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Relative Uptake of Low- and High-Osmolality Contrast Media in CT of Brain Tumors

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The magnitude and time course of contrast enhancement in spontaneous canine brain tumors was determined for two contrast agents: meglumine iothalamate and sodium meglumine ioxaglate. Tumor enhancement during contrast infusion and at 5, 10, 15, 30, and 45 min was measured using quantitative computed tomography. Blood iodine was measured using x-ray fluorescence. Peak contrast enhancement occurred during the infusion, and the magnitude was the same for both agents. Per gram of iodine infused, blood iodine was 12.4% higher with ioxaglate than iothalamate. The monoionic dimer ioxaglate is as effective as iothalamate for enhancement of canine brain tumors.

Conventional contrast media are ionic salts of triiodinated substituted benzoic acids. These agents have a molar concentration five to eight times that of normal body fluids and can induce a number of adverse reactions that appear to be, at least in part, due to their osmotic properties [1, 2]. Low-osmolality nonionic monomer or monoionic dimer intravenous contrast media have an osmolality about one-third that of conventional agents and may be advantageous in that they appear to be better tolerated by patients [1-4]. Although there is considerable evidence of clinical advantage of these media in angiographic studies [3, 4], the relative efficacy of the nonionic or low-osmolality agents in contrast enhancement of lesions characterized by blood-brain barrier defects is unknown.

The canine brain has been shown to be a good model system to evaluate radiation-induced damage [5] and spontaneously occurring brain tumors [6, 7]. Methods for quantification of contrast enhancement and noncontrast tissue densities [8], tissue characterization by dual-energy computed tomography (CT) [9], and kinetic studies to characterize tissue pathology [10] have been developed. We have used this model to study quantitatively the relative efficacy of the commonly used ionic contrast agent meglumine iothalamate (Conray 60, Mallinckrodt) and the monoionic dimer sodium meglumine ioxaglate (Hexabrix, Mallinckrodt) for enhancement of spontaneous brain tumors. The absolute uptake of the two contrast materials in tumor tissue was determined and compared with measured blood iodine levels.

Materials and Methods

Animals

Dogs with suspected neurologic disease were referred for veterinary medical evaluation. A full physical and laboratory examination including blood cell count, serum biochemistry, and urinalysis was done. A complete neurologic examination assessing sensory and motor functions was performed as described previously [6, 7]. Ancillary neurologic studies on all animals included cerebrospinal fluid (CSF) analysis and pressure measurement, skull radiography, and electroencephalography. A ^{99m}Tc brain scan was obtained in most cases. The full neurologic examination has been shown to be effective in selecting animals with neoplastic disease and in preliminary localization of lesions [6, 7]. After this initial screening, animals

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with suspected mass lesions were referred for CT evaluation. Five adult dogs of various breeds weighing 23–36 kg were used in our investigation. All animals were returned to the University of California, Davis, for radiation treatment of their disease [11].

Contrast Agents

Animals were examined first with one agent and 48 hr later with the second, assigned randomly. Route and rate of administration and volumes of contrast were identical. Total contrast dose was 2.2 ml/kg body weight. The monoionic dimer sodium meglumine ioxaglate has a molecular weight of 1269, an iodine content of 320 mg I/ml, and an osmolality of 580 mosmol/kg. Meglumine iohalamate has a molecular weight of 809, an iodine content of 282 mg I/ml, and an osmolality of 1440 mosmol/kg. Total iodine load was 13.5% higher with ioxaglate than with iohalamate, based on equivalent volumes of contrast administered.

CT Scanning

CT studies were performed on a General Electric CT 9800 scanner. Radiologic technical factors were 140 kVp and 280 mAs. A reconstruction diameter of 25 cm and pixel size of 0.485 mm were used. Animal positioning and anesthesia have been reported [8]. A CT number calibration standard containing solutions of water, saline, 10% serum albumin, and mineral oil was positioned under the head during scanning (fig. 1).

A lateral computed radiograph was used to define the limits to be scanned. As precontrast baseline, 12 to 14 contiguous 5-mm-thick transverse CT scans were obtained in 3 min of scanning, extending from the external occipital protuberance rostrally to the cribriform plate [8]. Postcontrast scans at the same levels were obtained during a mechanical infusion of contrast material via an 18 gauge catheter in a cephalic vein. To establish a high blood iodine level, a loading dose of contrast material of 25–50 ml was given at a rate of 8 ml/min. A reduction in rate to 4 ml/min was maintained for 2 min before and during the 3 min of scanning. Blood iodine levels remained constant during the scanning sequence for all animals regardless of size. Immediately after the last infusion scan the pump was turned off and timing for the washout scans begun. Infusion scans were evaluated immediately after the infusion to localize the precise region of enhancement, and washout scans were obtained through this region. Washout scans were obtained at 5, 10, 15, 30, 45, and in some cases 60 min after the end of the infusion.

