The effect of dexamethasone phosphate on the production rate of cerebrospinal fluid in the spinal subarachnoid space of dogs

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The effect of intravenous dexamethasone on cerebrospinal fluid (CSF) production was studied in dogs by a method of caudocephalad perfusion of the spinal subarachnoid space with an inulin-containing buffer. The CSF production rate began to reduce immediately after the injection of 0.15 mg/kg and attained a maximal reduction of 50% in 50 minutes.

Key Words - dexamethasone phosphate - cerebrospinal fluid production - spinal subarachnoid space - intracranial space

Since the classical experiments of Dandy and Blackfan, the choroid plexus has been considered to be a main source of cerebrospinal fluid (CSF). The suggestion of extraventricular fluid formation was reviewed by Weed and substantiated by many others; however, no one has accurately measured the rate quantitatively.

Various techniques have been used to study the rate of CSF formation, the most satisfactory being the perfusion of the cerebrospinal fluid system developed by Papenheimer, et al. They performed ventriculocisternal perfusion in the goat with artificial CSF containing inulin as a tracer and showed that only very small amounts of inulin leave the ventricles by either diffusion or active transport into the brain or blood. Rall, et al., also confirmed this and concluded that decrease in the inulin concentration occurring during perfusion was almost exclusively related to the volume of newly formed CSF in the system.

Applying this technique to kaolin-induced hydrocephalic dogs, Sato and Bering measured the formation rate of CSF in the intracranial subarachnoid space at 0.014 ml/min. Sato, et al., reported a production rate of 0.018 ml/min in the spinal subarachnoid space using the same technique.

Since the work of Prados, et al., which showed that adrenal cortical and anterior pituitary extracts reduced cerebral edema, much attention has been paid to the value of steroids in the treatment of cerebral edema and intracranial hypertension. However, there have been only a few papers reporting the effect of steroids in the production and absorption of CSF.

Sato has reported that the CSF production rate of 0.047 ml/min in the whole intracranial space can be reduced by about 50% with the use of 0.15 mg/kg of intravenous dexamethasone.

It is the purpose of this paper to clarify whether or not there is any difference in the
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Effect of dexamethasone on the production rate in the whole intracranial space including the choroid plexus and ependymal layer, and the spinal subarachnoid space that does not contain these structures.

Materials and Methods

For this study we used 26 adult mongrel dogs, weighing between 10 and 15 kg. The whole perfusion system followed the method described by Pappenheimer, et al., and the technique of spinal subarachnoid space perfusion has been stated in detail previously. Perfusions of artificial CSF containing 25 mg% of inulin solution as a tracer were carried out in a caudocephalad direction for about 3 hours without changing the perfusion pressure, which ranged from 70 to 180 mm H₂O. After a stable state was reached, two 10-minute samples were taken; the dogs were then given 0.15 mg/kg of dexamethasone phosphate intravenously. After the injection, samples were taken every 10 minutes in the first 30 minutes and every 20 minutes thereafter for 2 hours. Inulin determination was carried out on these samples by means of resorcinol. Figure 1 illustrated the experimental set-up.

Results

The net rate of CSF formation was calculated by the means of Heisey, et al. The rate of formation was equal to inulin clearance plus the difference between outflow and inflow rates.

According to Sato, et al., the formation rate of CSF in the spinal subarachnoid space of dogs is expressed as:

Vf = 0.0201 (±0.0024) - 0.288 × 10⁻⁴ CSFP ml/min.

CSFP was the CSF pressure when zero pressure was taken at the level of the spinal cord.

Inulin was removed from the subarachnoid space by bulk absorption at a rate that varied linearly with the hydrostatic pressure. However, pressure was proved to have only a little effect on the CSF production in the spinal subarachnoid space.

In the present series, perfusions were carried out in 26 dogs; only in 10 dogs were the data considered satisfactory from the technical point of view (Table 1). The reduction in the CSF production rate was estimated at about 50%, and began 10 to 20 minutes after the dexamethasone was administered; it reached its maximum decrease in approximately 30 to 50 minutes.

