Massive Doses of Steroids in Cryogenic Cerebral Injury and Edema

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SUMMARY Cryogenic lesions were produced in the brains of rhesus monkeys and the accompanying edema measured by quantitative chemical methods. No effect on this type of edema could be demonstrated in animals treated with massive doses of steroids.

USE OF STEROIDS in the management of intracranial neoplasms is well established and it is generally accepted that the favorable clinical response is due to reduction of the accompanying cerebral edema. This observation has led to the use of steroids in other clinical situations in which there is also an accompanying cerebral edema, one of these being the management of acute strokes. The impetus to use steroids in strokes came about in spite of the fact that the pathogenesis of the edema in stroke is not the same as with tumors but on the assumption of a similarity in biologic behavior. The effectiveness of steroids in the management of strokes is controversial and it is not clear from the published experimental data whether or not the edema associated with ischemic infarction can be reduced by steroids. In the present report, an attempt was made to treat the edema associated with cryogenic cerebral lesions in the rhesus monkey by massive doses of steroids.

Review

There are 2 different types of cerebral edema associated with acute strokes in the human. One of these is characterized by the presence of a protein-rich extracellular fluid accumulating within the lesion and in the adjacent white matter. This is the type associated with intracerebral hemorrhage and with ischemic infarction when there is a significant hemorrhagic component. It corresponds to Klatzo's vasogenic edema which is also the type of edema associated with cerebral tumors. The second type is characterized by status spongiosis of the infarcted tissue with evidence of cell necrosis. This is seen in ischemic infarction and is sufficiently different from what Klatzo has described as cytotoxic edema to warrant a separate classification as ischemic brain edema. The various experimental models involving the production of generalized or localized cerebral edema

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ischemia have to a greater or lesser degree reproduced this second form of edema.²

Although there have been several attempts to reproduce intracerebral hemorrhage² and hemorrhagic infarction³-⁴ in experimental animals, none of these has included a description of an accompanying vasogenic edema as is seen in the human. The experimental prototype is the edema associated with the cryogenic lesion.⁵ The primary lesion here is a focus of hemorrhagic necrosis produced by focal freezing of the brain. The element of ischemic cell swelling seen in human infarction is lacking but the lesion borders are clearly defined and the edema which develops in the adjacent white matter is histologically indistinguishable from the vasogenic edema occurring in human strokes. The cryogenic lesion, as developed in our laboratory, involves freezing through the intact skull with liquid nitrogen as the refrigerant.⁷ Subsequent techniques developed in other laboratories, have involved exposing the dura⁸ or the brain,⁹ in order to produce the lesion. With these techniques a milder refrigerant, solid carbon dioxide, is used, and lesions of uniform size are produced. The advantage of utilizing the intact skull is that cerebral hemodynamics are preserved; the disadvantage is that the lesion size is variable and must be determined. This is done by measuring the surface area from a template of clear plastic. In order to compare different groups of animals, it must be shown that the lesion size is the same.

Since the cryogenic lesion involves only one hemisphere, chemical changes in the damaged hemisphere may be compared with the opposite hemisphere which serves as an inbuilt control. If total edema is to be assessed, then the total hemisphere must be analyzed; tissue samples can only give information about a portion of the hemisphere. In the techniques which we have developed, the hemisphere is separated from the brain stem and homogenated. The tissue is then analyzed for water and electrolytes.¹⁰ The degree of hemorrhage is determined from the increase of iron in the damaged hemisphere. Protein exudation is assessed from the uptake of ¹³¹ labelled albumin (RISA) and by quantitatively measuring the amount of Evans blue in the damaged hemisphere.¹¹ Since this dye is albumin bound, its presence in tissue quantitatively reflects albumin exudation.¹² The most valuable measurement for assessing edema, however, is simply the increase in weight of the damaged hemisphere as compared to the opposite hemisphere.

Various forms of therapy for cerebral edema were investigated in the rhesus monkey utilizing the above techniques. It was demonstrated that this form of edema could be reduced by treatment with pentobarbital, furosemide¹³ and reserpine.¹⁴ It was also decreased by systemic hypothermia¹⁵ and increased with hyperthermia.¹⁶ These publications demonstrate the validity of the chemical methods used in demonstrating changes in cerebral edema.

The general subject of the response of experimental cerebral edema to steroids was renewed in a prior publication¹⁷ and the response of ischemic edema in a recent review.² In spite of repeated efforts, including pretreatment, we have not been able to demonstrate suppression of the cerebral edema associated with cryogenic lesions in the rhesus monkey through the use of steroids.¹¹,¹⁷ Others, however, have reported suppression of edema in lesions made in cats¹⁶,¹⁸ and rabbits.²⁰ In all cases, the lesions were produced through the open skull with solid carbon dioxide as the refrigerant. In lesions produced with liquid nitrogen in both mice²¹ and cats,²² negative results were reported. There is evidence that the positive response is related to a lack of cellular inflammation.²

In 2 recent studies of acute head injury, decreased mortality was reported in patients receiving massive doses of dexamethasone, as compared to a group receiving the normal dose.²³,²⁴ In one of these,²³ diminished intracranial pressure was also reported. In addition, there is a recent report of patients with brain tumors who were not responding to conventional pharmacologic doses of steroids, but showed clinical improvement when massive doses were used.²⁵ In both our own studies and in the negative studies reported,²¹,²² conventional pharmacological doses of steroids were used. We have, therefore, repeated our studies on steroids in the rhesus monkey using massive doses.

