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AJNR Am J Neuroradiol 1984, 5 (1) 41-43
http://www.ajnr.org/content/5/1/41

Effect of Intravenous Contrast Material on the Integrity of the Blood-Brain Barrier: Experimental Study

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Increasingly large doses of contrast medium have been advocated for enhanced computed tomography. It is assumed that such large intravenous doses, which increase the osmolality of the blood, do not affect the blood-brain barrier in the same way as intracarotid injections of the same solutions. Using a qualitative marker, Evans blue dye, and a quantitative marker, ^{99m}Tc-pertechnetate, a study was performed in rabbits to assess the effect of intravenous sodium iothalamate (Conray-420) at a dose of 8 ml/kg on the integrity of the blood-brain barrier. No qualitative or quantitative evidence of disruption of the blood-brain barrier was demonstrated. Since histologic examination was not done, morphologic changes cannot be excluded.

During computed tomography (CT), it is usually presumed that intravenous injections of contrast media demonstrate only vascular structures, the blood-brain barrier (BBB) rendering cerebral capillaries impermeable to iodine contrast agents [1, 2]. Therefore, the cerebral parenchyma shows only a slight increase in attenuation since the cerebral blood content represents only 4%–5% of total brain volume [1]. Any abnormal increase in the attenuation of cerebral parenchyma is thought to be from loss of the integrity of the BBB existing before intravenous injection, allowing leakage of contrast medium into the brain parenchyma [2]. The use of high doses of intravenous contrast media for enhanced CT has been advocated [3–6]. Recently, it has been suggested that intravenous contrast medium may itself alter the morphologic characteristics [7] and permeability of the BBB [8, 9]. A study was undertaken to further investigate the effect of intravenous contrast medium on the permeability of the BBB in rabbits.

Materials and Methods

Thirty rabbits (New Zealand Short Hair, IMVS strain) of both genders were used in the study. The animals were anesthetised with a 25% solution of urethane (Ajax Chemicals, Sydney) in 0.9% saline injected intravenously at a dose of 7 ml/kg. After satisfactory anesthesia was established, 10 rabbits were injected with isotonic saline at a dose of 8 ml/kg. The injection was given manually into a marginal ear vein within 60 sec. A further 10 rabbits were injected with Conray-420 (sodium iothalamate, 420 mg I/ml, May & Baker, Dagenham, England) at a concentration of 8 ml/kg; four animals in this series became dyspneic during the injection, and the injection was ceased until breathing returned to normal. Another 10 rabbits received no bolus injection and were used as controls.

Immediately after the injection of the test solutions, an intravenous injection of 2% Evans blue in 0.9% saline (membrane-filtered) at a dose of 3 ml/kg was administered to allow qualitative assessment of gross breakdown of the BBB. This was followed by an intravenous injection of ^{99m}Tc-pertechnetate (100 μCi [3.7 MBq] in about 0.2 ml of saline). Pertechnetate was selected because it has a molecular size considerably smaller than contrast media and it does not cross the normal BBB [10]. Evans blue and ^{99m}Tc-pertechnetate were also administered to the 10 control animals.

Sixty minutes after the pertechnetate injection, 1 ml of cardiac blood was removed and

Received February 18, 1983; accepted August 8, 1983.

This work was supported by the Australian Brain Foundation.

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AJNR 5:41–43, January/February 1984
0195-6108/84/0501-0041 $00.00

TABLE 1: **Mean Ratio of ^{99m}Tc-Pertechnetate Counts/ml Blood to Counts/g Brain for Each Set of Studies**

Injected solution	Mean Ratio (ml Blood/g Brain ± SD)
Control (no intravenous injection) ($n = 10$)	0.024 ± 0.005
Isotonic saline ($n = 10$)	0.023 ± 0.005
Sodium iothalamate ($n = 10$)	0.026 ± 0.005

Note.—No statistical differences were detected between the sets ($p > 0.1$). t Test values = 0.22 for control vs. saline; 1.27, saline vs. sodium iothalamate; and 1.09, control vs. sodium iothalamate.

the animals killed immediately with 5–10 ml of saturated potassium chloride solution injected intravenously. The brains were then removed as quickly as possible and rinsed with Hartmann solution to remove superficial blood and cerebrospinal fluid. Subjective assessment of the degree of Evans blue staining was then made on a scale established previously [11].

