Impermeability of the Blood-Brain Barrier to Intravenous High-Iodine-Dose Meglumine Diatrizoate in the Normal Dog

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The effect of an intravenous bolus of 4.3 ml/kg of 60% meglumine diatrizoate on the blood-brain barrier (BBB) was studied in five adult unanesthetized dogs. Intravenous 3% Evans blue dye (4 ml/kg) was used as an indicator of BBB disruption. The animals were observed for signs of neurotoxicity for 1 hr after contrast-medium injection and then sacrificed. Their brains were removed and sectioned. None of the dogs displayed clinical evidence of neurotoxicity, and none of the brain specimens showed evidence of BBB disruption. The authors concluded that there is a statistically significant lack of correlation between the intravenous administration of 4.3 ml/kg of 60% meglumine diatrizoate and BBB disruption (p < 0.05 with a probability of 90%). A previous publication reported local BBB disruption in anesthetized dogs with dosages of 4 ml/kg and 6 ml/kg of 60% intravenous contrast agent given as an initial bolus followed by a drip infusion. The present study duplicated this prior experiment using the 6 ml/kg dose followed by infusion in three additional unanesthetized dogs and failed to substantiate the previous findings. This discrepancy leads to the assumption that the BBB damage noted in the previous experiment was somehow related to a factor(s) other than the intravenous contrast-medium injection. The BBB cannot be disrupted in the unanesthetized dog with intravenous doses of 60% contrast media of even 8 ml/kg.

During the past decade, research has greatly expanded our knowledge of the blood-brain barrier (BBB) and its importance in maintaining the neuronal environment [1]. Normally, it renders central nervous system capillaries significantly less permeable than other capillaries to iodinated, ionic contrast agents. A recent report attributes BBB disruption in dogs to 4 and 6 ml/kg intravenous doses of 60% meglumine diatrizoate [2]. A 4.3 ml/kg dose is currently used for clinical head and body computed tomography (CT) and digital subtraction angiography (DSA) [3–8]. Because of the possible clinical implications of this prior report, the present study was undertaken.

Materials and Methods

Eight mongrel dogs from 2 months to 1 year of age and weighing 10–20 kg were studied. A central catheter was inserted under local anesthesia via the right jugular vein into the superior vena cava. Through this catheter, in five dogs 4 ml/kg of 3% Evans blue dye was injected over a 1 min period. This was immediately followed with 4.3 ml/kg of 60% meglumine diatrizoate (282 mg I/ml; 1500 mosmol/L) injected as a bolus over a 90 sec period. The dogs were observed for signs of contrast media neurotoxicity (i.e., seizures or neurologic deficits). After 1 hr, they were sacrificed with 0.3 ml/kg intravenous euthanasia agent T-61 (American Hoechst Co., Summerville, NJ). The brains were immediately removed, gently washed in normal saline, and sectioned in the coronal plane at 3–5 mm intervals. The cut surfaces were inspected for evidence of Evans blue staining. A chi-square test was performed to determine statistical significance of the observations.

The other three dogs received an intravenous bolus of 6 ml/kg of 60% meglumine diatrizoate over a 90 sec period followed by a 0.035 ml/kg/min infusion of 60% meglumine diatrizoate, which was started 20 min after the contrast media bolus and continued for 45
min. The dogs were observed and then sacrificed. Their brains were examined in the manner described above.

Results

In the 1 hr observation period between contrast injection and sacrifice, no signs of contrast neurotoxicity were observed; all eight dogs appeared alert throughout the period. After sacrifice, intense Evans blue dural staining was apparent in all eight animals. No staining was evident on any of the cut brain sections in either the bolus 4.3 ml/kg or the 6 ml/kg bolus plus infusion group. Observations of each brain were made by three authors (L. A. H., J. J. P., and J. R. S.). The absence of brain staining in all five dogs in the 4.3 ml/kg group is a statistically significant observation (p < 0.05, \( \chi^2 = 5.00, 1 \text{ df at a probability level of 90\%} \)), indicating a lack of correlation between the 4.3 ml/kg body weight bolus of 60\% meglumine diatrizoate and the production of BBB damage.

