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Plasma and cerebrospinal fluid pharmacokinetics of cytosine arabinoside in dogs*

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Summary. Cytosine arabinoside (ara-C) is a component of many protocols for the treatment of CNS (central nervous system) leukemia and lymphoma in humans and dogs. It is also used for the prophylaxis of CNS metastasis in acute lymphoblastic leukemia. Although ara-C enters the cerebrospinal fluid (CSF) of human cancer patients after i.v. administration, it is unclear whether a similar CNS distribution occurs in humans whose blood-brain barrier has not been compromised by invasive disease. No information on the penetration of ara-C into the CSF in dogs is available. We studied the plasma and CSF pharmacokinetics of 600 mg/m^2 ara-C in ten healthy male dogs after its administration as a rapid i.v. bolus (six dogs) or as a 12-h i.v. infusion (four dogs). Ara-C concentration in blood and CSF samples was determined by high-performance liquid chromatography (HPLC). After an i.v. bolus of ara-C, the mean plasma distribution half-life was 7.1 ± 4.5 min and the mean elimination half-life was 69 ± 28 min. The mean plasma clearance was 227 ± 125 ml min^{-1} m^{-2}. The peak concentration of ara-C in the CSF was 29 ± 11 μM, which occurred at 57 ± 13 min after the ara-C bolus. The CSF elimination half-life was 113 ± 26 min. During a 12-h infusion of ara-C (50 mg m^{-2} h^{-1}), the plasma steady-state concentration was 14.1 ± 4.2 μM, the CSF steady-state concentration was 8.3 ± 1.1 μM, and the CSF: plasma ratio was 0.62 ± 0.14. The plasma elimination half-life was 64 ± 19 min and the plasma clearance was 214 ± 69 ml min^{-1} m^{-2}. The CSF elimination half-life was 165 ± 28 min. No clinically significant toxicity was observed over a 21-day period following drug administration in either of the treatment groups. Our data indicate that ara-C crosses the blood-brain barrier in normal dogs and that i.v. administration of this drug has potential as a treatment modality for neoplasia involving the CNS.

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Introduction

Cytosine arabinoside (ara-C) is an S-phase-specific antineoplastic agent that is one of the drugs of choice for the treatment of acute myelogenous leukemia (AML) in man [5, 14, 27, 30]. Ara-C is a component of many protocols for the treatment of lymphoma and some types of leukemia in dogs [6, 7, 24, 32, 35]. Intrathecal and high-dose i.v. ara-C have been demonstrated to clear the cerebrospinal fluid (CSF) of malignant cells in meningeal leukemia and lymphoma in both dogs [6] and man [2, 12, 23, 34, 36] and to decrease the incidence of CNS relapse in cases of acute lymphoblastic leukemia and lymphoma in man [17, 21, 28, 31]. Ara-C has also been used in protocols for the treatment of other primary and metastatic malignancies of the nervous system [13, 29].

The pharmacokinetics of ara-C in the plasma and the CSF have been well established in human cancer patients [1, 3, 4, 8, 10, 15, 16, 23, 26, 33]. In these patients, penetration of ara-C into the CNS after i.v. administration has been well documented. However, it is not known whether the blood-brain barrier of these subjects has remained uncompromised in view of their invasive disease. Although a limited number of studies have investigated the plasma pharmacokinetics of ara-C in dogs [9, 11, 19, 22], the CSF pharmacokinetics of this drug in dogs have not been studied. An understanding of the behavior of ara-C in the CSF in dogs is necessary for the development of treatment protocols for CNS neoplasia in this species. If significant differences in ara-C pharmacokinetics were observed in normal dogs as compared with those reported for human cancer patients, the question as to whether neoplastic disease processes can significantly alter the penetration of ara-C into the CNS should be addressed more fully. The objectives of the present study were to establish whether ara-C penetrates the canine blood-brain barrier and to investigate the plasma and CSF pharmacokinetics of ara-C in normal healthy dogs.

Materials and methods

Animals and samples. Ten male hound dogs were used in this study. The animals ranged in weight from 13–32 kg and were established to be in good health based on the results of physical examinations, complete blood counts, and serum biochemical analyses. CSF collected at the start of each experiment was analyzed and found to be normal in all dogs. Two series of experiments were performed: in the first, six dogs received 600 mg/m^2 ara-C as a rapid i.v. bolus, and in the second, four dogs received the same dose of ara-C as a 12-h infusion.

