



WATER-SOLUBLE CONTRAST MEDIA

AND

THE BRAIN INTERFACES

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## SUMMARY

The blood, cerebro-spinal fluid (CSF) and the extracellular fluid of the brain parenchyma form the fluid compartments of the brain with three interfaces between, namely the blood-brain interface (BBB), the CSF-brain interface and the blood-CSF interface. One or more of these interfaces are exposed to water-soluble contrast medium (CM) following intra-arterial, intravenous, or intrathecal CM administration during cerebral angiography, computerised tomography (CT) or myelography.

Studies were performed in dogs to demonstrate that CT could be used to assess the distribution and the degree of BBB disruption after the intra-arterial injection of hypertonic solutions. Utilising this fact, further studies were performed to assess the effect of intra-arterial injections of various water-soluble CM on the permeability of the BBB. Whereas isotonic saline resulted in no change, hypertonic ionic methylglucamine iothalamate produced consistent, although variable breakdown of the BBB as demonstrated by both Evans' Blue staining and CT enhancement. Although this was thought to be due to the hyperosmolality of the methylglucamine iothalamate, a solution of 25% mannitol which has a similar osmolality to methylglucamine iothalamate did not produce the same degree of breakdown at a similar dose. This indicates that although the osmolality of particular solutions remains a major factor in producing BBB disruption following intra-arterial injections, other factors must play a part. The viscosity of methylglucamine iothalamate is more than twice that of 25% mannitol at 37 degrees centigrade and it is postulated that this may be a factor in BBB

disruption by increasing the contact time with the endothelium of the cerebral capillaries following intra-arterial injection.

Using similar dose rates and iodine concentration as methylglucamine iothalamate, the non-ionic CM, metrizamide, iopamidol and iohexol failed to produce any evidence of BBB disruption. This is thought to reflect their lower osmolality when compared with methylglucamine iothalamate and 25% mannitol. As neurotoxicity appears to be at least partly related to the effect of CM on the blood-brain interface, the blood-brain barrier, these studies suggest that non-ionic CM with their lower osmolality should replace ionic CM for intra-arterial angiography.

Large intravenous doses of ionic CM are recommended for CT enhancement and digital intravenous angiography. Such large doses of ionic CM may briefly increase the osmolality of blood and hence lead to BBB disruption. However, studies with large doses of ionic sodium iothalamate in rabbits failed to demonstrate any quantitative evidence of BBB disruption. This probably reflects the rapid distribution of water-soluble CM into the plasma and also the extracellular fluid of non-neural tissue following intravenous injection resulting in rapid dilution of the CM within blood.

Intrathecal ionic CM are known to be more neurotoxic than equivalent iodine concentrations of non-ionic CM. It has been suggested that the toxicity of metrizamide is related to brain penetration and concentration. Studies were therefore carried out to compare the rate of brain penetration and concentration of ionic methylglucamine iothalamate and non-ionic metrizamide and iopamidol.



The depth of penetration and the concentration of CM in the brain parenchyma 60 minutes after intrathecal injection were found to be the same for each. This indicates that the relative difference in neurotoxicity is not due to a different rate of penetration across the CSF-brain interface but must be related to the molecular structure of the individual CM. Studies with iopamidol showed that there is rapid passage of CM across the CSF-brain interface and that a positive rate of diffusion across the CSF-brain barrier continues at least up to 60 minutes with an increase in concentration within the brain parenchyma.

Although there is no active CSF circulation in the spinal subarachoid space, a clinical study indicated that following lumbar myelography in which metrizamide was deliberately pooled in the lumbar thecal sac both during and after the examination, the CM passed cranially and by 6 hours was demonstrated in the intracranial CSF in the majority of patients with obvious brain penetration. This brain penetration of CM persisted for 24 hours, with an increase in depth of penetration and without a reduction in the concentration within the brain parenchyma. Gross brain penetration by metrizamide was demonstrated in the absence of any headache, neurological sequelae or post-myelographic EEG changes. No change in the density of the white matter was demonstrated in the absence of any intraventricular reflux to suggest penetration of CM into the white matter and there was no evidence of a reduction in density to suggest the development of brain oedema.

It was recently suggested that following a large intravenous dose of water-soluble CM that the CM may pass into the CSF across the

blood-CSF interface, allowing intravenous CT myelography to be performed. Studies with ionic sodium iothalamate showed that there was only minimal passage of CM across the blood-CSF interface after intravenous injection indicating that intravenous enhancement of the CSF is not possible.