Effect of Mannitol on rCBF in Canine Thalamic Ischemia — An Experimental Study

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SUMMARY Using the canine thalamic infarction model, we have investigated the effects of 10 ml/kg of 20% mannitol on the hemodynamics of the ischemic brain. Mannitol was found to cause an increase in rCBF, but it is not marked in animals with severe ischemic foci. Increases were statistically significant in the animals with moderate ischemia. Increases in rCBF due to mannitol administration lasted for about 1 hour, as did the rise in serum osmolarity. The actual relationship between these two parameters, remains unclear.

EXPERIENCE with a case in which direct surgery on a cerebral aneurysm was performed under normothermia and normotension, and long occlusion of cerebral vessels was unavoidable, led to the idea that mannitol may have a suppressive effect on the development of cerebral infarction. Since then, various animal experiments to test this idea have been undertaken and reported extensively.1-9

Mannitol has been widely used to decrease cerebral volume and it has been demonstrated by various investigators that it increases cerebral blood flow4,10,11 and that such increases are unrelated to changes in blood pressure.10,12 Unfortunately, little work has been done to determine whether or not mannitol has the ability to increase cerebral blood flow in pathological states, such as brain ischemia.

The present paper reports an investigation on the effects of administration of mannitol on the regional cerebral blood flow (rCBF) at a focus of brain ischemia.

Materials and Methods

(1) Determination of rCBF at the ischemic focus (fig. 1)

Nineteen adult mongrel dogs weighing roughly 10 kg each were used. As an experimental model for cerebral infarction, we used the canine thalamic infarction model previously developed by us.8 Briefly, under the intravenous administration of 35 mg/kg sodium pentobarbital, an endotracheal tube was inserted and, under spontaneous respiration, right temporal craniotomy was performed. After placing the dogs in a stereotaxic apparatus, a deep recording electrode was placed in the anterior portion of the nucleus ventralis of the thalamus, using the stereotaxic atlas of Lim et al.13 Correct placement of the bipolar electrode was confirmed by the appearance of rhythmical activity and waxing and waning at about 100 µV and 10 Hz.14 The electrode for EEG recording was a bipolar electrode made of two 0.25 mm stainless steel wires, insulated except for 0.5 mm at their tips and with the tips separated by 1 mm. For rCBF measurements, a needle-type platinum electrode (0.3 mm diameter) insulated except for the final 0.5 mm, was cemented to the EEG elec-
trode. After implantation of the electrode, a small incision in the dura mater was made over the temporal lobe using a surgical microscope and 4 of the trunk arteries at the base of the brain (internal carotid artery, anterior cerebral artery, middle cerebral artery, and posterior communicating artery) were dissected and exposed. Next, the animal was connected to a Harvard respirator. For immobilization purposes, 0.04 mg/kg/hr of pancuronium bromide was administered intravenously and adequate anesthesia was maintained by intravenous administration of 2.5 mg/kg/hr of sodium pentobarbital. Intermittent sampling of arterial blood was also done, and pH, PaO\textsubscript{2}, and PaCO\textsubscript{2} levels measured using a blood gas analyzer were maintained within physiological limits. Continuous recordings of systemic blood pressure were made on a strain gauge manometer via a catheter inserted into the abdominal aorta. Rectal temperature was also monitored and maintained within physiological limits.

Ten ml/kg of 20\% mannitol was administered over a 10 minute interval by intravenous drip 30 minutes after occlusion of the 4 cerebral vessels. rCBF measurement were made at 10, 45, 80 and 120 minutes following occlusion. The value of rCBF was determined from the initial slope method of the clearance curve following 3 minutes of inhalation of 5-10\% hydrogen gas.

The actual procedure was as follows: following the preocclusion rCBF measurement, the 4 intracranial arteries which had previously been exposed were occluded in rapid succession with Scoville clips. Those animals showing rCBF decreases to less than 30\% of the preocclusion value were considered "severe ischemia" animals, and those showing decreases to 30-60\% were considered as "moderate ischemia" animals. After completion of the experiments, autopsies were performed and placement of the electrode tip in the anterior thalamus confirmed.

There were 9 dogs in the severe ischemia group, 5 of which received no drug treatment and 4 of which received mannitol. There were 10 dogs in the moderate ischemia group, 6 of which received no drugs, and 4 of which received mannitol.

