Effect of Steroid on Ischemic Brain Edema

Analysis of Cytotoxic and Vasogenic Edema Occurring During Ischemia and After Restoration of Blood Flow

UMEO IT0, M.D., KIKUO OHNO, M.D., YASUO SUGANUMA, M.D., KENICHI SUZUKI, M.D., AND YUTAKA INABA, M.D.

SUMMARY Mongolian gerbils were observed for the effects of β-methasone on ischemic brain edema which developed during ischemia or after blood flow restoration. The severity of brain edema was determined by measuring water content of the ischemic cerebral hemisphere, using the wet and dry methods. Sodium and potassium ions were extracted from homogenized brains with 0.75N HNO₃ and ion concentration measured by flame photometry. Passage of RISA from blood into the cerebral parenchyma, as an indicator of blood-brain barrier change, was determined with a γ-scintillation counter.

In the cytotoxic edema model, animals were killed after 9 h permanent ischemia or 3 h after 1 h ischemia. In the simultaneous cytotoxic and vasogenic edema model, the animals were killed either 20 h or 3 days following 1 h ischemia, or 3 h after blood flow restoration following 6 h ischemia.

Steroid treatment was ineffective in ischemic brain edema of the cytotoxic or vasogenic type.

CEREBRAL EDEMA is one of the most serious complications in acute cerebral infarction, frequently leading to patient morbidity and mortality. Clinical studies evaluating the efficacy of steroid therapy have been equivocal to date as some investigators found it to be beneficial, while others did not. Using steroid therapy in experimental animals, some investigators reported good results, while others that it was not effective in the treatment of ischemic cerebral edema. Bartko et al., had studied the pure focal oligemic ischemia model, using measurement of water and electrolyte content as an exact indicator of brain edema. Hoppe et al., studied the same model, found that steroids had beneficial effects on blood-brain barrier (BBB) change.

In our previous study we measured water, sodium and potassium content as well as RISA permeability in the ischemic hemisphere of Mongolian gerbils and found that pure cytotoxic edema occurs during ischemia and during a short time after blood flow restoration. Subsequently, vasogenic edema was caused by the leakage of plasma constituents from blood due to BBB change. We also noted that the degree of cytotoxic and vasogenic edema depends on the duration of the ischemic insult.

Review of the literature revealed that the effect of steroids on brain edema which occurs after restoration of the blood flow following temporary ischemia, has not been investigated to date. In the present study we evaluated the effect of steroid treatment on cytotoxic and vasogenic edema in the ischemic brains of Mongolian gerbils.

Materials and Methods

In each experiment, Mongolian gerbils weighing from 60 to 80 g were used. Eight animals per group received steroid administration and 8 were injected with a placebo. Five animals served as the control.

The animals were lightly anesthetized with ether and after careful isolation of the left common carotid artery under an operating microscope, it was clipped with Scovill's aneurysmal clip. Only animals with the typical clinical symptoms of ischemia (about 30%) were used. In the cytotoxic edema model, animals were sacrificed after 9 h clipping (Group 1) or, alternatively, the clip was released after 1 h ischemia and the animals were killed 3 h thereafter (Group 2). In the simultaneous cytotoxic and vasogenic edema model, 3 groups of animals were used. Following 1 h ischemia, the animals were sacrificed either 20 h (Group 3) or 3 days (Group 4) after restoration of the blood flow, or 3 h after blood flow restoration following 6 h ischemia (Group 5).

Double-blind procedures were applied in each experimental set. Each steroid-treated animal received 4 intraperitoneal injections at 6 h intervals of a total of 2.5 mg/kg/day of β-methasone. Each placebo animal received intraperitoneal injections of 0.125 ml saline at the same injection schedule. The inception of steroid administration was 48 h prior to the clipping of the carotid artery and continued until the animals were killed.

Animals used for the measurement of water, sodium and potassium content were killed by decapitation and the posterior two-thirds of the left cerebral hemisphere was removed immediately and measured. The percentage of water content was determined by the wet and dry methods. After homogeniza-
tion of the dried brain, sodium and potassium ions were extracted with 0.75N HNO₃, ion content measured by flame photometry, and calculated for mEq/kg dry weight.

For determination of ¹²³I-albumin (RISA) permeability, 3 h prior to killing the animal, an intravenous injection of 10 μCi of RISA (8.77 μCi/mg protein: protein 11.4 mg/ml: 2.12% free or loosely bound iodide) was administered, following the removal of free iodide by Dowex 1-X8 (50-100 mesh) column. Venous blood — 0.1 ml — was collected in a plastic tube with a tight plug before killing the animals by flushing the cerebral vessels with saline. The posterior two-third of the left cerebral hemisphere was immediately removed and placed in a plastic tube with a tight plug. After weighing each sample by chemical balance, the gamma activity of ¹²³I in the blood and brain samples was measured with an Aloka well scintillation counter and the ratio of tissue:blood radioactivity was calculated. Procedures used in determining water, sodium and potassium content as well as RISA permeation, were described earlier.¹⁹

Results

Cytotoxic Edema

Determination of water, sodium and potassium content in the ischemic hemisphere of Group 1 animals revealed that there was no significant difference between the steroid-treated and placebo groups (fig. 1). In Group 2 animals, we noted a slight but statistically significant (p < 0.05) sodium content increase in the steroid-treated animals (fig. 2).
Simultaneous Cytotoxic and Vasogenic Edema

Determination of water, sodium and potassium content and passage of RISA from blood into ischemic brain tissue revealed that in Group 3 animals there was a moderate, statistically significant ($p < 0.05$) water increase in the steroid-treated animals (fig. 3). No statistically significant differences were noted among the steroid-treated and placebo animals of Groups 4 and 5 (figs. 4, 5).

