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Permeability of the Blood-Brain Barrier to Different Doses of Diatrizoate Meglumine-60

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High doses of diatrizoate meglumine-60 were administered intravenously in varying concentrations to determine what effect they might have on the blood-brain barrier. In dogs, doses of 4 ml/kg and above appeared to disrupt parts of the blood-brain barrier, disruption being manifested on computed tomographic scans as enhancement and on corresponding brain sections as Evans blue stains. Disruption of the blood-brain barrier was variable from animal to animal. Limited transmission electron microscopic studies suggested that this disruption was accompanied by swelling of the perivascular astrocytic foot processes.

The use of high doses of radiographic contrast agents for both angiography and contrast-enhanced computed tomography (CT) has been advocated with increasing frequency [1–5]. For CT, intravenous injections of diatrizoate meglumine-60 or its equivalent have been given in doses approaching and even surpassing 4 ml/kg (1.13 g I/kg) body weight. The trend toward the more liberal use of contrast material is based on the presumption that increased diagnostic accuracy is achieved with little or no added risk to the patients at these higher doses.

Contrast agents can have potentially adverse effects on the central nervous system through their impact on the blood-brain barrier (BBB) [6, 7]. It has been shown that high-osmolar solutions, such as contrast material, can shrink the capillary endothelial cells and thereby open tight junctions [8, 9]. The opening of these junctions allows leakage of contrast material from the vascular compartment into the parenchyma, where the contrast material is neurotoxic [10]. In addition, contrast material may pass through the membranes of the intact endothelial cells where its movement is primarily dependent on its lipid solubility [6]. Other less well understood mechanisms that might allow contrast material to cross the BBB include pinocytosis and active transport systems.

It has generally been assumed that intravenous injections of contrast material are almost nonneurotoxic, and, therefore, studies on the effects of contrast agents on the permeability of the BBB have concentrated on intracarotid [10–12] or intracisternal injections [13]. However, some reports have indicated that intravenous contrast materials, especially in individuals with focal brain disorders, might result in seizures [14, 15]. This study was undertaken to assess the effects that various high doses of intravenous contrast agents might have on the integrity of the BBB in young, healthy mongrel dogs.

Materials and Methods

Thirteen healthy mongrel dogs, each weighing about 15 kg, were used in this study. The dogs were divided into four groups. The first group of three dogs received 3 ml of contrast material (diatrizoate meglumine-60: iodine content 282 mg/ml, osmolarity 1,500 mOsm/L) per kilogram body weight (0.85 g I/kg); a second group of four dogs received 4 ml/kg of

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contrast material/kg (1.13 g I/kg); a third group of three dogs received 6 ml of contrast material/kg (1.7 g I/kg); and a fourth group of three dogs acted as controls. In each group, a vital dye (Evans blue) was also injected so that areas of BBB disruption observed in brain specimen could be correlated with the corresponding CT scans.

All the dogs were anesthetized with intravenous pentobarbital (30 mg/kg), intubated, and control-ventilated with 100% oxygen. The animals were then immobilized supine on a CT table. Electrocardiographic leads were placed and an intraarterial line was established to permit constant monitoring of blood pressure and arterial blood gases. Arterial blood gases were maintained at physiologic levels to avoid the inadvertent effects of hypoxia, hypercapnia, and acidosis on the BBB [16–19].

A blood sample (3 ml) and a coronal CT scan through the posterior part of the frontal lobes, anterior part of the temporal lobes, and the body of the lateral ventricles were obtained immediately before the intravenous injection of 3% Evans blue (4 ml/kg) and at 0, 3, and 7 min after the injection. Ten minutes after the injection of Evans blue the prearranged dose of contrast material was intravenously administered over 90 sec. Additional blood samples and CT scans at 3, 7, 10, 20, 30, 40, 50, and 65 min were taken after the injection of contrast material. CT scans were obtained on a Technicare 2020 using a 512 × 512 format. The scans were obtained with a 4 mm collimator at 120 kVp, 50 mA, and 8 sec.