Blood Sampling

All blood samples were obtained via a 20 gauge catheter in a saphenous vein. Before scanning, a 2–3 ml sample was placed in an EDTA tube for determination of packed cell volume and plasma protein. A series of 1 ml samples was withdrawn during the infusion of contrast material and during the washout sequence. Samples were placed in heparinized plastic vials and evaluated for iodine concentration using x-ray fluorescence excitation analysis [12].

Data Analysis

Quantitative analysis of contrast uptake was done by measurement of CT number changes in defined regions of interest (ROI) in the tumors. Tumor was identified for analysis on a minimum of two consecutive scans for each study. An elliptical or circular cursor was used to define an ROI within the tumor on the "infusion" scan (fig. 1), and the mean CT number of the ROI was determined for each scan

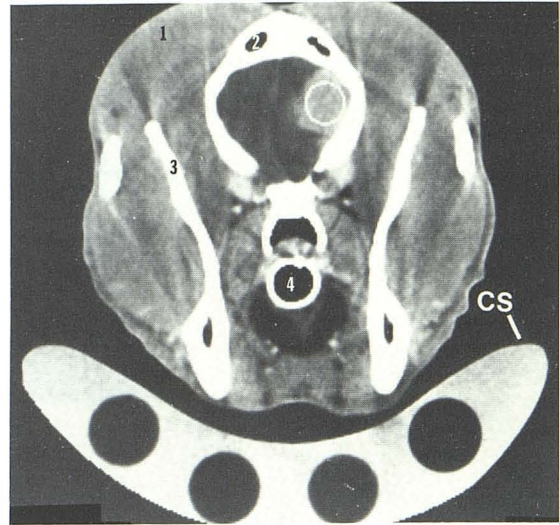


Fig. 1.—Setup for CT scanning. Transverse CT scan of a dog's head showing positioning relative to CT calibration standard (CS). Scan was obtained at level of frontal/olfactory lobes of brain and is viewed looking rostrally with left side of animal to viewer's left. Large enhancing lesion can be seen in right brain. Round ROI used in data analysis is indicated within mass. Histologic diagnosis of this tumor was meningioma. Other identifiable structures include temporalis muscle (1); frontal sinus (2); ramus of mandible (3); and endotracheal tube (4).

at that level (precontrast, infusion, and washout) without repositioning of the ROI. A mean CT number for each time point was determined by averaging the values obtained on the multiple scans containing tumor. Contrast enhancement was calculated by subtracting the CT number of an ROI in the precontrast scan from the corresponding postcontrast ROI.

Mean CT number and contrast enhancement were plotted as a function of time for each contrast material as was blood iodine concentration. Significance of differences between data points either in time or between contrast materials was determined using a paired *t* test. Analysis included correction for the differences in iodine content of ioxaglate and iohalamate.

Results

Neurologic signs and CSF analyses in the five animals studied were consistent with the presence of tumor [6, 7], and CT evaluation demonstrated mass lesions in all five animals, ranging from a small plaque-like tumor near the pituitary gland to a large, round lesion with a significant mass effect (fig. 2). Four of the animals died and were necropsied; histologic diagnoses were one astrocytoma, two meningiomas, and one primitive neuroectodermal tumor.

Blood iodine levels during the infusion with both agents were maintained at a preselected level, as previously described [8]. The variation in iodine concentration during the 3 min of scanning was about 0.15 mg I/g blood, which has no apparent influence on the measured CT number [8]. Per milliliter of contrast material, blood iodine was 30.3% higher after infusion with ioxaglate averaged over the 60 min studied. After correction for the 13.5% greater iodine content of ioxaglate, the blood level per gram of iodine infused was an average of 12.4% higher with ioxaglate than with iohalamate