The six dogs in the bolus study were anesthetized using isofluorane as a single agent. A spinal needle was placed into the cervical subarachnoid space. Ara-C (50 mg/ml) was injected at a dose of 600 mg/m^2 as a rapid i.v. bolus over 20 s via an i.v. catheter in the saphenous vein. Blood and CSF samples were collected through a jugular catheter and the spinal needle, respectively, at 0, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 min after drug administration. Sample collection was discontinued if blood contamination of the CSF was detected visually or if the spinal needle became displaced from the subarachnoid space. Blood samples (2 ml) were collected into tubes containing ethylenediaminetetraacetic acid (EDTA), and plasma was recovered after centrifugation at 1,000 *g* for 5 min. CSF samples (0.5 ml) were collected in plain glass tubes. Plasma and CSF samples were stored on ice until extraction and assay, which were performed within 5 h of sample collection. At the conclusion of the sampling period, all dogs were allowed to recover from anesthesia. Dogs 1–3 were reanesthetized at 6 or 8 h after drug administration and additional blood and CSF samples were collected.

The four dogs in the infusion study received 600 mg/m^2 ara-C given as a continuous 12-h i.v. infusion (50 mg m^{-2} h^{-1}) using a Harvard infusion pump (Model 940; Harvard Apparatus, Millis, Mass.) via an i.v. catheter in the cephalic vein. The dogs were anesthetized at 1 h prior to the completion of the 12-h infusion and remained anesthetized until 3 h after termination of the infusion. Blood samples were collected at 0, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 690, and 720 min into the infusion and at 30, 60, 90, 120, 150, and 180 min after its completion. CSF samples were collected at 660, 690, and 720 min into the infusion and at 30, 60, 90, 120, 150, and 180 min after its completion. In this series of experiments, plasma and CSF samples were obtained as described above and were frozen and stored at –80° C. Samples were assayed within 48 h of collection.

All ten animals were monitored for 21 days after ara-C administration by daily physical examinations. Complete blood counts and platelet counts were performed three times weekly for 3 weeks.

HPLC assay for Ara-C. Aliquots (0.5 ml) of plasma and CSF were extracted on ice with 0.5 ml 0.66 M perchloric acid and were centrifuged at 2,000 *g* for 5 min. Aliquots (50 µl) of the clear supernatant were analyzed in duplicate by HPLC. The HPLC system consisted of a Waters model 6000 A pump, a Z-module radial compression unit, and a C-18 µ-Bondapak reverse-phase column (8 mm × 10 cm) containing 10 µm packing material (Waters Associates, Milford, Mass.). The mobile phase was 2.5 mM potassium phosphate (pH 3.25), which was run at a flow rate of 2 ml/min. Nucleoside detection was based on UV absorption at 270 nm using a Waters 490 programmable multiwavelength detector. Peak identity was confirmed by co-elution of samples with purified standards using a 254/270 nm absorbance ratio. Aliquots were injected onto the column by a Waters WISP 710 B autosampler, and the chromatograms were integrated and analyzed using the chromatography analysis software MAXIMA 820 (Dynamic Solutions, Milford, Mass.).

Assay validation. The assay was validated for intra-assay precision, recovery, sensitivity, and stability of fresh and frozen samples. Intra-assay precision was determined by three repeated measurements on aliquots of the same sample within one assay. Recovery was determined by adding known amounts of purified standards to canine serum or CSF samples and then measuring the recovery. Sensitivity was determined by adding known amounts of purified standards to canine serum and CSF and then establishing the minimum ara-C concentration that could be distinguished from the baseline value. The stability of fresh and frozen samples in the presence and the absence of tetrahydrouridine (THU) was determined by repeated measurements on aliquots of the same sample over 5 h and 7 days, respectively. Since we found no difference in the ara-C concentration measured in the presence or absence of THU in our initial validation experiments, all plasma and CSF ara-C assays were performed in the absence of THU.

Pharmacokinetics. Pharmacokinetic curve-fitting based on sums of exponentials was carried out using the nonlinear regression program SAS PROC NLIN (SAS Institute Inc., Cary, N. C.), with starting values being obtained from a preliminary analysis using the curve-fitting software RSTRIP (Micromath, Inc., Salt Lake City, Utah.). The goodness of fit for each fitted curve was assessed by calculating the coefficient of determination (CD) as defined by the equation:

$$CD = 1-[\Sigma(y_i-\hat{y}_i)^2/\Sigma(y_i-\bar{y})^2],$$

where y_i is the observed concentration at the ith observation time, $\hat{y}_i$ is the corresponding fitted concentration, and $\bar{y}$ is the time average of the observed concentrations. Derived quantities such as half-lives were calculated from the fitted curves.

