The effect of dexamethasone on the rate of formation of cerebrospinal fluid in the monkey

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The standard ventriculocisternal perfusion technique was used to determine what effect a single large intravenous dose of dexamethasone would have on CSF formation rate in the rhesus monkey over a 4-hour period. Three monkeys received 0.15 mg/kg, four received 0.4 mg/kg and five served as the untreated controls. With time, CSF formation rates decreased in both treated and control groups. The magnitude of the decrease in the treated and untreated controls did not differ significantly. We conclude that the therapeutic benefit of dexamethasone for intracranial spatial decompensation derives from a mechanism of action that leaves the rate of CSF formation unchanged.

Keywords: dexamethasone • cerebrospinal fluid formation • ventriculocisternal perfusion

For more than a decade, dexamethasone and other glucocorticosteroids have been used clinically to mitigate the effects of intracranial space-occupying lesions and their associated brain edema. Yet the mechanism of action of these extraordinarily useful agents remains to be precisely identified. Some investigators have concluded from experiments with dogs that the general beneficial effect of glucocorticosteroids on brain water and ions in disease is due in part to a reduction in the rate at which cerebrospinal fluid (CSF) is formed.1,6,10,13

This communication reports the results of an investigation to determine the effect of a single large intravenous dose of dexamethasone on CSF formation within a 4-hour period in the rhesus monkey.

Materials and Methods

Rhesus monkeys unselected as to sex and weighing 3 to 5 kg (mean 3.6 kg) were anesthetized with intravenous pentobarbital, intubated endotracheally and placed prone in a sphinx-like position in a stereotactic apparatus. Respiration was supported with a small-animal respirator during the preparatory period and subsequent 7-hour perfusion. From a catheter in the femoral artery, the blood pressure and the heart rate were monitored continuously and arterial blood was sampled every half hour for measurement of pCO2, pO2 and pH. Blood gases were kept stable and within physiological limits by adjustments of the ventilatory rate. Lactated Ringer’s solution was given intravenously at 5

550 J. Neurosurg. / Volume 41 / November, 1974
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ml/kg/hr. A heating pad externally applied kept the rectal temperature at 39°C ± 0.5°C. A 22-gauge needle was passed stereotaxically into the body of the left lateral ventricle. A 19-gauge needle with a polyethylene tube attached, was passed percutaneously into the cisterna magna and the free (outflow) end of the tube was kept at the level of the cisterna magna.

Ventriculocisternal perfusion was carried out in a manner similar to that previously described. The perfusion fluid was a balanced salt solution* with its pH adjusted to 7.35 by exposure to 5% CO₂ in oxygen. Trace amounts of ¹²⁵I-labeled human serum albumin† (Albumotope-Squibb) and 1 mg/ml blue dextran (molecular weight 2 million) were added to the perfusion fluid to serve as non-diffusible indicators.

The prepared perfusion fluid, warmed to 38°C, was infused by pump through the needle in the ventricle at a rate that varied less than 0.001 ml/min during each experiment, but ranged from 0.181 to 0.193 ml/min among all experiments. A pressure transducer connected in parallel to the ventricular inflow tube continuously monitored the intraventricular pressure, which ranged between 2 and 7 mm Hg, and usually varied less than 2 mm Hg during each experiment. During the 7-hour perfusion, the outflow fluid from the cisterna magna was collected in tared covered vials as separate specimens each half hour. Specimens from the first 2 hours of ventriculocisternal perfusion were discarded. Each of the 10 specimens from the remaining 5 hours of perfusion were weighed to determine gravimetrically the outflow rate, then centrifuged at 3600 rpm for 6 minutes to remove cellular debris. Five aliquots of 0.25 ml each (± 0.001 ml) were taken from each half-hour specimen for measurement of radioactivity in a well-type scintillation counter; each aliquot was counted three times. The remainder of the specimen was used to measure the concentration of blue dextran with a Beckman spectrophotometer* at a wave length of 610 μm. At the end of each experiment, the animal was sacrificed and its brain removed to verify the location of the needle entrance into the ventricle.

CSF formation rates (Vf) for each half-hour period were calculated using the formula derived by Heisey, et al.:

\[ Vf = \frac{Ci - Co}{Co} \]

in which Vi is the perfusion rate, Ci is the concentration of indicator in the inflow fluid and Co is the concentration of indicator in the outflow fluid.

One group of three animals received 0.15 mg/Kg of dexamethasone. A second group of four animals received 0.4 mg/kg of dexamethasone. The third group of five animals served as the untreated control. The dexamethasone was injected intravenously as a bolus, within a period of a few seconds, at the end of the third hour of perfusion, immediately after the preceding half-hour specimen had been collected. Specimens were then collected during each subsequent half-hour period for the ensuing 4 hours.

