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Borocaptate sodium: A potential boron delivery compound for boron neutron capture therapy evaluated in dogs with spontaneous intracranial tumors

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ABSTRACT **Borocaptate sodium ($Na_2B_{12}H_{11}SH$) is a boron-carrying compound under consideration for use in boron neutron capture therapy. The biodistribution of boron from borocaptate sodium administration will partly determine boron neutron capture therapy efficacy and normal tissue radiation tolerance. The biodistribution of boron was determined in 30 dogs with spontaneous intracranial tumors at 2, 6, or 12 hr after intravenous borocaptate sodium infusion. Blood and tissue boron concentrations were measured using inductively coupled plasma atomic emission spectroscopy. Mean tumor boron concentration (mean ± standard error) was 35.9 ± 4.6 (n = 15), 22.5 ± 6.0 (n = 9), and 7.0 ± 1.1 μg of boron per g (n = 6) at 2, 6, and 12 hr, respectively, after borocaptate sodium infusion. Peritumor boron concentrations were elevated above that of normal brain in half of the dogs. Normal brain boron concentration (mean ± standard error) was 4.0 ± 0.5, 2.0 ± 0.4, and 2.0 ± 0.3 μg of boron per g at 2, 6, and 12 hr after infusion, respectively. Some cranial and systemic tissues, and blood, had high boron concentration relative to tumor tissue. Geometric dose sparing should partly offset these relatively high normal tissue and blood concentrations. Borocaptate sodium biodistribution is favorable because tumor boron concentrations of recommended magnitude for boron neutron capture therapy were obtained and there was a high tumor-to-normal brain boron concentration ratio.**

Boron neutron capture therapy (BNCT) is an experimental form of radiation therapy for cancer that results in targeted high linear energy transfer (LET) radiation. BNCT has a number of theoretical advantages over conventional low LET radiation therapy and has recently been reviewed (1, 2). The localization of a boronated compound within tumor tissue is critical to the success of BNCT, and multiple compounds are under development as potential boron carriers. Promising biodistribution results were obtained with the administration of borocaptate sodium (BSH) in rodents with experimental tumors (3). BSH has low relative toxicity, is available in a standardized form, and has produced favorable results during Japanese clinical trials in humans with malignant brain tumors (4). However, few data are available on biodistribution and pharmacokinetics of BSH, and data are needed prior to approval of human pharmacokinetic trials in the United States. Studies using dogs with spontaneous brain tumors were performed to evaluate the relative biodistribution of BSH and potential implications for use of BSH for BNCT are discussed.

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MATERIALS AND METHODS

Dogs with spontaneous intracranial tumors were referred by regional veterinary practitioners. Diagnosis of intracranial tumors was based on results of pre- and post-contrast magnetic resonance imaging and computed tomography of the brain. BSH (natural isotopic ratio: 80% ^{11}B, 20% ^{10}B; Callery Chemical, Pittsburgh) was administered intravenously at 55 mg of boron per kg of body weight dissolved in 11 ml of physiological saline per kg of body weight at a rate of 1 mg/kg of body weight·min^{-1}. Serial venous blood and urine samples were obtained during and following infusion. Euthanasia was performed by an intravenous overdose of barbiturate 2, 6, or 12 hr following the end of BSH infusion. Multiple samples of tumor, peritumor tissue, standard regions of normal brain, and other normal tissues were obtained for boron and histological analysis.

Total elemental boron (a summation of ^{10}B and ^{11}B) concentrations for serum and tissues were derived by inductively coupled plasma atomic emission spectroscopy (5). Size and number of tumor and peritumor samples were dictated by the sensitivity of boron analysis. Initial studies with dogs sampled 12 hr postinfusion required 1-g sample sizes. Sample sizes of 100 mg were adequate for analysis of tissues obtained from dogs killed up to 6 hr following BSH infusion, due to higher boron concentrations in earlier postinfusion time periods. Smaller samples can be analyzed if tissue boron concentration > 0.8 μg/g. Relative accuracy and precision were evaluated by use of percent recovery standard (scandium) to verify acceptability of sample preparation, an internal standard (yttrium) to correct for variation in sample aspiration rates, and duplicate sample analysis with calculation of relative percent differences.