In the bolus study, plasma and CSF data were fitted by biexponential curves. Fitted curves were restricted to satisfy the following biological constraints: (1) Both plasma and CSF curves were restricted to give nonnegative concentrations at all times. (2) CSF curves were forced to a concentration of zero at time zero. (3) Plasma curves were restricted such that the concentration at time zero ($c_{pk\ max}$) could not exceed a maximal value calculated from the smallest possible volume of distribution for ara-C (total plasma volume); this maximum was determined from the body weight, assuming that the total plasma volume constitutes 5% of the body weight [20]. The clearance, mean residence time (MRT), and steady-state volume of distribution (V_{dss}) were calculated from the fitted curves using the following formulae:

$$\text{Clearance} = \text{dose/AUC},$$
$$\text{MRT} = \text{AUMC/AUC}, \text{ and}$$
$$V_{dss} = \text{dose} \times \text{AUMC/AUC}^2,$$

where AUC is the area under the curve and AUMC is the area under the moment curve.

In the infusion study, the plasma steady-state concentration for each dog was calculated as the average of the last five concentrations measured before the induction of anesthesia. The CSF steady-state concentration for each animal was calculated as the average of the first three concentrations measured following the induction of anesthesia and prior to termination of the infusion. The total body clearance was calculated from the formula clearance = infusion rate/plasma steady-state concentration. Decay data were fitted to single exponential curves. In both the bolus and the infusion studies, the clearance and V_{dss} values were normalized to each dog's body surface area.

Results

Assay validation

Good baseline separation of ara-C from its metabolite arabinofuranosyl uracil (ara-U) and from the naturally occurring nucleosides cytidine and deoxycytidine was achieved (Fig. 1). Typical retention times were 4.7 min for cytidine, 5.4 min for ara-C, 6.2 min for hypoxanthine, and 8 min for ara-U. The mean intra-assay coefficient of variation was 1.6%, and recovery ranged from 96% to 106%. In all, <5% of the ara-C was lost from fresh serum and CSF samples over 5 h at room temperature or from samples that had been frozen at –80° C for 7 days. The addition of THU to the samples did not change the rate of loss of ara-C under these conditions, suggesting that very little cytidine deaminase is present in dog plasma [19] and that routine addition of THU to canine samples is unnecessary. The sensitivity

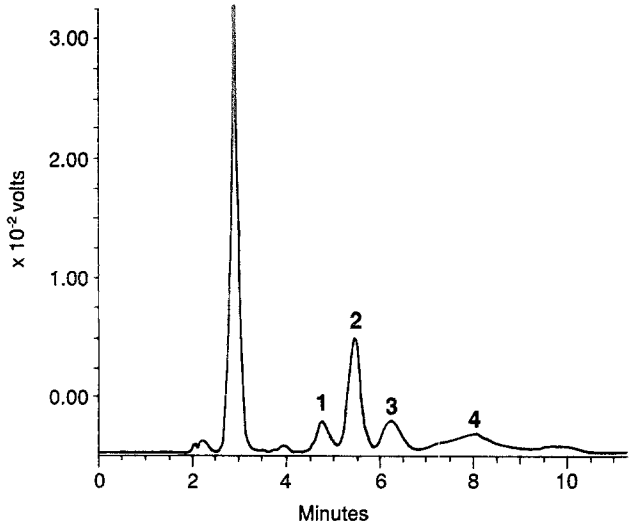

Fig. 1. HPLC chromatogram of a CSF sample in a dog that received i. v. ara-C. *Peak 1*, Cytidine (retention time, 4.7 min); *peak 2*, ara-C (retention time, 5.4 min); *peak 3*, hypoxanthine (retention time, 6.2 min); *peak 4*, ara-U (retention time, 8 min)

