Experimental Cerebral Infarction

Part 3: Protective Effect of Mannitol in Thalamic Infarction in Dogs

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SUMMARY Whether or not mannitol can prevent infarctions in ischemic brain tissues was investigated utilizing the thalamic infarction model in dogs. Twenty dogs were divided into equal control and mannitol treatment groups. Temporary 4 vessel clipping for 60 minutes was adopted as the standard procedure for both groups. The only difference between the groups was the administration of 2 g/kg of mannitol before the arterial occlusion. In the controls, 6 of 10 dogs showed infarctions verified by histological changes at the seventh post-ischemic day. In the mannitol group only 1 dog in 10 showed infarction. The difference is statistically significant.

IN EXPERIMENTAL STUDIES of cerebral infarction, it is important to develop a method for constant production of cerebral infarction by temporary occlusion of cerebral arteries. However, difficulties in achieving temporary cerebral ischemia in animals have delayed studies of the prevention and treatment of cerebral infarction. As described, we have succeeded in producing thalamic infarction in dogs following simultaneous occlusions for 60 and 120 minutes respectively of all 4 brain arteries.

In this paper, the protective effect of mannitol in cerebral infarction is explored utilizing the thalamic infarction model in dogs.

Methods

Twenty adult mongrel dogs weighing about 10 kg were anesthetized with intravenous sodium pentobarbital (Nembutal 35 mg/kg). After the removal of the zygomatic arch and temporal craniectomy, simultaneous occlusions were performed on all four cerebral arteries (the internal carotid, anterior cerebral, middle cerebral and posterior communicating arteries) using the Scoville aneurysmal clip and the Zeiss operating microscope. The 20 dogs were divided into 2 equal groups: control and mannitol treatment. Temporary clipping for a period of 60 minutes was used as a standard for both groups. The only difference between the groups was the administration of 2 g/kg of mannitol to one group before the arterial occlusions.

All dogs were sacrificed on the seventh postoperative day and coronal slices, taken from a point 5 mm behind the optic chiasma, were microscopically examined. The thalamic infarctions were estimated and graded according to the following 4-point scale: grade 0, no infarction in the thalamus, grade 1, small infarction foci less than half of the thalamus, grade 2, infarction affecting about half of the thalamus, grade 3, infarction more than two-thirds of the thalamus.

We found that the electroencephalogram (EEG) of dogs with thalamic infarction before and after administration of mannitol following arterial occlusion was significantly different. The EEG in control animals showed low voltage slow wave activities just after the arterial occlusion but with thalamic infarction before and after administration of mannitol, few with thalamic infarction before and after administration of mannitol.

In the control group, 6 out of 10 showed infarction of grade 2 or 3, and in the mannitol treated group, 1 of 10 showed infarction of grade 3 (table 1). The differences were statistically significant ($P < 0.03$).

Discussion

Although various experiments have been carried out on infarction after ischemia, few have evaluated the effect of mannitol on ischemia. Cantu and Ames reported significant protection against vascular lesions in acute experimental cerebral ischemia induced by occlusion of aorta in rabbits when serum osmolarity was increased with mannitol. In other reports the protective effect of mannitol on ischemic renal damage and ischemic myocardium has been documented. The value of mannitol in protecting against ischemia has only been studied in acute ischemia induced by complete circulatory arrest. Powell et al. revealed that in dogs subjected to 12 hours of occlusion, necrosis was remarkably widespread in untreated dogs in comparison with those treated with mannitol.

We found that the electroencephalogram (EEG) of dogs with thalamic infarction before and after administration of mannitol following arterial occlusion was significantly different. The EEG in control animals showed low voltage slow wave activities just after the arterial occlusion but with administration of mannitol before arterial occlusion, few changes in the EEG took place (fig. 1).

In summary, it was shown that mannitol was effective in

| Grade 0  | 4  | 9  |
| Grade 1  | 0  | 0  |
| Grade 2  | 2  | 0  |
| Grade 3  | 4  | 1  |
| Total    | 10 | 10 |

(P < 0.03 Fisher)

Grade 0: no infarction in thalamus.
Grade 1: small infarction foci in thalamus.
Grade 2: infarction affecting about half of thalamus.
Grade 3: infarction affecting more than two-thirds of thalamus.

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Controlled Trial of Ornithine Alpha Ketoglutarate (OAKG) in Patients with Stroke

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SUMMARY A double blind controlled trial of ornithine alpha-ketoglutarate (OAKG) was carried out on 50 patients admitted to the Royal Free and Royal Northern Hospitals, London, suffering from a recent stroke. Significant improvement was found in patients treated with OAKG when examined on the fifth day of therapy as compared to their control cases. The therapy was given for 5 days. When the patients in the treated and the control groups were compared 10 days after the beginning of treatment, there were no differences between the 2 groups. Implications of these findings are discussed.

THE DRUG ornithine alpha-ketoglutarate (OAKG) has been used for many years in Europe for the treatment of hepatic encephalopathy. It has been shown to reduce blood ammonia concentration and to partly reverse the brain metabolic changes of hepatic encephalopathy but in clinical use for fulminant hepatitis it has been less successful.

Both experimental hypoxia and ammonia intoxication in animals have long been known to provoke cerebral anaerobic glycolysis with resultant lactate formation. The anaerobic glycolysis due to hyperammonemia can be attenuated by the administration of ornithine alpha-ketoglutarate. The mechanism by which these changes occur has not been established. Possible mechanisms include the bypassing of the pyruvate dehydrogenase stage of glucose breakdown or the replenishing of the intermediates of the citric acid cycle depleted by ammonia. For many years glucose was considered to be the only substrate that the brain could use. This is now known to be incorrect. Since brain glucose consumption falls and oxygen rises after or-

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