Discussion

Controversial results and questionable conclusions concerning the appropriate contrast dosage for human CT and DSA were drawn from a dog experiment reported by Zamani et al. [2], which had limited resemblance to either of these types of clinical examinations. In their experiment, a series of dogs was placed under general anesthesia for over an hour and given a 3, 4, or 6 ml/kg body weight intravenous, 90 sec bolus injection of 60\% meglumine diatrizoate. CT scans 3, 7, 10, and 20 min after the bolus injection indicated no BBB disruption. However, after 20 min, a second dose of 0.035 ml/kg/min of contrast medium was intravenously infused for 45 min. The subsequent CT scans of two of the four dogs in the 4 ml/kg group and in one of the three dogs in the 6 ml/kg group displayed focal areas of brain enhancement as well as diffuse enhancement of the cerebral hemispheres. These regions of enhancement persisted for the duration of the experiment. The focal areas of enhancement on CT corresponded to areas of Evans blue dye extravasation found at autopsy. These findings indicated that disruption of the BBB occurred during the latter part of the experiment. The authors concluded that intravenous administration of contrast medium caused the BBB disruption.

The first part of our reported study simulated the contrast-enhancement technique recommended for the performance of high-dose head and body CT [4–8]. General anesthesia and the second infusion of contrast medium were not included. Our results show that the administration of an intravenous bolus of 4.3 ml/kg of 60\% meglumine diatrizoate over 90 sec into the dog did not disrupt the BBB in any of the five animals studied. This lack of correlation between the high-dose contrast bolus and BBB disruption is statistically significant (p < 0.05). Therefore, the focal BBB damage previously reported [2] was not due to a high-dose bolus injection of contrast medium but was possibly related to alterations in other variables. These may include changes in the blood pressure, blood pH, blood osmolality, or level of oxygenation during general anesthesia. The previous authors measured some of these variables and tried to maintain them at "physiologic levels" throughout their experiment. Transient, undetected alterations in any of these parameters are known to produce BBB disruption. In fact, the focal lesions that were illustrated in the previous work were distributed symmetrically in watershed zones of the cerebral cortex and in the area supplied by the terminal radicles of the striate arteries in the basal ganglia. This type of localization and the generalized changes throughout both cerebral hemispheres are compatible with the pathology seen after brain ischemia.

It is possible that the small second intravenous contrast infusion given by Zamani et al. could have caused the BBB damage they observed. This is unlikely based on the following experimental findings. Huge doses of hypertonic solutions must be given into the carotid artery to break the BBB. Drayer et al. [9] reported a canine experiment in which they disrupted the BBB by injecting 150 ml of hypertonic (20\%) mannitol over 2 min into the common carotid artery. Immediately before this injection, they intravenously infused 20\% mannitol at a rate of 80 ml/min for 6 min. In another dog experiment [10], 60\% meglumine iothalamate was used to disrupt the BBB. In this study, an intracarotid infusion of 45 ml of Conray 60 at 1.5 ml/sec for 30 sec followed by two subsequent intravenous infusions of 1.6 ml/kg body weight of Conray 60 was required to disrupt the BBB. The large intravenous infusions accompanying the intracarotid injections surely increased the osmotic effect on the BBB. Undoubtedly, the prolonged intracarotid injections used in these two experiments produced cerebral hypoxia, which also contributed to the observed BBB disruption. If series of short injections of contrast medium are given via the carotid artery without accompanying intravenous infusions, even larger doses of contrast medium are needed to disrupt the BBB [11]. In rabbits, 25 intracarotid injections of 1 ml of 50\% sodium diatrizoate every 2 sec are needed to disrupt the BBB. An equivalent human dose would be 3750 ml intracarotid injections of the same contrast medium every 2 sec [11]. Considering how much medium is needed to disrupt the BBB when the hyperosmolar and hypoxic effects of intracarotid injections are virtually eliminated (as they are in intravenous injections), it is difficult to postulate that the small second intravenous infusion given after the intravenous bolus injection could have produced the BBB disruption seen by the authors of the previous study. However, to be certain that the BBB disruption seen previously was due to technical factors and not to the contrast medium, the second group of three dogs in our study was given a 6 ml/kg bolus plus the 45 min infusion of 60\% diatrizoate meglumine. This duplicated the highest contrast dose in the previous work, except that the general anesthesia and blood drawing to determine iodine levels were omitted. The absence of detectable blue-dye extravasation in the brains of all of the animals supports our previously outlined argument that high-dose intravenous contrast medium was not responsible for BBB disruption in normal dogs.

In summary, we conclude that intravenous injection of 60\% meglumine iothalamate in unanesthetized normal dogs, even at doses that far exceed current clinical high-dose infusions for CT and DSA, does not produce BBB disruption.
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REFERENCES