In order to challenge the BBB with a concentration of contrast material, an attempt was made to maintain a constant blood-iodine level throughout the last 45 min of the study. This was achieved by beginning an infusion of diatrizoate meglumine-60 20 min after the initial bolus of contrast material. The infusion was based on the dilution curve for that particular group of animals, the weight of the animal, and the concentration of contrast material. For example, in a 15 kg dog whose initial bolus was 4 ml/kg, the perfusion was performed at a rate of about 0.4 ml/min [17]. The dog thus received another 18 ml of contrast material during the final 45 min of the study. The ability to maintain steady-state blood-iodine levels was evaluated by CT scanning the blood samples and noting the variations in attenuation values. By this it was insured that blood-iodine levels obtained after infusion remained relatively constant and did not exceed the levels obtained by bolus injections. At the conclusion of the experiment, the dogs were sacrificed and their brains were removed, fixed, and examined.

To simplify quantitative analysis and eliminate bias in the evaluation of CT attenuation changes the process was automated [20]. Each brain scan was automatically divided into a left and a right hemisphere. Each hemisphere was in turn divided into four concentric rings; each ring was then divided into 10 subcompartments. The mean attenuation value for each subcompartment and its standard deviation was then recorded in a printout. The initial and the final infusion printouts were compared to determine which subcompartment showed maximal enhancement. The intervening time printouts during the last 45 min of the experiments were also identified, recorded, and graphed. Thus, in each experiment, the attenuation value obtained at 20 min was used as a baseline value with which subsequent values were compared. The values during the initial 20 min after the injection of contrast material were omitted because of the rapid changes in the attenuation values that corresponded to the dilution of contrast material in the body. Excluded from this study were the midline subcompartments that contained vessels and the lateral ventricles.

The CT images were compared with the gross brain specimens and to brain sections studied by light microscopy. In selected cases, transmission electron microscopy was also carried out. The dogs that were studied by electron microscopy received horseradish peroxidase as a marker of BBB breakdown.

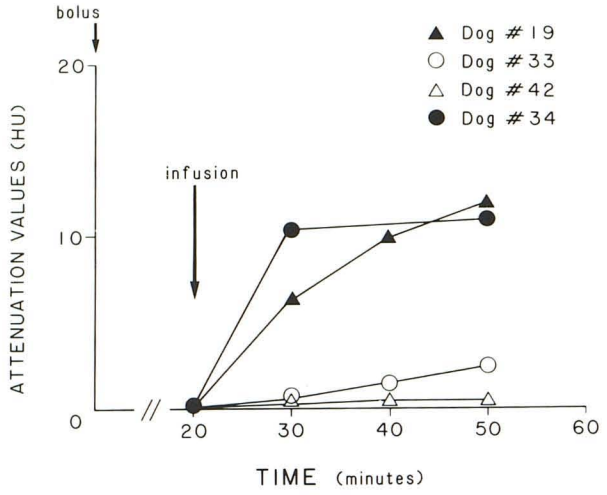

Fig. 1.—Curves of maximal enhancement in 4 ml/kg group. Note interanimal variability.

Results

The dogs that received 3 ml/kg of contrast material and the control dogs showed no BBB breakdown, either on the CT scans or in their brain specimens. In the 4 ml/kg group, two of the four dogs showed a rise in attenuation values after contrast administration (fig. 1). One of these (dog 19) showed areas of focal enhancement in the cortex that correlated well with areas of Evans blue staining in the gross specimens; there were also small areas of staining in the thalamus (fig. 2). The other dog showed one small area of staining in the cortex. One of the three dogs in the 6 ml/kg group showed a marked rise in attenuation values after contrast administration (fig. 3). The disruption of the BBB in this 6 ml/kg dog was more generalized than in the 4 ml/kg dogs.