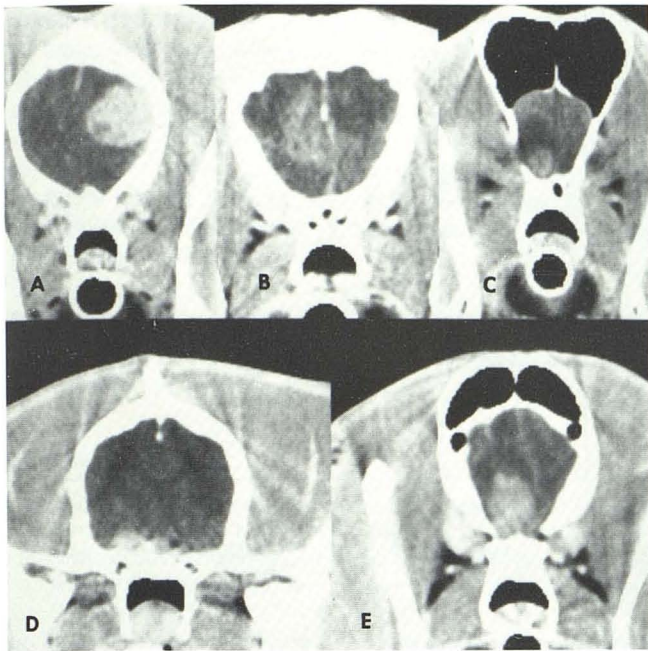


Fig. 2.—Representative transverse CT scans of the five brain tumors were obtained during infusion of iothalamate. Tumors are located in frontal olfactory lobes in four animals (A, B, C, and E) and near pituitary gland (D). Histologic diagnosis was made in four cases: malignant astrocytoma (B), meningioma (A and C), and primitive neuroectodermal tumor (E).

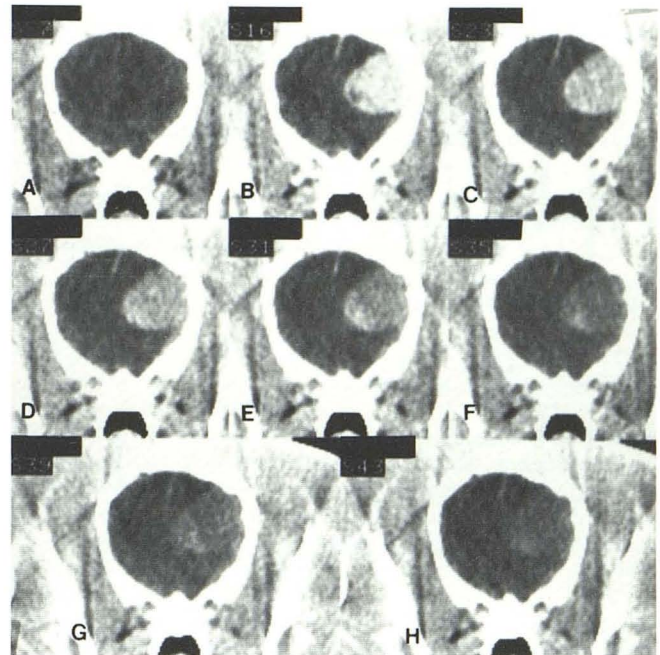


Fig. 4.—Representative transverse CT scans through center of canine brain tumor (meningioma) obtained before (A), during (B) and 5 (C), 10 (D), 15 (E), 30 (F), 45 (G), and 60 (H) min after infusion of iothalamate. Maximum enhancement was observed during infusion, and washout of contrast was apparent as early as 5 min after infusion.

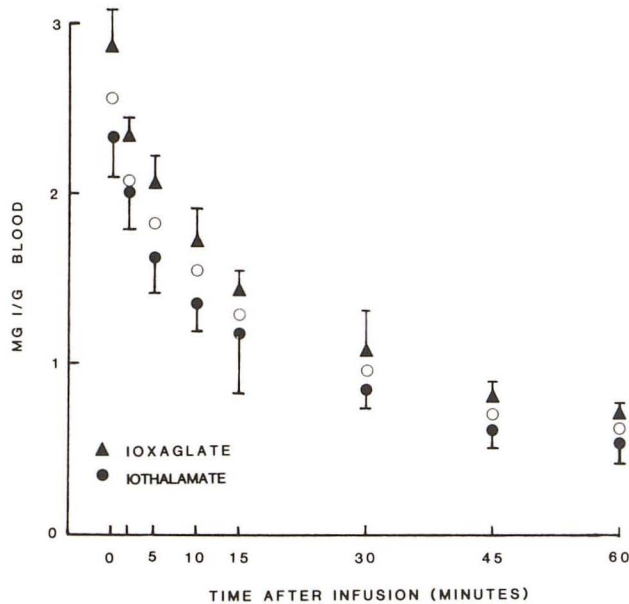


Fig. 3.—Change in blood iodine as function of time after infusion with ioxaglate (triangles) and iothalamate (circles). Open circles represent values for ioxaglate after correction for 13.5% higher iodine content. Solid symbols represent mean values for the five dogs, and error bars are standard errors of the mean.