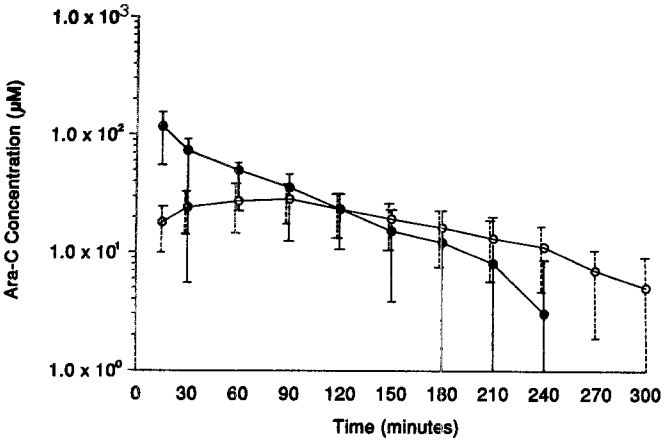

Fig. 2. Mean plasma and CSF concentrations of ara-C in 6 dogs after i. v. administration of 600 mg/m^2 ara-C. *Closed circles* denote plasma ara-C concentrations and *open circles* denote CSF concentrations. Points are joined by line segments for ease of viewing; note that fitted curves are not shown. Bars denote 1 SD from the mean

was approximately 0.5 μM in CSF and 1 μM in plasma. Assay sensitivity was sometimes limited by the amount of interfering endogenous metabolites in each animal's serum or CSF, necessitating the assay of a preinfusion sample to ensure that the calculations were accurate.

Pharmacokinetic analysis

The mean plasma and CSF ara-C concentrations obtained for all dogs in the bolus study are plotted on a semilogarithmic scale in Fig. 2. The decline in the plasma concentration was well described by a biexponential model. In dog 6, the alpha half-life could not be estimated from the data, as the best-fitting curve showed zero contribution from the alpha phase, apparently because the alpha phase in this dog was extremely short. The constraints at time zero affected only the fitted curves for dogs 2 and 4, holding their fitted concentration at time zero to 1,590 and 1,450 μM, respectively. The pharmacokinetic parameters for ara-C in plasma are listed in Table 1. The elimination half-life was 69 ± 28 min and the AUC was 11,700 ± 5,100 μM min.

Table 1. Plasma pharmacokinetic parameters for individual animals after a single i. v. bolus of 600 mg/m^2 ara-C

Dog	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	AUC ($\times 10^2$ μM min	MRT (min)	C (ml min^{-1} m^{-2})	V_{dss} (l/m^2)	CD
1	5.9	64	116	78	185	14.5	0.99
2	2.5	62	160	61	134	8.3	0.99
3	12.2	122	171	145	126	18.1	0.99
4	3.5	51	146	42	147	6.2	0.99
5	11.4	72	58	86	370	32	1
6	–	42	53	61	403	24.6	1
Mean	7.1	69	117	79	227	17.3	0.993
SD	4.5	28	51	36	125	9.8	0.005

All values were calculated from fitted biexponential curves. $t_{1/2\alpha}$, Distribution half-life; $t_{1/2\beta}$, elimination half-life; AUC, area under the curve; MRT, mean residence time; C, total body clearance; V_{dss}, volume of distribution at steady state; CD, coefficient of determination

Table 2. CSF pharmacokinetic parameters for individual animals after a single i. v. bolus of 600 mg/m^2 ara-C

Dog	$t_{1/2}$ (min)	AUC $\times 10^2$ μM min	PT (min)	PC (μM)	CSF/ Plasma	CD
1	118	89	46	40	0.62	0.95
2	140	80	56	30	0.47	0.96
3	122	83	76	30	0.57	0.9
4	109	93	62	40	0.87	0.94
5	126	40	60	16	0.59	0.93
6	64	23	40	17	0.37	0.97
Mean	113	68	57	29	0.58	0.94
SD	26	29	13	11	0.17	0.02

All values were calculated from fitted biexponential curves. $t_{1/2}$, Elimination half-life; AUC, area under the curve; Pt, time of peak concentration; PC, peak concentration; CSF/plasma, ratio of CSF concentration to plasma concentration at the time of the CSF peak; CD, coefficient of determination

The change in CSF ara-C concentration following an i. v. bolus was well described by a biexponential model, demonstrating a distribution phase into the CSF and an elimination phase from the CSF. The pharmacokinetic parameters for ara-C in the CSF are shown in Table 2. The elimination half-life was 113 ± 26 min. The AUC was 6,800 ± 2,900 μM min which was significantly smaller (Student's t-test, $P = 0.0047$) than the mean plasma AUC. The peak concentration of ara-C in the CSF after i. v. bolus administration was 29 ± 11 μM, which occurred at 57 ± 13 min after drug injection. The CSF: plasma concentration ratio at the time of the CSF peak was 0.58 ± 0.17. Concentrations of ara-C were not detectable in plasma or CSF at 6 or 8 h after i. v. bolus injection in the three dogs from which these samples were collected.