The greatest increase in mean attenuation values of corresponding subcompartments was seen in the group that received 6 ml/kg of contrast material (fig. 4). The group that had received 3 ml/kg showed no increase, while the 4 ml/kg group showed an increase intermediate between that of the 3 ml/kg and that of the 6 ml/kg groups. A limited comparison between the dogs that showed definite Evans blue staining in at least one part of their brains revealed an increase of 11 Hounsfield units (H) in the 4 ml/kg group and of 22 H in the 6 ml/kg group.

Histologic examination of brain sections showed no evidence of petechial hemorrhage that might account for the observed attenuation rises. Limited electron microscopic study showed no definite passage of horseradish peroxidase through tight junctions into the extravascular compartment. There was, however, some swelling of astrocytic foot processes in the dog that received 6 ml/kg of contrast material (fig. 5).

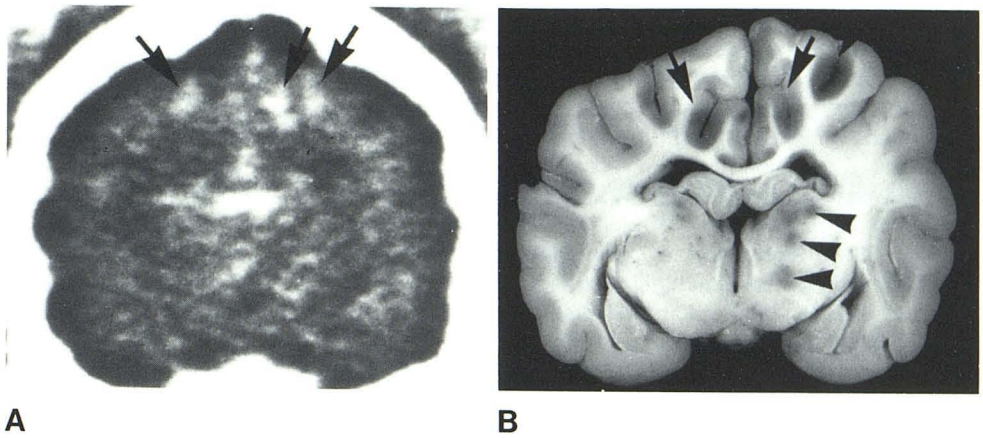

Fig. 2.—Dog 19. **A**, Areas of enhancement (*arrows*) in cortex close to vertex. Enhancement also present in vascular midline structures and choroid plexus of lateral ventricle. **B**, Note similarity between CT appearance and corresponding Evans blue stains on brain specimens (*arrows*). Areas of staining in thalamus (*arrowheads*) are less evident on CT scan.

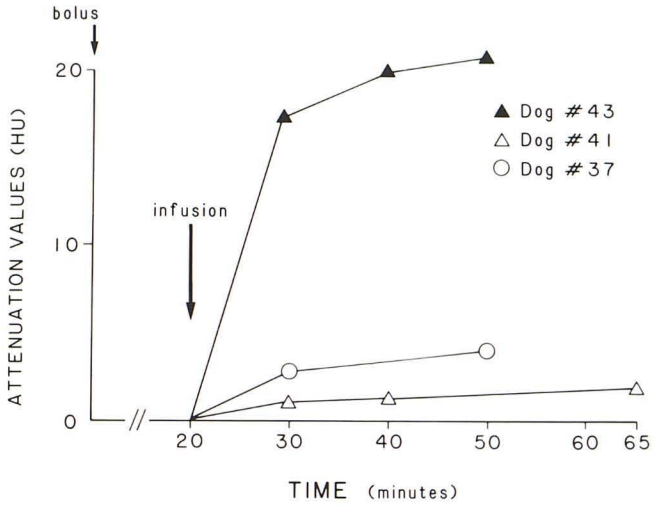

Fig. 3.—Curves of maximal enhancement in 6 ml/kg group. Significant rise in attenuation values in one of three dogs.