Although Table 1 indicates that CSF production in the space examined was

![Diagram of the perfusion system](image-url)
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<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Before Dexamethasone (ml/min)</th>
<th>After Dexamethasone (ml/min)</th>
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<tbody>
<tr>
<td></td>
<td>20 min</td>
<td>10 min</td>
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<tr>
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<td>.028</td>
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<td>DSP-23</td>
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abolished, or virtually so, at the end of the experiments in four of the animals, no definite conclusion was reached as to whether this indicated actual cessation of CSF production or deterioration of the preparation after a 5-hour period of perfusion.

Discussion

There are many theories to explain the efficacy of glucosteroids in the treatment of cerebral edema of intracranial hypertension. Among these are such postulations as the possibility that steroids reduce the cerebral edema, inhibit the growth of tumor cells, reduce the production of CSF, or act on some extracerebral site. Actually, satisfactory explanations of the basic mechanism of steroid therapy are fragmentary; little attention has been paid to the influence of steroids on production and absorption of CSF.

Garcia-Bengochea administered cortisone acetate 20 mg/kg/day to non-castrated cats for 2 weeks and found a significant reduction of CSF as measured by spinal catheterization; he ascribed the reduction to augmented diuresis. However, others believed this was not an exact measurement of CSF production.

Using a ventriculocisternal perfusion method with artificial CSF containing inulin as an indicator, Sato measured the CSF production rate quantitatively after administration of dexamethasone in dogs; he reported that the CSF production rate was reduced by 50% in 30 minutes with rapid administration of the doses of 0.15 mg/kg dexamethasone, and suggested that dexamethasone works closely on the water-ion transport system. It is important to notice that Garcia-Bengochea used large doses of cortisone for 2 weeks while Sato's experiments involved a single injection.

Amano also studied the influence of dexamethasone on the CSF production rate in the edematous brains of dogs. Brain edema, produced by shaking the dog's head, resulted in a significant fall of CSF production. Weiss and Nulsen made dogs hydrocephalic by the intracisternal injection of a suspension of kaolin and compared these to normal dogs with regard to the influence of dexamethasone on CSF production. Ventricular drainage of hydrocephalic dogs and cisternal drainage of normal dogs were used for the evaluation of measurement 30 cm below the level of the right atrium. They found a reduction of 40% in hydrocephalic dogs and 50% in normal dogs compared to control groups within 30 minutes after the administration of 0.25 mg/kg of dexamethasone. This corresponds well with Sato's result. No difference between these two groups was noted. They further analyzed the CSF and serum osmolality, electrolytes, and chemical constituents that would influence the flow of CSF, and found no significant differences between controls and animals.
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treated with dexamethasone. They suggested alteration of some undefined active cellular process as the underlying mechanism; they could not show any significant change in the parameters that would establish a passive diffusional gradient between the subarachnoid and vascular compartments.

Recently, Schwartz, et al., claimed that normal brain, and especially the choroid plexus, shows a rapid uptake of radioactive hydrocortisone; this may indicate a direct and specifically located action that reduces CSF production. Using mice of strain C57BL and autoradiography, they found penetration into normal brain tissue, especially the choroid plexus, within 2 minutes, and clearance by 60 minutes. No comment was made on the reason for this significant uptake by the choroid plexus.

The choroid plexus was conventionally considered the site of CSF production. However, more recently it has been generally accepted that CSF is also produced in extraventricular cerebrospinal subarachnoid spaces. Choroid plexus was proven to form 30% to 40% of the CSF produced in the ventricular system rostral to the fourth ventricle of the rhesus monkey, and CSF formation in the ventricular system amounted to 42% in dogs.

Our results were similar to those of our previous study; that is, the CSF production rate began to reduce within 10 minutes and reached about 50% reduction within 50 to 60 minutes after intravenous dexamethasone administration. This means that Schwartz's findings may only indicate its accumulation in the blood vessels of the choroid plexus and that a steroid does not exert its action on the choroid plexus selectively. Since the actual mechanism of CSF production is still not clearly defined, the reason why steroid reduces the CSF production remains obscure. However, our present study shows the effect of steroid on the intracranial CSF system to be similar to its effect on the spinal subarachnoid space.

We can only agree with Weiss's comment that alteration of some undefined active cellular process is the underlying mechanism in the production of CSF.

References


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