The mean plasma and CSF ara-C concentrations found for the four dogs in the infusion study are plotted on a

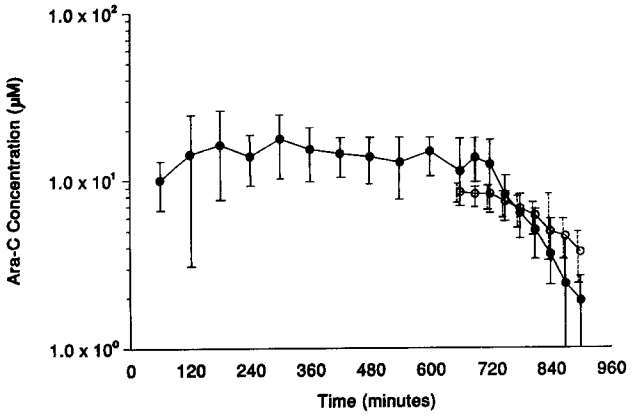

Fig. 3. Mean plasma and CSF concentrations of ara-C in 4 dogs both during and for 3 h after the termination of a 12-h continuous i. v. infusion of 600 mg/m^2 ara-C. *Closed circles* denote plasma concentrations and *open circles* denote CSF concentrations. Anesthesia was induced at 630 min, and the infusion was terminated at 720 min. Points are joined by line segments for ease of viewing; note that fitted curves are not shown. Bars denote 1 SD from the mean

semilogarithmic scale in Fig. 3. The pharmacokinetic parameters for ara-C in plasma and CSF are shown in Table 3. The steady-state plasma concentration was 14.1 ± 4.2 μM, and the steady-state CSF concentration was 8.3 ± 1.1 μM. The CSF: plasma ratio was 0.62 ± 0.14. The decline in both plasma and CSF drug concentrations after termination of the infusion was well described by a single exponential model, demonstrating a plasma elimination half-life of 64 ± 19 min and a CSF elimination half-life of 165 ± 28 min.

Toxicity

No clinical abnormalities were detected during the 3 weeks of observation in any of the ten dogs. Hematologic evaluation revealed mild thrombocytopenia in three of the six dogs that were given 600 mg/m^2 ara-C as an i.v. bolus (range, 115–170,000 platelets/mm^3; normal values >200,000 platelets/mm^3; nadir, 8–10 days). Thrombocytopenia was not observed in dogs that received the same dose as a 12-h infusion. No abnormalities were detected in the total leukocyte count, the neutrophil count, or the hematocrit of any of the dogs following ara-C administration by either route.

Discussion

The present study confirmed that ara-C crosses the blood-brain barrier in normal dogs under the experimental conditions described. In this study, as in other canine studies [9, 19], the disappearance of ara-C from the plasma was biphasic, showing a rapid distribution phase and a slower elimination phase. The half-life of drug elimination from plasma was similar in both of the treatment groups but was slightly shorter than the values reported elsewhere for the dog (2–3 h) [9, 19]. The total body clearance of ara-C from plasma in the present study was similar in both treatment groups (Tables 1, 2). This parameter has not been reported in previous canine studies. The V_{dss} value calculated for ara-C in this study (17.3 ± 9.8 l/m^2 or 0.64 ± 0.39 l/kg), however, was comparable with that reported elsewhere for the dog (1.07 l/kg) [9]. In our study, the half-life of ara-C elimination from the CSF was about 30% shorter following an i.v. bolus injection than after the termination of a 12-h i.v. infusion (Student's t-test, $P = 0.017$). This was expected since after i.v. infusion, the distribution of ara-C between plasma and CSF is at steady-state, whereas after i.v. bolus injection, it continues between the CNS and the other systemic compartments. The plasma and CSF steady-state concentrations achieved after a 12-h infusion (Table 3) were above or within the range of 1–10 μM, which is considered to be cytotoxic for sensitive neoplastic cells [18, 25].