Boron concentration means and standard deviations (SD) were calculated for each dog's normal brain, tumor, and peritumor tissues. Mean tissue boron concentrations and standard errors of the mean (SEM) were calculated for each sampling time, using mean tissue boron concentrations for all dogs sampled at that time period. Boron concentration data from individual dogs are expressed as means ± SD; tissue boron concentration data averaged from multiple dogs sampled at a particular time period are shown as means ± SEM. The 99% confidence interval for normal brain boron concentration was calculated for each sample time and used as a standard for evaluating the magnitude of peritumor boron concentrations.

Abbreviations: BNCT, boron neutron capture therapy; BSH, borocaptate sodium; LET, linear energy transfer; TumBrnR, tumor-to-normal brain boron concentration ratio; TumBldR, tumor-to-blood boron concentration ratio.

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Linear regression analysis was used to evaluate the relationship of time with mean absolute tumor boron concentration, tumor-to-normal brain boron concentration ratios (TumBrnRs), and tumor-to-blood boron concentration ratios (TumBldRs). TumBrnR was calculated by dividing each dog's mean tumor boron concentration by the dog's mean normal brain boron concentration, and TumBldR was calculated by dividing each dog's mean tumor boron concentration by the dog's blood boron concentration at the time of euthanasia.

RESULTS

Thirty dogs with intracranial tumors were studied (Table 1 and Fig. 1). Most tumors were focally distinct, with the exception of dogs 43, 49, and 55, sampled at 6 hr, which had diffusely infiltrating low-grade astrocytomas. Five additional dogs with nonneoplastic intracranial lesions (not shown) received BSH and their data are included in the normal tissue boron concentrations.

Mean tumor boron concentration for all dogs at each sample period was 35.9 ± 4.6, 22.5 ± 6.0, and 7.0 ± 1.1 μg of boron per g at 2, 6, and 12 hr, respectively. Focal tumor boron concentrations had a linear relationship with time ($P < 0.01$, $r^2 = 0.5846$, $n = 27$) (Fig. 2). TumBrnRs ranged from 1.3 to 19.8 μg of boron per g (Table 2). TumBldRs were <1.0 for all but three dogs (dogs 25, 59, and 127), ranged from 0.04 to 1.4, and did not change with time (Table 2). Normal brain boron concentration 99% confidence intervals were 2.5–5.4 (4.0 ± 0.5), 1.3–3.2 (2.0 ± 0.4), and 0.8–3.2 (2.0 ± 0.3 μg of boron per g) at 2, 6, and 12 hr, respectively.

Table 1. Tumor-bearing subjects in BSH biodistribution study

Dog no.	Breed	Age, yr	Gender	Tumor type
	Sampled 2 hr after end of BSH infusion			
20	Golden retriever	10	♂	Meningioma
39	Dachshund	13	♂	Meningioma
59	Blue heeler	11	♀	Meningioma
62	Schnauzer	9	♂	Meningioma
67	Keeshound	6	♂	Astrocytoma
70	West highland	11	♂	FA
71	Pointer cross	10	♂(c)	CPP
86	German shepherd	>5	♂(c)	Pit adenoca
101	Golden retriever	5	♂(s)	CPP
104	Airedale	7	♂	CPP
117	Miniature poodle	7	♂(c)	CPP
121	Dachshund	10	♂(c)	Pit adenoca
126	Labrador retriever	11	♂	Pit adenoca
127	Miniature poodle	6	♀(s)	Reticulosis
136	Doberman pinscher	11	♂(s)	CPP
	Sampled 6 hr after end of BSH infusion			
30	Great dane cross	9	♀(s)	Pit adenoca
32	Boxer	9	♀(s)	Meningioma
33	Labrador retriever	>3	♀	Anaplastic nasal malignancy
43	Standard poodle	7	♂	Diffuse astro
49	Boxer	4	♀(s)	Diffuse astro
50	Miniature schnauzer	11	♂	Meningioma
55	Golden retriever	9	♂	Diffuse astro
76	Collie	4	♂	Protoplasmic astrocytoma
88	Basset hound	9	♂	Pit adenoca
	Sampled 12 hr after end of BSH infusion			
1	German shepherd cross	5	♂(c)	Pit adenoca
14	American Eskimo	13	♀(s)	Nasal adenoca
15	Labrador retriever	9	♂	Nasal adenoca
18	Coon hound	5	♂	Nasal adenoca
23	Boxer	>3	♂(c)	Pit adenoca
25	Golden retriever	9	♂	Meningioma

