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Comparison of Blood-Brain Barrier Disruption by Intracarotid Iopamidol and Methylglucamine Iothalamate

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Using a canine model, the effect of intracarotid injections of the ionic contrast medium methylglucamine iothalamate was compared with that of the nonionic contrast medium iopamidol of similar iodine concentration (280 mg I/ml). The degree and distribution of blood-brain barrier disruption was assessed using Evans blue stain as a visual marker and by contrast enhancement measured by a computed tomographic (CT) scanner. In all studies with methylglucamine iothalamate, Evans blue staining was demonstrated, and CT enhancement demonstrated a significant mean difference (p < 0.01) between the control and injected hemispheres. In contrast, no Evans blue staining was demonstrated with iopamidol, and CT studies failed to show any significant difference (p > 0.1) between control and injected hemispheres. The absence of blood-brain barrier disruption with iopamidol is probably related to its lower osmolality (570 mosmol/kg) compared with methylglucamine iothalamate (1,424 mosmol/kg) and the absence of any cation.

Increased permeability, or breakdown, of the blood-brain barrier (BBB) has been demonstrated in both experimental animals [1–4] and humans [5] after the intracarotid injection of various contrast media. The osmolality of the contrast media is a factor in the degree of breakdown [3, 4] and the neurotoxicity [6, 7]. To reduce the osmolality and hence neurotoxicity, nonionic metrizamide was developed by Nyegaard, Oslo, following the concept of Almén [8]. This has been shown to be less neurotoxic [9] and have less effect on the BBB [10] than ionic methylglucamine iothalamate of an equivalent iodine concentration. Modification of the metrizamide design by substituting different side chains has resulted in iopamidol, developed by Bracco, Milan. Using an established canine model [11, 12], we compared the effects of nonionic iopamidol and ionic methylglucamine iothalamate (Conray 280, May & Baker; Conray-60, Mallinckrodt, St. Louis) on the BBB.

Materials and Methods

Studies were performed on anesthetized adult greyhound dogs of both genders weighing 28–35 kg. Respiration was controlled at eight breaths/min by an Oxford ventilator. The carotid artery was exposed and retrograde catheterization of the lingual artery was performed using 1 mm ID polyethylene tubing. The tip of the catheter was positioned opposite the origin of the internal carotid artery and the remaining branches of the external carotid artery were ligated.

Evans blue stain was used as a visual marker of BBB disruption. A 3 ml/kg solution of Evans blue (2% in 0.9% saline, membrane filtered) was administered intravenously 5 min before intracarotid injections. Five studies were performed with both iopamidol (280 mg I/ml) and methylglucamine iothalamate (Conray-280, May & Baker; Conray-60, Mallinckrodt, St. Louis) by injecting the left carotid artery only, leaving the right hemisphere to act as a control. Intracarotid injections were administered at body temperature at a rate of 1.5 ml/sec for a period of 30 sec, previous studies having demonstrated that this volume is just sufficient to blanch the cortical surface in dogs [11]. During injection, the common carotid artery was occluded to prevent retrograde flow and to ensure delivery of the test volume.
into the internal carotid artery. Immediately after intracarotid injection of either iopamidol or methylglucamine iothalamate, an intravenous dose of sodium iothalamate (Conray-420, May & Baker; Conray-400, Mallinckrodt) was administered, the volume being adjusted such that it and the intracarotid injection combined were equivalent to 1.6 ml/kg of sodium iothalamate (670 mg I/kg). A second intravenous injection of sodium iothalamate (1.6 ml/kg) was administered 20 min after the first injection to maintain plasma iodine levels.

Forty minutes after intracarotid injections the animals were killed by an intravenous injection of 10–15 ml of saturated potassium chloride solution. After brain removal, assessment of intensity and distribution of Evans blue staining was performed by two independent observers. Visible staining in the distribution of the middle cerebral artery was graded on a scale of 0–3 as follows: 0 = no staining; + = just visible staining; ++ = easily visible diffuse staining; and +++ = dark diffuse staining. The brain was then suspended in an isotonic solution (Hartmann solution) in a sealed, cylindrical, perspex container and positioned in the CT scanner (EMI model 5005). Coronal scans were obtained at 1 cm intervals, using 13 mm collimation (fig. 1). The coronal CT sections were assessed for evidence of enhancement, and quantitative measurements were made by calculating the mean EMI number in a 100 pixel region of interest in the distribution of the middle cerebral artery in both the control and injected hemispheres. For each solution, an overall mean was computed for the injected hemispheres (EMI-injected) and control hemispheres (EMI-control). EMI-control was then subtracted from EMI-injected to give a mean difference between the injected and control hemispheres for iopamidol and methylglucamine iothalamate. These mean differences were then compared by the Student t test.

Results

Table 1 shows the degree of Evans blue staining assessed visually in the distribution of the middle cerebral artery in the injected hemisphere. A variable degree of staining was demonstrated in the studies with methylglucamine iothalamate, but no staining was demonstrated with iopamidol.

Table 2 shows the mean EMI numbers for control and injected hemispheres in both sets of studies. The mean differences between control and injected hemispheres with each agent are also shown. With iopamidol there was virtually no difference between control and injected hemispheres, while with methylglucamine iothalamate the mean difference was 11.0 EMI units. This was statistically significant (p < 0.01).

In every study with methylglucamine iothalamate, the difference between the control and injected hemispheres was statistically significant (p < 0.01). The difference was not statistically significant in any of the iopamidol studies (p > 0.1).

Discussion

Previous studies indicate a reasonable correlation between the assessment of the degree of distribution of BBB disruption as assessed by Evans blue as a visual marker and assessment by contrast enhancement measured by CT [11, 12]. Both Evans blue staining and CT enhancement were demonstrated in the distribution of the middle cerebral artery in the five hemispheres injected with intracarotid methylglucamine iothalamate (fig. 1). In comparison, no obvious staining or enhancement was demonstrated in any of the studies using intracarotid iopamidol, despite the use of an equivalent iodine dose.

Iopamidol has been shown both in experimental animals [13] and by clinical trials [14] to be less neurotoxic than equivalent ionic water-soluble contrast media. This lack of neurotoxicity is thought to be at least partly due to a reduced
effect on the integrity of the BBB. Using both qualitative (Evans blue) and quantitative (CT enhancement) assessment of BBB, we failed to demonstrate any disruption of the BBB with iopamidol, while a variable but significant disruption occurred after intracarotid methylglucamine iothalamate.

Various hypertonic solutions of electrolytes and nonelectrolytes, including contrast media, have been shown to disrupt or increase the permeability of the BBB [1–3, 15, 16]. The reduced breakdown with iopamidol is presumably due to its lower osmolality when compared with equivalent iodine concentration of 280 mg/ml (570 mosmol/kg) being considerably less than methylglucamine iothalamate (1,424 mosmol/kg). Both metrizamide and iopamidol have about the same osmolality of about one-third that of conventional monomeric contrast media, instead of the theoretical reduction of one-half [7]. While the osmolality of contrast media is a definite factor in neurotoxicity [6, 7] with ionic monomeric contrast media, methylglucamine iothalamate, while having an osmolality similar to mannitol 25% (1,424 mosmol/kg and 1,524 mosmol/kg, respectively), has been shown to produce a greater degree of BBB breakdown [12]; and in other studies [17, 18], hypertonic glucose and sodium fluoride, with osmolalities similar to contrast media, produce similar but less pronounced effects, indicating that, in the case of ionic contrast media, BBB disruption cannot be explained by osmotic reaction alone [19].

REFERENCES

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