The brains were weighed and then the blood samples and brains were counted separately in a Searle gamma counter using a "well" attachment. After correction for background radiation, a ratio of blood (cpm/ml) to brain (cpm/g) was calculated. By calculating the ratio of blood to brain, variations were accounted for in blood volume and quantity of isotope injected to individual animals. The difference between the blood to brain ratios for each series of studies was compared using Student t test.

Results

Evans blue staining was not demonstrated in the brains of control animals or in those given saline or sodium iothalamate. The results of the three series of experiments are given in table 1. No significant difference between the three different sets of studies was detected ($p > 0.10$).

Discussion

Increased permeability of the BBB after intraarterial injection of various contrast media has been well documented in both experimental animals [12–16] and in humans [17]. This increased permeability or disruption of the BBB appears to depend at least partly on the hyperosmolality of the solutions [11, 14, 18].

While such an effect of intraarterial injections of contrast media is well established, normal brain tissue is thought to be protected from intravenous contrast media by the BBB. The normal slight increase in attenuation of the cerebral parenchyma is thought to represent the contrast media within the cerebral blood vessels in the absence of pathology. However, in 1978, Caillé et al. [9] studied the attenuation of the cerebral parenchyma after 2 ml/kg intravenous injections of contrast media with different osmolalities. They concluded that iodine contrast media do not remain totally within the intravascular space and that leakage across the BBB is probably related to the liposolubility of the solutions rather than to their osmolality. Recently increased vesicular transport (pinocytosis) has been demonstrated in the cerebral capillaries after administration of intravenous contrast material in experimental animals [7]. Increased permeability of the BBB has also been demonstrated experimentally using both qualitative Evans blue and quantitative CT assessment after large doses of intravenous ionic contrast media [8].

If such changes in the morphology and permeability of the cerebral capillaries follow an intravenous injection, the proposed use of high doses of intravenous contrast media to demonstrate pathologic alterations in the BBB would be inappropriate. Although Paling [19] concluded that the administration of doses larger than 25.2 g of iodine do not provide more useful diagnostic information during CT, others have advocated larger doses of intravenous contrast medium [3–6]. Presumably, such authors assume that the large intravenous doses of contrast media that increase the osmolality of the blood do not affect the normal BBB in the same way as intracarotid injections of the same solutions.

Our studies have indicated that, after a large intravenous dose of sodium iothalamate, no obvious increase in the permeability of the BBB to Evans blue (molecular weight, 961) or pertechnetate (molecular weight, 163) was demonstrated. The first pass concentration of contrast medium was not measured, but, from other unpublished results from this laboratory, a five- to sixfold dilution of the amount of contrast medium delivered to the brain might be expected for the dose administered in these studies. Hence, after intaarterial injection, when blood is virtually displaced by contrast medium, a much higher concentration is in contact with the cerebral capillary wall. Although minor morphologic alterations in the normal cerebral capillaries cannot be excluded, the integrity of the BBB appeared to be maintained despite a large contrast load. Therefore, the studies suggest that in the rabbit model the BBB protects the normal cerebral parenchyma from direct penetration by contrast media.

A recent retrospective study [20, 21] suggested that the prognosis of cerebral infarction is worse in patients who have undergone enhanced CT. It does suggest the possibility that the presence of water-soluble contrast media within the extracellular fluid of the brain may have a direct toxic effect, and hence it has been important to establish that the integrity of the BBB is at least maintained in the presence of a large intravenous contrast load. This seems to be the case in the normal rabbit.