♀(s), Spayed (ovariohysterectomized) female; ♂(c), castrated male. CPP, choroid plexus papilloma; pit adenoca, pituitary adenocarcinoma; nasal adenoca, nasal adenocarcinoma; diffuse astro, diffuse astrocytoma; FA, fibrillary astrocytoma.

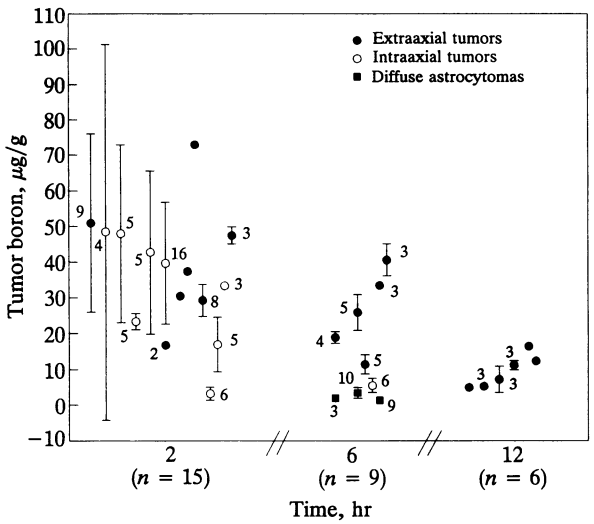

FIG. 1. Canine intracranial tumor boron concentrations (mean ± SD) for 30 dogs receiving BSH (55 mg of boron per kg of body weight). *n*, Number of dogs sampled at each time period; numbers near data points, number of tumor samples averaged per dog.

Peritumor regions (with and without vasogenic edema on MR images) were sampled in 20 of 30 dogs (Fig. 2). Mean peritumor boron concentrations were highly variable but exceeded that of normal brain for 10 of the dogs sampled (Table 3). In 5 dogs, the mean peritumor boron concentration was similar to or exceeded the tumor boron concentration.

Mean boron concentrations for blood and several cranial tissues were higher than mean tumor boron concentrations (Figs. 3–5). Mean boron concentrations of liver, lung, and kidney exceeded that of blood and other systemic tissue (Fig. 6 *A* and *B*). Rates of boron concentration decline were similar for all tissues and blood.

