improved blood–brain barrier penetration.

Although the median CSF penetration of topotecan observed during a 24-h continuous infusion (0.31) was similar to that reported in the nonhuman primate model [3], two patients exhibited higher CSF AUC ratios (0.54 and 0.59). Additionally, the administration of a 72-h continuous infusion was associated with increased CSF AUC ratios (median 0.42, range 0.11 to 0.97). The increased CSF AUC ratios of topotecan observed in this study compared to those in nontumor-bearing primates may reflect the phenomenon of a more permeable blood–brain barrier at sites of tumor involvement.

The CSF clearances (CL_{CSF}) observed in this pharmacokinetic study were highly variable (Table 5), although the median CSF clearances were in or near the range of bulk CSF flow (~ 20 to 30 ml/h). The higher CSF clearances observed were in those patients with ventricular-peritoneal shunts, which may be explained by the ability of these shunts to remove large volumes of CSF (e.g. 1000 ml/day). Since CL_{CSF} is the sum of all physiologic processes removing drug from the CSF, it is likely that other processes, in addition to bulk CSF flow, may be responsible for clearance of drug from the CSF (e.g. distribution into tissue). The median CSF half-lives observed during continuous infusion topotecan were longer than those observed in the plasma (Table 5); these findings are consistent with the observation that the half-lives of most anticancer agents are longer in the CSF than in the plasma [21].

When topotecan is given primarily as the lactone form, the equilibrium between the lactone and hydroxy-acid is established within 1 to 6 h at physiologic pH [6, 7, 9, 25, 29, 32]. The median value for the lactone to hydroxy-acid equilibrium constant (K_{LH}) (Table 5) was similar to that published for nonhuman primates [6, 7, 29], whereas, the median values for the hydroxy-acid to lactone equilibrium constant (K_{HL}) for both the 24-h (1.53 hr^{-1}) and the 72-h (1.7 hr^{-1}) continuous infusion were approximately fivefold higher. However, the accuracy of estimating a physicochemical parameter in a highly parameterized pharmacokinetic model is problematic, especially if the sampling strategy is not designed to be informative of that parameter specifically. During both the 24-h and the 72-h continuous infusion, the plasma lactone to total ratios, apparent plasma half-lives, and systemic clearances reported in this study were similar to values described previously in pediatric patients receiving continuous infusion topotecan (Table 5) [2, 28].

A three-compartment model adequately described the topotecan lactone and total concentrations in the CSF and plasma (Fig. 4). More complex pharmacokinetic and physiological models have been used to describe CSF concentration data for other anticancer agents. A few features of these models include the addition of separate compartments for brain tissue, the ventricles, and the lumbar space, and the incorporation of physiologic flow rates between compartments [4, 10]. The three-compartment model presented here does not incorporate all physiologic processes affecting drug disposition in the CSF. Additionally, it does not explicitly account for differences in drug concentrations between the ventricles and the lumbar space, as has been previously described for other anticancer agents [26]. Nevertheless, the model presented here adequately described CSF concentration data available from ventricular and lumbar sites in different patients.

In addition to the treatment of primary CNS tumors, the significant CSF penetration of topotecan suggests the potential of this anticancer agent in the treatment of meningeal leukemia. Continuous infusion topotecan is currently being evaluated in phase I and phase II trials for the treatment of acute leukemia. Furthermore, the direct intrathecal administration of topotecan is under study in pediatric patients with CNS leukemia. Further clinical evaluation will determine the therapeutic utility of topotecan administered either systemically or intrathecally in the treatment of meningeal leukemia.

The significant CSF penetration of topotecan observed in this study, and the antitumor activity seen in both the xenograft model and during early phase I and phase II evaluation, suggest that topotecan may be an important new addition to the treatment of primary CNS tumors, as well as for meningeal leukemia. As topotecan undergoes further clinical development, the pharmacokinetic model presented here may aid in the design of optimal doses and schedules of administration.

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