The plasma half-lives following i.v. bolus injection and i.v. infusion and the CSF elimination half-life after i.v. infusion in dogs were comparable with those previously reported in most human studies [1, 4, 15, 16, 23, 26]. The total body clearance of ara-C in dogs was substantially lower than the values reported for humans [4, 16, 26, 33]. For example, Capizzi et al. [4] reported a mean total body clearance of 1,440 ml/min for a group of five patients. Since the mean body surface area of these patients was 1.8 m^2, this clearance value is equivalent to 800 ml min^{-1} m^{-2} which is approximately 4-fold that obtained in the

Table 3. Plasma and CSF pharmacokinetic parameters for individual animals after a 12-h i.v. infusion of 600 mg/m^2 ara-C

Dog	Plasma [SS] (μM)	CSF [SS] (μM)	CSF/plasma	Plasma $t_{1/2}$ (min)	CSF $t_{1/2}$ (min)	CD (plasma)	CD (CSF)	C (ml min^{-1} m^{-2})
7	19.2	8.9	0.46	48	186	0.98	0.95	146
8	13	7.6	0.58	64	167	0.86	0.92	215
9	9.1	7.2	0.79	54	125	0.92	0.99	308
10	15.1	9.5	0.63	90	182	0.95	0.93	185
Mean	14.1	8.3	0.62	64	165	0.93	0.95	214
SD	4.2	1.1	0.14	19	28	0.05	0.03	69

Plasma [SS], Steady-state plasma concentration; CSF [SS], steady-state CSF concentration; CSF/plasma, steady-state CSF: plasma concentration ratio; Plasma $t_{1/2}$, plasma elimination half-life calculated from the fitted exponential curve; CSF $t_{1/2}$, CSF elimination half-life calculated from the fitted exponential curve; CD (plasma), coefficient of determination for the plasma fitted exponential curve; CD (CSF), coefficient of determination for the CSF fitted exponential curve; C, total body clearance calculated from the plasma steady-state concentration and the ara-C infusion rate

present study. This difference in ara-C clearance in dogs as compared with humans was also reflected in the higher plasma steady-state concentration following i.v. infusion that was obtained in our study as compared with that found in equivalent human studies [8, 23]. The reason for this interspecies difference is not clear, but it may reflect lower plasma cytidine deaminase activity [19] or lower excretion of ara-C and its metabolites in dogs. It is difficult to compare the CSF ara-C concentrations achieved in the present study with those achieved in human studies because of the wide variation in doses and rates of infusion; however, the steady-state CSF: plasma ratio obtained in our study was higher than that achieved in most human studies [3, 18, 26]. Values reported for the CSF: plasma ratio in human studies range from 0.1 [3, 26] to 0.4 [18]. No clinically significant toxicity was observed in dogs after i.v. bolus injection or i.v. infusion of ara-C at 600 mg/m^2. This is consistent with the data reported for human cancer patients, in whom only very high doses of ara-C produced hematotoxicity after a single bolus injection.

There were two factors in the design of the present study that could have affected the penetration of ara-C into the CSF. Placement of the spinal needle could have disrupted the integrity of the blood-brain barrier and increased the penetration of drug into the CSF. This effect was minimized by placing the spinal needle only once and by discontinuing the study if the needle became displaced or if blood contamination of the CSF sample was detected. General anesthesia also has the potential to modify the characteristics of the blood-brain barrier. The effect of anesthesia was minimized by the use of a single gaseous anesthetic (isofluorane) without additional premedication or induction agents. Also, in the infusion study, anesthesia was not induced and CSF samples were not collected until steady-state plasma and CSF concentrations had been reached. Since ara-C concentrations in the CSF did not increase with repeated sampling during the infusion, this suggests that needle placement and anesthesia had little effect.

We conclude from the present study that ara-C crosses the blood-brain barrier in normal dogs. The CSF and plasma pharmacokinetics of ara-C in dogs were similar in many respects to those reported in human studies. However, differences such as lower total body clearance and higher CSF: plasma ratios were observed in dogs. Cytosine arabinoside has potential as a treatment modality for neoplasms involving the CNS in dogs. In humans, all studies investigating the pharmacokinetics of ara-C have been performed in patients presenting with leukemia, many of whom may have clinical or subclinical neoplastic CNS involvement [21]. The penetration of ara-C into the CNS in normal humans has not been investigated. We showed that ara-C penetrates the blood-brain barrier in normal dogs to an extent similar to that previously documented in human cancer patients.

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