(2) Sequential measurements of serum osmolarity and electrolytes

Five adult mongrel dogs were used. Intravenous infusion of 10 ml/kg of 20\% mannitol was done over 10 minutes and serum osmolarity and electrolytes were measured prior to and 1, 2, 4 and 6 hours subsequent to mannitol administration.

Experimental Results

(1) Changes in rCBF at the ischemic focus during vascular occlusion

i. Severe Ischemia Group (fig. 2)

In the 5 untreated animals, the preocclusion rCBF was 39.6 ± 9.8 ml/100 g/min. The rCBF, measured at 10 minutes after occlusion, fell to 8.2 ± 2.3 ml/100 g/min. The post-occlusion value was 21 ± 3\% of the preocclusion value. Thereafter, rCBF were 8.8 ± 2.0, 8.8 ± 2.5 and 8.5 ± 2.2 ml/100 g/min measured at 45, 80 and 120 minutes intervals following occlusion. In the 4 mannitol treated dogs, the preocclusion rCBF was 38.1 ± 2.5 ml/100 g/min. The rCBF, measured at 10 minutes after occlusion, fell to 7.6 ± 1.5 ml/100 g/min. The postocclusion value was 20 ± 3\% of the preocclusion value. After completion of mannitol administration, rCBF were 9.3 ± 2.3, 7.5 ± 1.5 and 7.3 ± 1.7 ml/100 g/min measured at 45, 80 and 120 minutes following occlusion. Differences between rCBF in the untreated group and in the mannitol treated group was not statistically significant.

ii. Moderate Ischemia Group (fig. 3)

In the 6 untreated animals, the preocclusion rCBF was 30.6 ± 8.3 ml/100 g/min. The rCBF, measured at...
FIGURE 3. Effect of mannitol on rCBF in moderate thalamic ischemia. ** P < 0.01. ● untreated animals, ○ mannitol treated animals. ■ occlusion.

10 minutes after occlusion, fell to 12.2 ± 2.8 ml/100 g/min. The post-occlusion value was 43 ± 7% of the preocclusion value. Thereafter, rCBF were 12.4 ± 2.7, 11.8 ± 2.1 and 11.3 ± 2.1 ml/100 g/min measured at 45, 80 and 120 minutes following occlusion. Among the 4 mannitol treated animals, the preocclusion rCBF was 29.1 ± 5.3 ml/100 g/min. The rCBF, measured at 10 minutes after occlusion, fell to 12.9 ± 2.6 ml/100 g/min. The post-occlusion value was 45 ± 10% of the preocclusion value. After mannitol administration, rCBF values were 21.0 ± 6.7, 15.6 ± 3.0 and 11.3 ± 5.4 ml/100 g/min measured at 45, 80 and 120 minutes following occlusion. The rCBF values measured at 45 and 80 minutes followed occlusion, were significantly greater among the mannitol treated group than in the untreated control group.

Results for continuous systemic blood pressure measurements (mean arterial pressure) were as follows. In the untreated dogs, no significant changes occurred, but in the mannitol treated group, blood pressure rose to a maximum at the completion of drug administration (5–15 mm Hg, averaging 9 ± 3 mm Hg). The time required for recovery to preadministration levels was, however, short (5–19 min, averaging 9 ± 4 min).

(2) Sequential Changes In Serum Osmolarity and Electrolytes (fig. 4 and 5)

Prior to mannitol administration, serum osmolality was 291–310 mOsm · Kg/H₂O, averaging 301 ± 6 mOsm. After completion of drug treatment, osmolality reached a maximum of 309–347 mOsm, one hour after which osmolarity declined to 299–320 mOsm (averaging 311 ± 8 mOsm), but values were still 10 mOsm greater than the preadministration level. Nonetheless, there were slight decreases until, after 6 hours, normal values of 304 ± 5 mOsm was reached.

With regard to serum electrolytes, Na⁺ and Cl⁻ showed transient decreases of roughly 10 mEq/l due to mannitol, but gradually returned to preadministration levels. No definite trend with regard to K⁺ was evident.

Discussion

A number of previous studies have been concerned with the relationships between mannitol administration and rCBF. From clinical experiences, Meyer et al. reported that mannitol causes an increase in CBF in patients with recent cerebral infarction. Johnston et al. demonstrated experimentally that mannitol causes an increase in CBF unrelated to changes in intracranial pressure. In normal dogs, we have made measurements of rCBF in the thalamus using the hydrogen clearance and heat clearance methods. By intravenous infusion of 20% mannitol (10 ml/kg) over 10 minutes, rCBF increases to a maximum of 4–14 ml (29 ± 13%) and after 60–90 minutes, rCBF levels return to preadministration levels.