Results

The rate at which CSF was formed gradually decreased in both the treated and the untreated groups (Table 1). For each group, straight lines were fitted (least-squares method) to their mean rate of CSF formation at each half-hour interval plotted against time (Fig. 1). With time, the rate of CSF formation decreased significantly in all three groups; that is, the slope of CSF formation rate versus time differed significantly from zero (p < 0.05). When the magnitude of decrease of CSF formation rate with time (i.e., slopes) of the treated and untreated groups were compared by the analysis of covariance, there was no significant difference (p > 0.05). The slope common to all three groups was 1.5 μl/hr.

The data were also analyzed as follows. The CSF formation rate for each group dur-

*Solution composed of NaCl, 7.4 gm; NaHCO₃, 2.2 gm; dextrose, 1.0 gm; KCl, 0.25 gm; urea, 0.21 gm; CaCl₂, 0.2 gm; MgSO₄ 0.7 H₂O, 0.1 gm; NaHPO₄, 0.075 gm; H₂O, enough to make 1000 ml. Adjusted to 290-300 mOsm with H₂O or NaCl.

*Spectrophotometer manufactured by Beckman Instrument Company, Scientific Process and Instrument Division, 2500 Harbor Boulevard, Fullerton, California 92634.
<table>
<thead>
<tr>
<th>Group</th>
<th>Collection Period Before Treatment (min)</th>
<th>Collection Period After Treatment (min)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>60 to 30</td>
<td>30 to 0</td>
</tr>
<tr>
<td>0.15 mg/kg dexamethasone</td>
<td>36.7 ± 2.7</td>
<td>33.4 ± 4.4</td>
</tr>
<tr>
<td>(3 monkeys)</td>
<td></td>
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<tr>
<td>0.4 mg/kg dexamethasone</td>
<td>42.9 ± 7.3</td>
<td>39.2 ± 4.3</td>
</tr>
<tr>
<td>(4 monkeys)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>40.7 ± 6.0</td>
<td>40.5 ± 6.4</td>
</tr>
<tr>
<td>controls</td>
<td></td>
<td></td>
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<tr>
<td>(5 monkeys)</td>
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* Rate of CSF formation is measured in µl/min; mean ± S.D.
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First, dogs were used in the investigations cited. In certain important respects the physiology of the CSF of dogs and primates differ. For instance, dogs possess accessory routes for CSF drainage through nasal lymphatics that are not available to primates. However, it seems unlikely that a fundamental difference in response to glucocorticosteroids between the two mammalian species at a molecular level accounts for the disparate results.

Second, neither Sato nor Amano used untreated control animals. Our data indicate that even after 3 hours of ventriculocisternal perfusion, the apparent rate of CSF formation continues to decline spontaneously for the next 4 hours at about 1.5 μl/hr. Whether this is an artifact due to incomplete mixing of the indicator molecules with sequestered CSF, or a real decline due to experimental trauma is not clear. In either case it emphasizes the need for controls in any investigation that aims to determine the effect of an agent on the rate of CSF formation.

Third, Weiss and Nulsen used a simple drainage technique to measure the rate of CSF formation, which is considered to be less accurate than the ventriculocisternal perfusion technique. Yet the inaccuracy inherent in their technique seems insufficient to account for the striking differences between their findings and our own. To reduce the loss of CSF through endogenous drainage, they collected the CSF at a pressure of -300 mm H₂O. According to Davson, negative pressure may result in the addition of an abnormal fluid exudate to the CSF. Moreover, transitory changes in either intracranial blood volume or pressure within the thorax or abdomen will result in a sudden change in the rate of CSF outflow that does not reflect a change in the rate of CSF formation. Weiss and Nulsen minimized this source of error by collecting CSF over many hours. Within 1 hour after giving dogs 0.25 mg/kg of dexamethasone intravenously, they observed a dramatic fall in the rate at which CSF drained, while the rate in the control animals remained unchanged for 9 hours or more. From the available data, we cannot satisfactorily reconcile the difference between their findings and our own.

Dexamethasone may have a delayed effect on the rate of CSF formation that will not be detected during the first 4 hours after its administration. On the other hand, some reports
suggest that dexamethasone and other glucocorticosteroids quickly enter the brain to affect membrane permeability. Within minutes after injecting labeled cortisol intravenously, Schwartz, et al., found that it accumulated in high concentration in the choroid plexus. In addition, Eisenberg, et al., have shown that dexamethasone diminishes both the increased uptake of water and the increased permeability of the blood-brain barrier to albumin in the thalamus of cats made to convulse with pentylentetrazol. This effect was observed in animals given 0.3 mg/kg of dexamethasone as a single dose intravenously concurrently with the appearance of seizure activity. Consequently, one would expect, a priori, that if dexamethasone can change the rate of CSF formation, its activity would have been apparent within 4 hours of an intravenous injection.

Acknowledgments

Dr. Sheldon Levin and Mr. William Jackson performed the statistical analysis of the data. Mr. Walter Stringfield gave technical assistance.

References


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