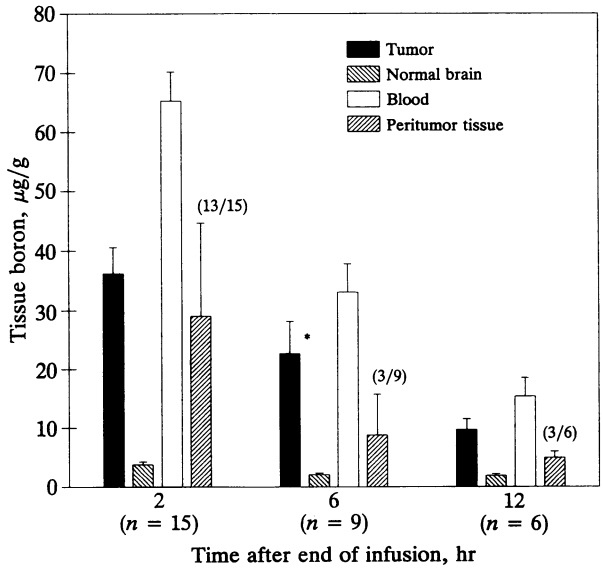

FIG. 2. Boron concentrations (mean ± SEM) for tumor, peritumor, normal brain tissue, and blood for 30 dogs receiving BSH (55 mg of boron per kg of body weight). The asterisk indicates the tumor boron concentration at 6 hr excludes 3 dogs with diffuse astrocytoma ($n = 6$). (n/n), Number of dogs for which peritumor samples were obtained/total number of dogs sampled at that time period.

Table 2. TumBrnR and TumBldR for dogs with intracranial tumors

Time, hr post-BSH	TumBrnR	*n*	TumBldR	*n*
2	10.2 ± 4.8	15	0.6 ± 0.3	15
6	9.2 ± 3.7	6*	0.5 ± 0.2	6*
12	3.5 ± 1.2	6	0.6 ± 0.4	6

Data are presented as mean ± SD.
*Average values exclude diffuse astrocytoma data (n = 3).

DISCUSSION

A spontaneous tumor was desired for evaluation of BSH biodistribution because experimental tumors may not predict behavior of their natural counterpart due to differences in tumor morphology, vascular permeability, kinetics, and blood flow. Dogs were chosen because the rate of spontaneous occurrence and types of malignant brain tumors are similar to that of human patients, with potential relevance to a human treatment situation (6). The BSH dose was similar to that currently administered to people, and route and method of administration were selected for a practical and simple treatment regimen (4). The spectrum of clinical conditions and tumor types provided a realistic range of blood and tissue boron concentrations. The same diagnostic and treatment methods can be used in dogs as for human patients because of the relatively large subject size.

Elemental boron, rather than the BSH molecule, was measured. These data, therefore, represent biodistribution of boron presumably unique to BSH. Other boron-containing compounds may lead to entirely different boron pharmacokinetics and biodistribution. Biodistribution data for BSH are limited but are critical in order to optimize dosimetric and treatment schedules. Most BSH data come from a few rodent studies using transplanted and induced tumors (3, 7–10). Additional data are available from ongoing Japanese treatment trials for malignant brain tumors and human pharmacokinetic studies in Europe (4, 11, 12). Previous studies were necessarily limited in the extent to which normal tissues could be sampled, whereas the relative large size of canine subjects permitted extensive sampling of tumor, peritumor, and many normal tissues.

Mathematical models estimate that, for tumor control, tumor boron concentration should be ≥16 μg of boron per g, assuming the use of an epithermal neutron beam, a TumBrnR of 3, and homogeneous (extra- and intracellular) boron microdistribution (13). This concentration was exceeded by all but a few canine tumors sampled 2 and 6 hr after BSH infusion. Diffuse canine tumors, with an intact or minimally disrupted blood–brain barrier, had boron concentrations similar to normal brain (14). The relatively favorable canine tumor and low normal brain boron concentrations were similar to results of other studies, although strict comparison is difficult due to extensive interstudy variation in compound origin and purity, method of boron analysis, route, dose, timing of administration and sampling, species, and tumor types.

Table 3. Elevated canine peritumor boron concentrations

Time, hr post-BSH	Dog no.	Peritumor boron conc., μg/g	*n*
2	20	204.0	1
	59	13.6 ± 6.3	7
	62	6.3	4
	71	7.7 ± 1.7	4
	117	68.6	1
	126	13.2 ± 9.1	10
	127	43.7 ± 63.7	8
6	50	22.6 ± 14.8	3
12	14	5.2	1
	18	6.6 ± 1.4	3

Data are presented as mean ± SD. Peritumor regions were not sampled from two dogs (2 hr), five dogs (6 hr), and three dogs (12 hr). The remaining dogs (not listed) had peritumor boron concentrations that were within the 99% confidence limits for normal brain. *n*, Number of samples obtained from each dog.