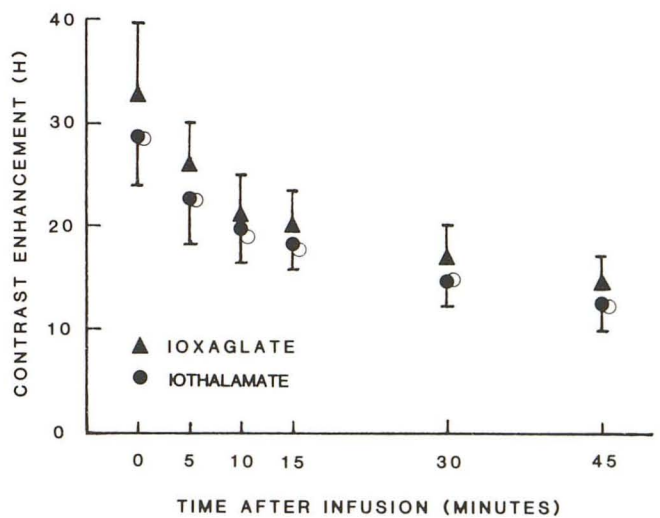


Fig. 5.—Change in contrast enhancement of canine brain tumors as function of time after infusion with ioxaglate (triangles) and iothalamate (circles). Maximum contrast enhancement was observed during infusion, and washout kinetics were the same with both agents. Open circles represent values of ioxaglate after correction for 13.5% higher iodine concentration. Solid symbols represent mean values for the five dogs, and error bars are standard errors of the means; standard errors are large because of range of maximum enhancement among tumors (11–38 H).

for the first 10 min ($p < 0.05$) and not significantly higher from 15–60 min (fig. 3).

The kinetics of contrast enhancement are shown qualita-

tively in figure 4 and quantitatively in figure 5. Per gram of iodine, absolute contrast enhancement of tumors was the same with both agents. The relation between contrast en-