Such experimental studies, however, have been concerned with the effects of mannitol on the normal brain, so that generalization of those results to the ischemic brain is not justified. In fact, with regard to the effects of mannitol on rCBF in animal models of cerebral ischemia, we have found only a single report by Brown et al. using a cerebral trauma model in the monkey. In no study have there been measurements at a focus of cerebral ischemia nor discussion of the effects of mannitol at the site.
Various possibilities have been suggested regarding the mechanism of increased rCBF caused by mannitol — including decreases of intracranial pressure, increases in mean arterial pressure, decreases in cerebral vascular resistance, and changes in viscosity of the blood. Recently, Little has reported measurements of the size of the lumen of cerebral capillaries using an ischemic model in the cat and shown that mannitol produces improvements in microcirculation of the brain.

In our experiments, an open cranium is required for producing the cerebral ischemia, so it is possible but unlikely that changes in intracranial pressure were responsible or contributed to the effects of mannitol. Since the increase in mean arterial pressure due to mannitol is only 10 mm Hg and lasted for about 10 minutes, the increase in rCBF being solely due to an increase in perfusion pressure is also thought to be unlikely. The fact that the period of increased rCBF follows closely the increase in osmolarity suggests that this is the principal mechanism whereby tissue pressure decreases as blood osmolarity increases due to dehydration of normal and ischemic brain. The present data from our experiments, however, are not sufficient to be able to draw definite conclusions. Why, for example, the increases in rCBF are not similar in modes of severe and moderate cerebral ischemia remains to be investigated.

Regardless of the final resolution of the above problems, the present results argue strongly for suppressive effects of mannitol therapy during the development of cerebral infarction, as reported elsewhere, and they cannot be explained solely in terms of rCBF increases. In light of the diverse effects produced on the brain by mannitol administration, already reviewed, the mechanisms of mannitol’s effects on ischemic brain function should be studied from several different aspects. Particularly interesting among these experiments with mannitol have been the following observations: Using a complete cerebral hemisphere infarction model in the dog (in which a bloodless cerebral hemisphere is produced), administration of mannitol prior to occlusion suppresses the development of pathological changes in neurons of the 3rd layer of the cerebral cortex.

Furthermore, using a canine model of a completely ischemic brain, data have been obtained suggesting that mannitol may also act as a free radical scavenger.

References
Histopathology of the Brain Vascular Network in Moyamoya Disease

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Summary

There is an unusual vascular network at the base of the brain in patients with moyamoya disease. We detected various histologic lesions in the perforating arteries of 22 patients. Vessels showing rupture ranged from 50 to 530 μm in diameter; they were dilated, some had fibrin deposits in the wall, fragmented elastic laminae and attenuated media. Non-ruptured perforating arteries (diameter 200 to 550 μm) revealed microaneurysm formation, focal fibrin deposits and marked attenuation of the wall thickness with diminution of the elastic lamina. These changes seem to predispose to rupture of perforating arteries. Stenotic changes such as fibrous intimal thickening, collapse of the lumen and thrombosis were detected in 14 out of 22 cases. Morphometric analysis of perforating arteries indicated that arteries showing extreme degrees of stenosis or dilatation were more frequent in the patients with moyamoya disease than in the control cases. Dilatative arteries were more frequent in the young patients and stenotic vessels were, in contrast, less frequent in the young patients.

MOYAMOYA DISEASE is a clinical entity with angiographical findings of bilateral stenoses or occlusion of the distal ends of internal carotid arteries and an unusual vascular network at the base of the brain.1 The disease is characterized by focal stenoses or occlusion at the distal ends of both internal carotid arteries and at the proximal regions of the anterior and middle cerebral arteries. Stenoses are due to eccentric fibrous intimal thickening with laminated elastic fibers.2,3 The morphogenesis of these intracranial vascular lesions remains obscure. We report the abnormalities of perforating arteries including lenticulostrate and thalamoperforate arteries in 22 Japanese patients with moyamoya disease.

Materials and Method

Twenty-two cases clinically diagnosed as moyamoya disease and autopsied during the years from 1970 to 1979 were examined pathologically. Nineteen of the 22 cases have already been reported with regard
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