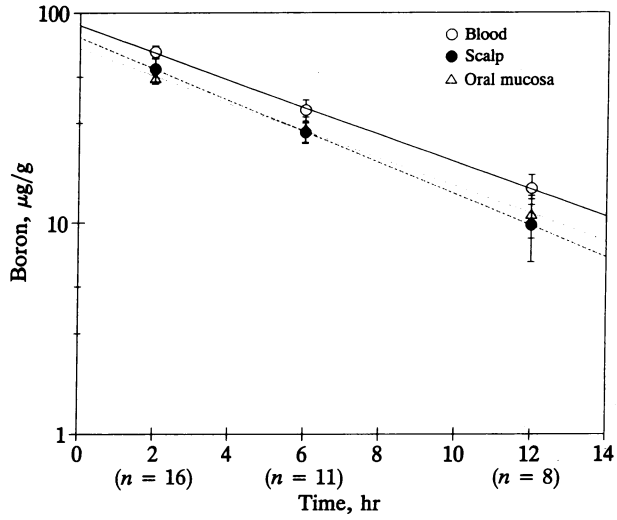

FIG. 3. Mean boron concentrations (mean ± SEM) through time for blood, scalp, and oral mucosa. Tissues were obtained 2, 6, or 12 hr following the end of intravenous BSH. Regression lines were automatically drawn using a software graphics package (SIGMAPLOT; Jandel, San Rafael, CA). *n*, Number of dogs sampled.

Mean tumor boron concentration declined through time, suggesting that boron was not significantly retained within tumor tissue, and at 12 hr tumor boron concentrations were suboptimal. The canine data lacked conclusive evidence for an increase in TumBldR at later postinjection sampling times (>12 hr), which has been reported for BSH (3, 4, 7, 8). This may be partly related to the predominance of low-grade canine brain tumors sampled at 12 hr, as similarly low TumBldRs were found for people with low-grade intra- and extracerebral tumors 12 hr after BSH administration (11).

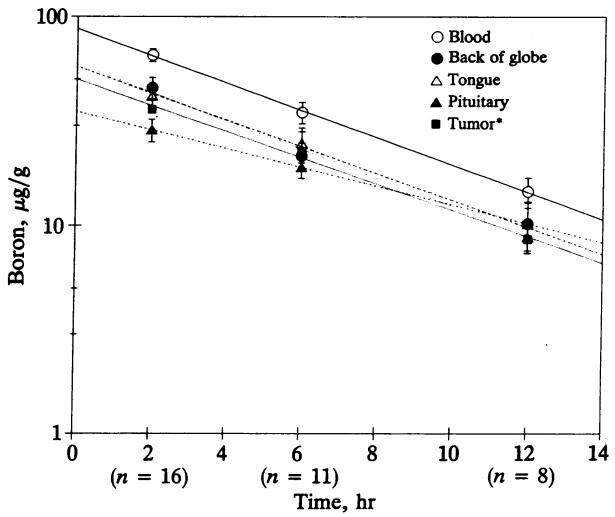

FIG. 4. Mean boron concentrations (mean ± SEM) through time for blood, back of globe, tongue, and pituitary. Tissues were obtained 2, 6, or 12 hr following the end of intravenous BSH. Regression lines were automatically drawn using the SIGMAPLOT software graphics package. *n*, Number of dogs sampled. The asterisk indicates the tumor boron concentration at 6 hr excludes 3 dogs with diffuse astrocytoma.

