Experimental Cerebral Infarction: Modification by Treatment with Hemodiluting, Hemoconcentrating, and Dehydrating Agents†

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Recent attempts to treat peripheral vascular obstruction by using agents designed to alter the rheologic characteristics of the blood have met with some success in humans and in experimental models in animals. Such agents, including low-molecular-weight dextran (dextran-40, Rheomacrodex), also have been used as plasma expanders and during cardiac surgery with extracorporeal circulation. The apparent success of these agents in favorably influencing the clinical response to peripheral vascular obstruction has suggested that they might be used in the treatment of acute cerebral infarction.

Our studies, and those of others, of the superficial microvasculature and microcirculation of the cerebral cortex of animals after occlusion of the middle cerebral artery have shown that definite changes result from ischemia. These changes can be modified by the intravenous administration of certain hemodiluting agents. Similar changes in the superficial vessels of the cortex have been observed, in dogs undergoing hypothermic perfusion, as the temperature of the brain approached 17°C. Hemodilution with saline and low-molecular-weight dextran alters the changes which occur with hypothermia (Nofzinger and Sundt, unpublished data). Thus, there are several reasons for investigating the effect of various hemodiluting, hemoconcentrating, and dehydrating agents on cerebral infarction in animals. One of these agents, low-molecular-weight dextran, has been used to treat experimental cerebral infarction in dogs, with somewhat favorable results.

In this paper we shall report the results of the modification of cerebral infarction in cats by a variety of agents. The agents include: hyperoncotic solutions of low-molecular-weight dextran, serum albumin, and urea, individually and in combination; homologous serum; physiologic saline; and packed erythrocytes.

Materials and Methods

Occlusion of Middle Cerebral Artery. In 64 cats, a middle cerebral artery was occluded under sterile conditions by a technique developed and standardized prior to this study. Briefly, by using a Zeiss operation microscope and microsurgical technique, the artery was approached extradurally through the retro-orbital space after removal of the greater wing of the sphenoid bone. The dura was incised over the optic nerve, and the delicate arachnoidal tissue, which forms a web around the major vessels of the circle of Willis, was dissected free. The loop of the middle cerebral artery was elevated at its origin at the circle of Willis without damage to small collateral or perforating vessels, and a small Mayfield clip was applied to it. Adequacy of the occlusion of the artery was verified by observing a decrease in the velocity of the flow of the formed elements of blood through the superficial vessels of the cortex (seen through the transparent dura with the operation microscope) and by noting that the entire width of the artery was in the jaws of the clip. The dura over the surface of the brain was left intact. The wound was irrigated and closed in three layers.

There was very little trauma to the brain in this procedure, and no hypotension was produced.
Treatments. Sixteen cats, a control group, received no treatment.

Five cats were given physiologic saline, 25 to 30 ml/kg, intravenously through a polyethylene catheter in a superficial vein of a hind limb during a 12-hour period beginning 15 to 30 minutes prior to the occlusion of the middle cerebral artery.

Five cats were given a single intravenous injection of homologous serum, 10 ml/kg, at 15 to 30 minutes prior to occlusion of the artery.

Five cats were given low-molecular-weight dextran (10% solution in physiologic saline) intravenously according to the following schedule: 15 to 30 minutes before occlusion of the artery, 10 ml/kg; and 12 hours postoperatively, 4 ml/kg; 18 hours postoperatively, 10 ml/kg; 24 hours postoperatively, 4 ml/kg; and 30 hours postoperatively, 10 ml/kg.

Ten cats were given salt-poor human serum albumin. A 25% solution of albumin was mixed with an equal amount of Ringer's solution and the mixture (12.5% albumin) was given intravenously as follows: 15 to 30 minutes before occlusion of the middle cerebral artery, 8 ml/kg; 6 and 12 hours postoperatively, 3 ml/kg; 18 hours postoperatively, 8 ml/kg; and 24 and 30 hours postoperatively, 3 ml/kg.

Six cats were given a concentrated urea solution (30% in 5% dextrose solution) intravenously: 6 hours postoperatively, 1 gm/kg; 24 and 36 hours postoperatively, 0.5 gm/kg.

Five cats were given packed erythrocytes, 10 ml/kg. The cells, obtained from heparinized donor animals, were infused 15 to 30 minutes after occlusion of the middle cerebral artery.

Two cats were given a combination of homologous serum and low-molecular-weight dextran in the amounts described above.

Ten cats were treated with a combination of albumin, low-molecular-weight dextran, and urea. The regimen in these animals was: albumin solution, 4 ml/kg, and low-molecular-weight dextran solution, 5 ml/kg, given intravenously 15 to 30 minutes before occlusion of the middle cerebral artery, followed by urea, 1 gm/kg, 6 hours postoperatively; albumin and low-molecular-weight dextran, 4 ml/kg each, 12 and 18 hours postoperatively; urea, 0.5 gm/kg, 24 hours postoperatively; albumin and low-molecular-weight dextran, 4 ml/kg each, 30 hours postoperatively; and urea, 0.5 gm/kg, 36 hours postoperatively.

Evaluations. Clinical evaluation. Each animal was examined daily for level of consciousness, ability to walk, tendency to circle while walking, weakness of the extremities, differences in posture of the forelimbs and hind limbs (such as doubling of the front paw and extension of the hind limb), and visual field defects.

Observation of the cortex. Five to 7 days after occlusion of the middle cerebral artery each animal was anesthetized with pentobarbital (25 mg/kg injected intrapleurally). An endotracheal tube was inserted, and the scalp wound was opened. The site of craniectomy was enlarged with rongeurs, the dura overlying the convexity of the cerebral hemisphere on the side of the occlusion was removed, and the brain was covered with plastic film (Saran). The superficial microvasculature and microcirculation of the cortex were examined with the operation microscope for degree of apparent increase or decrease in numbers of small cortical vessels and for velocity of the flow of formed elements of blood. In certain animals, photographs were made.

Evaluation of infarcts. The brain was perfused, through the brachiocephalic artery, with 10% formalin and removed. After fixation, each brain was sectioned in a contoured miter box, and the individual sections of brain were photographed. The volume of the cerebral infarct was computed by the average end-area method and corrected to a standard as described previously. Histologic sections of the infarct were prepared, compared with the photographs, and evaluated for histologic changes.

The means of the corrected volumes of the cerebral infarcts of each of the eight groups of animals to which agents were administered were compared statistically with the means of the corrected volumes of the untreated control group. Confidence intervals at the 95% level were computed for the comparisons.

Results

Immediate Effect of Occlusion of Middle Cerebral Artery. Immediately after occlusion