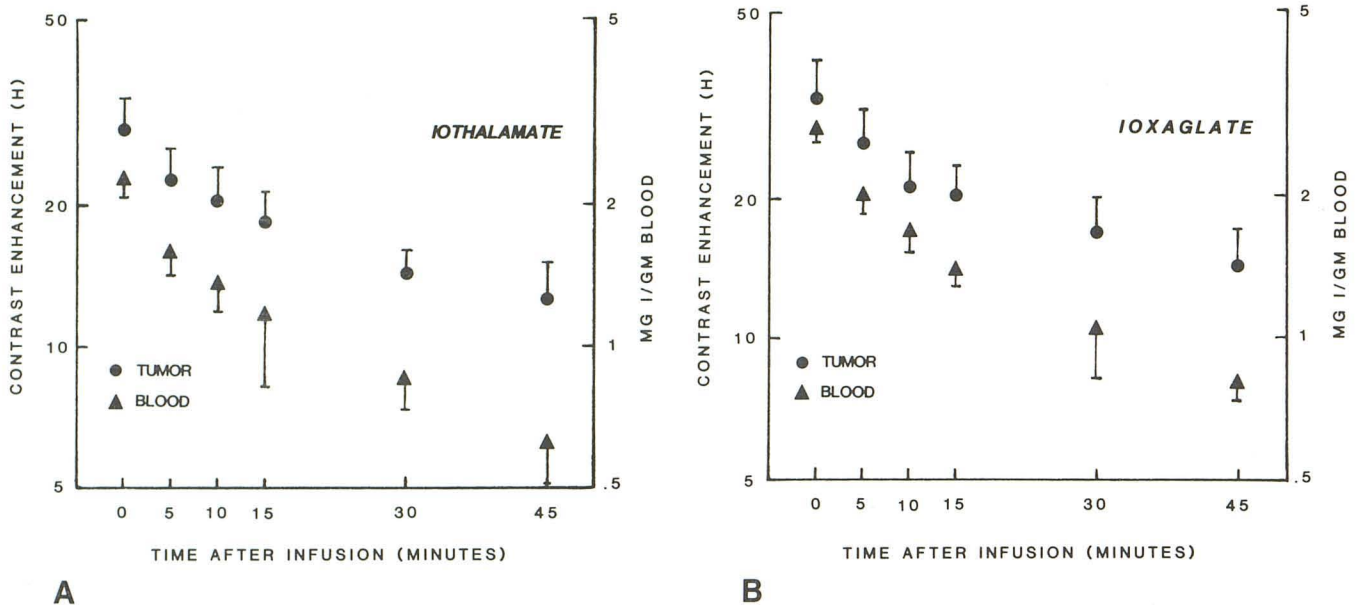


Fig. 6.—A, Change in contrast enhancement (circles) and blood iodine concentration (triangles) as a function of time after infusion with iothalamate. Similar rate constants for contrast washout were observed for first 15 min. Between 15 and 45 min rate of contrast washout was slower from tumor than from blood. B, Change in contrast enhancement and blood iodine concentration as function of time after infusion of ioxaglate.

enhancement and blood iodine levels for each of the materials is shown in figure 6. In both cases, the kinetics of contrast washout (rate constants) from tumor and blood were similar for the first 15 min after infusion. After 15 min, the tumor washout was somewhat slower than the blood iodine washout.

There was no apparent effect of the first agent administered on the results from the second. In all cases, blood profiles of packed cell volume and plasma protein showed each dog to be normal and unchanged between studies.

Discussion

The use of low-osmolality contrast media offers a number of theoretical advantages that have been confirmed experimentally and clinically [1-4]. The relative utility of these agents in the assessment of intracranial disease in which there is impairment of the blood-brain barrier has not, however, been established. It is not clear if the reduced osmolality or altered chemical configuration has any effect on the rate of contrast uptake into an affected site or on the magnitude of enhancement. The intraarterial administration of hypertonic solutions can result in disruption of the blood-brain barrier leading to a significant increase in contrast enhancement of tumors and surrounding normal tissues [13-16]. It has also been suggested that high doses of hypertonic contrast media given intravenously could lead to an increase in the hyperosmolality of the cerebral circulation and to a potential breakdown of the blood-brain barrier [17].

The studies carried out here made it possible to evaluate two contrast agents under virtually identical conditions. There was no apparent influence of the first agent on the results of the second, administered 48 hr later. The infusion volume and

rates were identical and the physical conditions of the animals, including state of hydration, were the same.

The rates of washout of iodine from the blood were similar for the two contrast agents, and both appeared to be two-component exponential functions, as would be expected in a two-compartment model system [18]. However, after correction for the higher iodine content of ioxaglate, this agent had a significantly higher blood level than iothalamate at the end of the contrast infusion and for the ensuing 10 min. This would be consistent with a reduced pool size for mixing of the less ionic agent with no apparent differences in renal clearance, but is also consistent with the thesis that higher osmolality agents expand the plasma volume by dilution with extracellular fluid more than less osmolar agents [2]. In studies in rats Dean et al. [19] concluded that osmolality was not a major factor determining blood concentration of iodinated contrast media.

The kinetics of contrast enhancement in the tumors we studied show no difference in absolute contrast enhancement between the two agents, per gram of iodine infused. However, because of the higher blood level of ioxaglate, the relative contrast of tumors as visualized qualitatively on a single scan theoretically will be slightly less than with iothalamate. That is, the CT number difference between tumor and normal brain will be slightly lower; however, this difference is only 1-2 H, or about 3% of total tumor contrast enhancement.

We have compared the contrast agents ioxaglate and iothalamate in terms of blood iodine level and contrast enhancement of spontaneous brain tumors in dogs. The results show that, although the blood iodine level of ioxaglate was slightly but significantly higher than that obtained with iothalamate, the degree of tumor enhancement did not differ. If we normalize our data per gram of iodine infused, our results

suggest that there is no difference in contrast enhancement of tumor with the agents used. We conclude that the difference in osmolality (580 vs. 1440 mosmol/kg) plays little or no role in contrast enhancement of brain tumors. The reduced osmotic load, increased blood iodine level, and similar contrast enhancement relative to meglumine iothalamate suggest that ioxaglate may be advantageous in routine clinical CT of the brain and in CT angiographic studies where vascular enhancement is important.

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