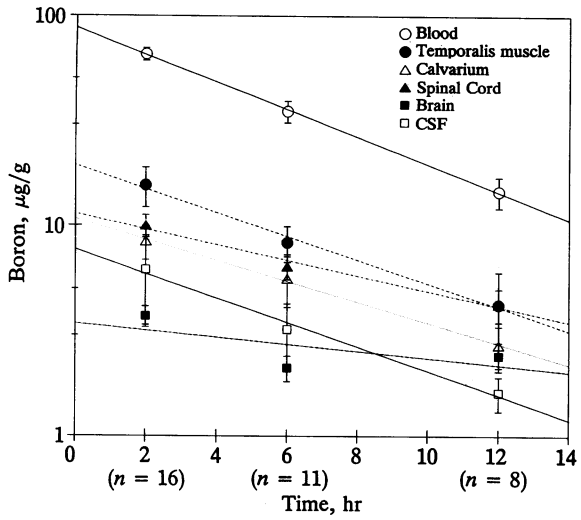

FIG. 5. Mean boron concentrations (mean ± SEM) for blood, temporalis muscle, calvarium, spinal cord, brain, and cerebrospinal fluid (CSF). Tissues were obtained 2, 6, or 12 hr following the end of intravenous BSH. Regression lines were automatically drawn using the SIGMAPLOT software graphics package. *n*, Number of dogs sampled.

Boron concentrations in peritumor regions were evaluated because survival of infiltrative neoplastic cells outside of grossly visible tumor margins has been cited as an important cause of conventional treatment failure (15). The potential advantage of BNCT thus depends partly upon the ability to kill peritumor neoplastic cells. The high variability in canine peritumor boron concentration was attributed to differences in peritumor edema, type, and grade of tumors. Elevated boron concentrations were found in peritumor regions in this and other studies (16). Currently, only gross tissue boron concentrations can be measured, and the quantitative microdistribution of boron (intra- versus extracellular, stromal versus parenchymal) is unknown. Cell killing is highly dependent upon an intracellular or nearby extracellular location for boron atoms, due to the extremely short track length (<10 μm) of the high LET radiation from boron capture. These initial results suggest a potential for high LET/BNCT effects upon peritumor neoplastic cells, but this critical issue will be poorly understood until high-resolution techniques capable of quantitating boron microdistribution are perfected. Boron concentrations an order of magnitude higher may be necessary for desired tumor killing effects if boron microdistribution is predominantly extracellular (17).

The low normal brain boron content can be accounted for by boron within the vascular volume of the brain. This is consistent with intravascular confinement of BSH by an intact blood brain barrier, due to the hydrophilic protein-bound nature of the molecule. TumBrnRs were high, indicating the potential for sparing normal brain parenchyma. Thus, blood boron concentration should ultimately determine normal brain tolerance through effects on vascular endothelium. This is supported by empirical evidence that neuronal death was associated with vascular endothelial damage in canine BNCT dose tolerance trials and early BNCT human treatment trials rather than as a primary entity (4, **). Since the lipid membrane of vascular endothelial cells is integral to the blood–brain barrier, it is hypothesized that little boron enters the endothelial cytoplasm. Most of the high LET dose experienced at the vascular endothelium should originate from boron within the bloodstream. Mathematical models predict geometric dose sparing of vascular endothelium due to the stochastic character and short track length of the α radiation, blood vessel diameters, and endothelial cell sizes (18, 19, **). Vascular sparing of endothelial cells of the brain has been confirmed in a recent study using BSH in a canine model, suggesting that the TumBrnR may be of equal or greater importance than the TumBldR (20). A boronated compound (such as BSH) that has a suboptimal TumBldR, but is strongly restricted by the blood–brain barrier, may indeed be preferable clinically to one that has a more favorable TumBldR but crosses the blood–brain barrier more readily.