These results evidenced no statistically significant beneficial effects of steroid therapy in the treatment of cytotoxic and vasogenic edema during ischemia and after blood flow restoration.

Discussion

Clinical evaluations of steroid therapy in edema associated with brain tumors and brain injury have been reported$^{23-26}$ and in these studies, clinical signs were used to determine the efficacy of steroid therapy. Recently, Reulen et al.$^{27}$ reported direct evidence for the effectiveness of dexamethasone in brain edema associated with brain tumors by measuring water, sodium and potassium content of biopsied peritumoral edematous brain tissue. Meinig et al.$^{28}$ using planimetry of peritumoral low density areas in CT scans, found dexamethasone to be effective in peritumoral brain edema. However, Kullberg$^{29}$ measured the intracranial pressure of traumatic brain edema patients and found that steroid treatment had little or no effect on the continuous elevation of intracranial pressure, while it had some effect on the high pressure pattern which showed plateau waves. His findings indicate that steroids are not always effective on brain edema itself. In experimental cold lesion edema, the steroid effect on water and electrolyte content is still under debate.$^{30, 31}$

In ischemic brain edema, the evaluation of steroid therapy has been based primarily on clinical signs.$^{1-9}$ No clinical studies directly assessing the degree of
Ischemic brain edema by water or electrolyte content determination or CT scan have been reported to date. In experimental studies using the permanent ischemia model, some investigators measured water and electrolyte content and reported good results.\textsuperscript{10-13} Water and electrolyte content were measured by Plum et al.\textsuperscript{14} and Siegel et al.,\textsuperscript{15} neither of whom obtained good results regarding the efficacy of steroid treatment. However, Plum et al. used a rather anoxic model and Siegel et al. a microembolism method which may have interfered with drug delivery to the ischemic lesion. Because of the slow effects of steroids,\textsuperscript{16} administration of \( \beta \)-methasone in the present study started 48 h prior to the beginning of the experiments.\textsuperscript{10,14,18}

Hoppe et al.,\textsuperscript{17} who measured pertechnetate uptake in the ischemia model, reported that steroids were effective on BBB change. However, we suggest that the BBB change effected by pertechnetate extravasation is different from that which is due to plasma protein extravasation, because these two agents are of different molecular sizes.\textsuperscript{19} Therefore, BBB change leading to vasogenic edema must be assessed by a plasma protein tracer such as RISA.\textsuperscript{19}

In our previous study,\textsuperscript{19} we used the ischemic cerebral hemisphere of Mongolian gerbils to measure water, sodium and potassium content and passage of RISA from blood to cerebral tissue. In the permanent ischemia group, water and sodium increased, and potassium content decreased with lengthening of the ischemic insult and no RISA uptake was observed even after 9 h permanent ischemia. Therefore, we suggest that brain edema observed during ischemia is cytotoxic in type.\textsuperscript{18,21}

In the 1 h temporary ischemia group, restoration of blood flow brought about a drastic reduction in the rate of water content increase, a reduction in sodium and a recovery in potassium content until 5 h. However, water and sodium content increased and potassium content decreased gradually from 8 to 72 h, while RISA passage increased markedly. These results suggest that cytotoxic edema predominates during the first 5 h after blood flow restoration and
that cytotoxic and vasogenic edema occur simultaneously thereafter.\textsuperscript{19, 21}

On the other hand, following 6 h temporary ischemia, a drastic increase in water and sodium content as well as a marked simultaneous increase in RISA passage was noted in the 3 h following release of the clip. It is estimated from the amount of RISA uptake that about 30% of water increase is due to vasogenic edema and 70% is thought to be derived from cytotoxic edema.\textsuperscript{19, 21}

Therefore, in the present study, animals from Groups 1 and 2 represent the cytotoxic, and those from Groups 3–5 the simultaneous cytotoxic and vasogenic edema model.

We found that \(\beta\)-methasone was not effective in cytotoxic or vasogenic edema following short or long duration of ischemic insult. Although \(\beta\)-methasone was administered for a total of 5 days in Group 5 animals, no beneficial effect was observed on either brain edema or BBB change.

Although our results indicate that steroid treatment has no effect on ischemic brain edema, steroid-treated animals in all groups were more active than those receiving placebo administration in the early stages of the experiment. In the later experimental stages, however, both sets showed signs of weakness, possibly due to progression of brain edema. Pappius\textsuperscript{30} also noted that steroid administration was not effective in cold lesion edema in cats, however, she reported observing a remarkable improvement in cortical EEG activity. As evaluations of the efficacy of steroid therapy based on clinical signs have been equivocal to date,\textsuperscript{19–9} further studies are under way in our laboratory to discover possible yet undetected benefits from this type of therapy in improving the prognosis of cerebral ischemia patients.
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FIGURE 5. Effects of β-methasone on water, sodium and potassium content, as well as RISA passage, 3 h after clip release following 6 h ischemia. Steroid-treated and non-treated columns: mean values and S.E. for 8 animals. Control column: mean values and S.E. for 5 animals.

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U Ito, K Ohno, Y Suganuma, K Suzuki and Y Inaba

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