REFERENCES

1. Caillé JM, Guibert-Tranier F, Calabet A, Billerey J, Piton J. Abnormal enhancement after contrast injection. In: Caillé JM, Salamon G, eds. *Computerized tomography*. Berlin: Springer-Verlag, **1980**;166–171
2. Sage MR. Blood-brain barrier: phenomenon of increasing importance to the imaging clinician. *AJNR* **1982**;3:127–138, *AJR* **1982**;138:887–898
3. Hayman LA, Evans RA, Hinck VC. Rapid high dose (RHD) contrast computed tomography of perisellar vessels. *Radiology* **1979**;131:121–123
4. Raininko R, Majurin ML, Virtama P, Kangasniemi P. Value of high contrast medium dose in brain CT. *J Comput Assist Tomogr* **1982**;6:54–57
5. Davis JM, Davis KR, Newhouse J, Pfister RC. Expanded high iodine dose in computed cranial tomography: a preliminary report. *Radiology* **1979**;131:373–380
6. Hayman LA, Evans RA, Hinck VC. Delayed high iodine dose

contrast computed tomography: cranial neoplasms. *Radiology* **1980**;136:677–684

7. Burns EM, Dobben GD, Kruckeberg MS, Gaetano PK. Effects of ionic and non ionic contrast media on blood-brain barrier integrity (abstr). *Invest Radiol* **1980**;15:395
8. Zamani AA, Morris JH, Kido DK, Lisbon A. Permeability of the blood-brain barrier to different doses of diatrizoate meglumine-60% (abstr). *Invest Radiol* **1981**;16:380
9. Caillé JM, Billerey J, Renou AM, Constant P. Cerebral blood volume and water extraction from cerebral parenchyma by hyperosmolar contrast media. *Neuroradiology* **1978**;16:579–582
10. Schwartz ML, Tator CH. Shortcomings of ^{99m}Tc-pertechnetate as a tracer for brain tumor detection as shown by well counting of human brain tumors and a mouse ependymoblastoma. *J Nucl Med* **1972**;13:321–327
11. Sage MR, Wilcox J, Evill CA, Benness GT. Comparison and evaluation of osmotic blood-brain barrier disruption following intracarotid mannitol and methylglucamine iothalamate. *Invest Radiol* **1982**;17:276–281
12. Harrington G, Michie C, Lynch PR, Russell MA, Oppenheimer MJ. Blood-brain barrier changes associated with unilateral cerebral angiography. *Invest Radiol* **1966**;1:431–440
13. Jeppsson PG, Olin T. Neurotoxicity of roentgen contrast media. Study of the blood-brain barrier in the rabbit following selective injection of contrast media into the internal carotid artery. *Acta Radiol [Diagn]* (Stockh) **1970**;10:17–34
14. Rapoport SI, Thompson HK, Bidinger JM. Equi-osmolal opening of the blood-brain barrier in the rabbit by different contrast media. *Acta Radiol [Diagn]* (Stockh) **1974**;15:21–32
15. Salvesen S, Nilsen PL, Holtermann H. Effects of calcium and magnesium ions on the systemic and local toxicities of the N-methyl-glucamine (meglumine) salt of metrizoic acid (Isopaque) *Acta Radiol [Suppl]* (Stockh) **1967**;270:180–193
16. Waldron RL, Bryan RN. Effect of contrast agents on the blood-brain barrier. An electron microscopic study. *Radiology* **1975**;116:195–198
17. Sage MR, Drayer BP, Dubois PJ, Heinz ER, Osborne DR. Increased permeability of the blood-brain barrier after carotid Renografin-76. *AJNR* **1981**;2:272–274
18. Grainger RG. Osmolality of intravascular radiological contrast media. *Br J Radiol* **1980**;53:739–746
19. Paling MR. Contrast dose for enhancement of computed tomograms of the brain. *Br J Radiol* **1979**;52:620–623
20. Pullicino P, Kendall BE. Contrast enhancement in ischaemic lesions. I. Relationship to prognosis. *Neuroradiology* **1980**; 19:235–239
21. Kendall BE, Pullicino P. Intravascular contrast injection in ischaemic lesions. II. Effect on prognosis. *Neuroradiology* **1980**;19:241–243