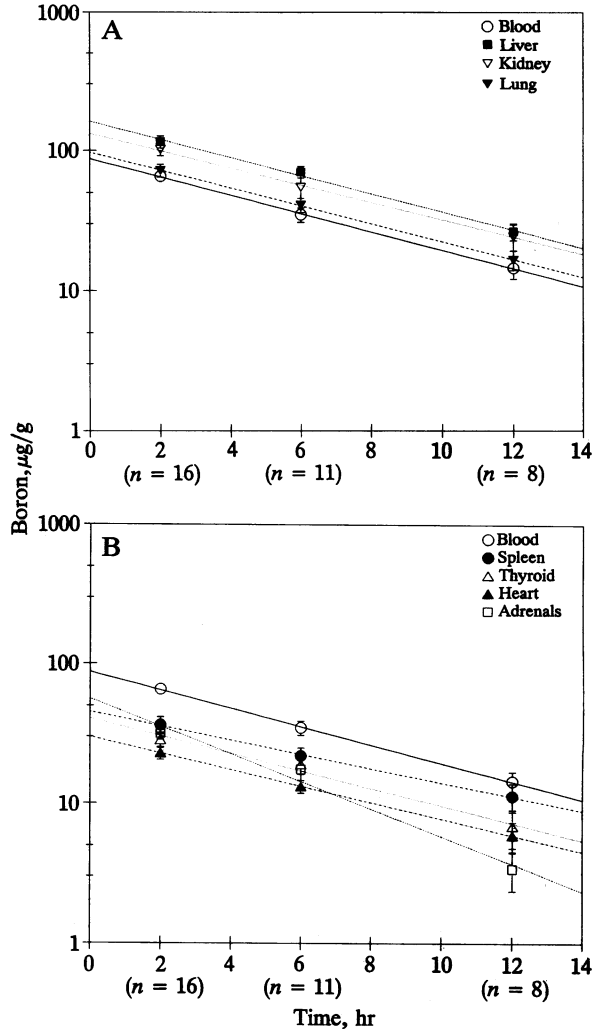

FIG. 6. (*A*) Mean boron concentrations (mean ± SEM) for blood, liver, kidney, and lung. Tissues were obtained 2, 6, or 12 hr following the end of intravenous BSH. Regression lines were automatically drawn using the SIGMAPLOT software graphics package. *n*, Number of dogs sampled. (*B*) Mean boron concentrations (mean ± SEM) for blood, spleen, thymus, heart, and adrenal glands. Tissues were obtained 2, 6, or 12 hr following the end of intravenous BSH. Regression lines were drawn as in *A*. *n*, Number of dogs sampled.

Boron concentrations of normal tissues partly determine BNCT tissue tolerance, but the relationship is extremely complex and not easily predicted. For instance, certain normal tissues of the canine head had high boron concentrations, suggesting an extravascular component of boron and the potential for parenchymal damage, yet high tolerance limits to BNCT have been noted empirically for normal cranial canine tissues (20–22). One explanation may be geometric dose sparing of parenchymal cells due to a hetero-

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geneous boron distribution, but microdistribution studies are needed. Additional complexities concerning normal tissue tolerance include variation inherent to cell and tissue types, variation in the LET of the decay products with distance traveled, variation in the mixed field of irradiation at different depths, blood and tissue boron concentrations, and energy spectrum of the neutron source. Microdistribution studies of boron at the cellular level are needed to better understand the radiation dose distribution. To date, there are no boron microdistribution studies with a subcellular resolution from *in vivo* models at concentrations obtainable clinically with present compounds.

The canine biodistribution of BSH was favorable because of adequate tumor boron concentrations and the low boron concentrations of normal brain, the critical dose-limiting tissue of the head. Dose sparing of vascular endothelium and other tissues through geometric effects need further study. The declining trend of mean tumor boron concentration is suboptimal but might be circumvented by irradiation soon after infusion or use of higher dose or alternate route of drug delivery. Continued development of accurate and precise quantitative techniques to study boron microdistribution are crucial to understand BNCT effects upon neoplastic and normal tissues.

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