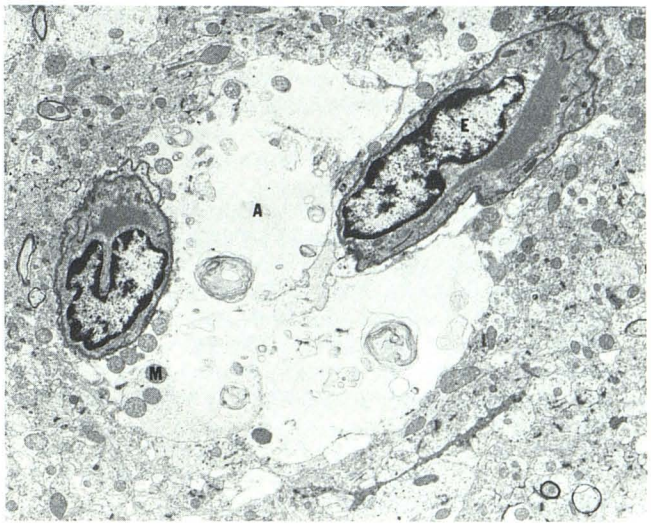

Fig. 5.—Dog 43. Electron micrograph of cortical neuropil shows swollen astrocytic foot processes (A) adjacent to endothelial cells (E) lining capillary. Mitochondria (M) are still identified in swollen processes. Magnification ×4,000.

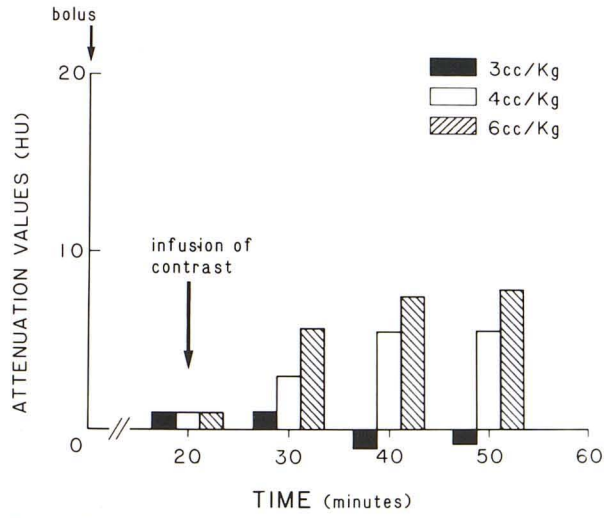

Fig. 4.—Comparison of intensity of enhancement in three contrast groups. At each time, averaged enhancement in each group was graphed.

Discussion

Intracarotid injections of contrast media may result in BBB disruption because of their osmotic effect [10–13]. In addition, intraarterial injection of contrast media can result in hemodynamic and hematologic alterations that can potentially affect the BBB [21, 22]. Finally, in prolonged or repeated injections, hypoxia may also result, which in itself may alter BBB permeability.

While it has been generally accepted that contrast media administered intravenously pose far less risk to the central nervous system than doses given intraarterially, the effects of intravenous contrast media on the central nervous system have not been adequately studied. With the increasing use of high doses of intravenous contrast media for CT and digital studies, the question of the neural toxicity has become of more than academic interest. Our study shows that

4 ml/kg (1.13 g I/kg), a dose level that is currently employed clinically, appears to break down the BBB in some dogs. These results, which were obtained in animals without central nervous system lesions, suggest what may occur in the normal human brain. With regard to high-dose studies in humans, a question might be raised as to whether some of the additional enhanced areas not seen with lower doses might have been produced iatrogenically.

Advocates of high doses of intravenous contrast media for CT have suggested that high contrast levels might break down the BBB in areas of focal disease and, thus, improve the detectability of these lesions [1, 3, 5]. This advantage is, however, countered by the known neurotoxicity of ionic water-soluble contrast agents on brain parenchyma, and the effects of high intravenous doses on the BBB. In patients with focal changes, the passage of contrast material into the extravascular space may occasionally result in acute changes such as seizure [14, 15, 23]. In patients with nonneoplastic brain diseases, extravasation of ionic contrast material may damage brain parenchyma and adversely affect their long-term prognosis [24, 25].

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