Material and Methods

Cryogenic cerebral lesions were produced in 17 rhesus monkeys anesthetized with pentobarbital and given intravenous Evans blue and ¹³¹ labelled human albumin (RISA) prior to injury. The animals recovered from anesthesia in about 5 h and no further anesthetic was given until the time of sacrifice, 24 h after injury. A sample of venous blood was obtained just prior to sacrifice. Six animals received no treatment. Five animals were given 2 intramuscular doses of 10 mg of dexamethasone (Decadron) on the day prior to injury. Two additional doses were given on the day of injury and one more on the following day. Two animals, not pretreated, were given intravenous dexamethasone in a dose of 6 mg/k over a 10 min period, beginning 30 min after injury. This was repeated 4 h later. Four animals received intravenous methylprednisolone in a dose of 30 mg/k in the same schedule as the intravenous dexamethasone. Following sacrifice, the brains were removed and the hemispheres separated from the brain stem. These were weighed separately and then homogenated. Samples of the homogenate were taken for chemical analysis as described previously.

Results

The cryogenic lesion is a sharply circumscribed area of hemorrhagic necrosis (fig. 1). In animals receiving Evans blue prior to injury the lesion is dark blue in color; when no dye is given it has a red appearance. The necrosis involves both white and gray matter (fig. 2). Areas of staining in the adjacent viable white matter correspond to foci of histologically rec-
FIGURE 1. Gross photograph of a cryogenic lesion in the rhesus monkey. The animal was given intravenous Evans blue prior to injury.

FIGURE 2. Cross section of the lesion shown in figure 1. There is vital staining of both the lesion and the adjacent edematous white matter.

Omniable cerebral edema in which the edema fluid contains abundant protein.

There were no spontaneous deaths in the control group or in the group receiving I.V. methylprednisolone. Two of the animals pre-treated with dexamethasone died during the first 20 h after injury as did both animals receiving the I.V. dexamethasone. The lesion sizes in these animals were 8.7, 9.9, 10.6 and 11.3 cm.  The brains of these animals were fixed in formalin and microscopic sections prepared. As compared with previous control groups, there was no histologic evidence of a diminished inflammatory response in these steroid-treated and pre-treated animals. Since there was no apparent difference between the measured parameters in the animals treated with dexamethasone and those receiving methylprednisolone, these groups have been combined to give 7 animals in the steroid treated group.

The concentrations of the chemical variables in the undamaged right hemisphere are given in table 1 and the mean increments in the damaged left hemisphere in table 2. These were computed from individual figures and since they represent the means of paired comparisons (left vs right hemispheres), "t" may be obtained by dividing the mean by the standard error. There is no statistical difference between the means of the treated and control groups. The degree of hemorrhage calculated from the iron content of the peripheral blood, and of plasma exudation, calculated from the counts in serum, were also the same for both groups.

**Discussion**

Since the favorable clinical response associated with massive doses of steroids in head injury patients was

| Table 1. Mean Weight and Mean Concentrations of Substances, Expressed in Terms of Dry Weight, in the Undamaged Right Hemisphere (S x = Standard Error). |
|-----------------|-----------------|-----------------|
| Control         | Treated         |                |
| **Weight gm**   | 35.2 ± 1.9      | 36.2 ± 1.1      |
| **Water gm/100 gm** | 310.3 ± 9.0    | 299.2 ± 4.3    |
| **Sodium mEq/100 gm** | 22.8 ± 1.0      | 21.3 ± 0.8     |
| **Chloride mEq/100 gm** | 16.1 ± 0.8      | 14.5 ± 0.5     |
| **Potassium mEq/100 gm** | 43.3 ± 1.5      | 37.9 ± 2.3     |
| **Iron mg/100 gm** | 11.0 ± 0.9      | 13.3 ± 0.8     |
| **RISA cts/min/mg** | 2.3 ± 0.4       | 2.4 ± 0.4      |
TABLE 2  Mean Lesion Size and Mean Increments in the Damaged Left Hemisphere, Expressed in Terms of Dry Weight.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion size cm³</td>
<td>9.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Weight gm</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Water gm/100 gm</td>
<td>40.4</td>
<td>36.7</td>
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<tr>
<td>Sodium mEq/100 gm</td>
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<td>9.5</td>
</tr>
<tr>
<td>Chloride mEq/100 gm</td>
<td>6.1</td>
<td>5.5</td>
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<tr>
<td>Potassium mEq/100 gm</td>
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</tr>
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<td>Iron mEq/100 gm</td>
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<td>4.9</td>
</tr>
<tr>
<td>RISA ct/min/mg</td>
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<td>61.1</td>
</tr>
<tr>
<td>Evans blue mg/100 gm</td>
<td>23.3</td>
<td>20.8</td>
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accompanied by an apparent reduction in intracranial pressure, the former has been attributed to a reduction in cerebral edema. The cryogenic lesion in both the dog and monkey is associated with increased intracranial pressure. This is reduced by intravenous hypertonic solutions through dehydroxylation of the undamaged hemisphere with no demonstrable reduction in cerebral edema. Therefore, the favorable clinical response to massive doses of steroids in head injury patients may have a different mechanism, such as treatment of incipient shock.

While the mortality rate differences in our experimental groups are not statistically significant, it may be noteworthy that 4 out of 15 animals treated with massive doses of steroids died, while there were no fatalities in the control group of 6. All of the deaths occurred in the group receiving dexamethasone and none in the group receiving methylprednisolone. Increased mortality in rats pretreated with steroids and subjected to anoxic ischemic injury has previously been reported.

The data in this report indicate that the previously reported negative results with steroids are not dose related. They do not support the view that massive doses of steroids will be of any benefit to the patient with hemorrhagic stroke through a reduction of cerebral edema. However, the possibility that such therapy may be beneficial for other reasons is not ruled out.

Acknowledgment

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References

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