Experimental effects of steroids and steroid withdrawal on cerebrospinal fluid absorption

IAN JOHNSTON, F.R.C.S., DAVID L. GILDAY, M.D., AND E. BRUCE HENDRICK, M.D., F.R.C.S.

Divisions of Neurosurgery and Nuclear Medicine, The Hospital for Sick Children, Toronto, Canada

The authors studied the effects on cerebrospinal fluid (CSF) absorption of chronic administration and acute withdrawal of steroids in dogs. CSF absorption was measured by determining the amount of isotope (indium $^{111}$DTPA) recovered over a 4-hour period after injection into the cisterna magna. Resistance to CSF absorption was estimated by determining rates of flow of Ringer's lactate infusion into the cisterna magna over a range of pressure gradients between CSF and sagittal sinus. Steroid withdrawal was associated with a marked reduction in CSF absorption and an increase in resistance to CSF flow. Dogs on steroids also showed reduced CSF absorption although the reduction was not statistically significant when compared with controls. The results are discussed in terms of possible mechanisms of action of steroids on CSF absorption, the etiology of the benign intracranial hypertension syndrome and the use of steroids in the control of intracranial hypertension.

KEY WORDS - steroids • steroid withdrawal • CSF absorption • resistance to CSF flow

STEROIDS are widely used in the control of intracranial hypertension. Their mode of action is probably complex; they may reduce cerebral edema directly$^{6,11,16}$ as well as altering cerebrospinal fluid (CSF) circulation.$^{15,19}$ Steroids are also, of course, used in many other conditions where intracranial dynamics are normal. Their effects on brain bulk and CSF flow under such circumstances have not, however, been extensively studied. There are now several reports of patients with initially normal intracranial pressure who developed intracranial hypertension after prolonged steroid therapy$^{1,10,16}$ although the cause of the increased pressure has not been determined. The suggestion has recently been made that this may be due to a reduction in CSF absorption secondary to an increase in resistance to CSF flow across the absorptive channels.$^{8}$

The experiments we are reporting were designed to examine this hypothesis and to gain further information on the effects of steroids on CSF circulation. CSF flow and absorption in dogs was studied first on chronic, high-dose steroid therapy and, second, after acute withdrawal of steroids following prolonged administration.
Effect of steroids on CSF absorption

Methods

Male beagle dogs, weighing between 20 and 30 lbs, were anesthetized with acepromazine maleate (10 mg IM) and Nembutal (10 mg/lb IV), intubated, and ventilated with a tidal volume adjusted to maintain normal PaCO₂ levels. Indwelling catheters in the left femoral artery and vein were used to monitor arterial and venous pressures, and an electrocardiogram was run continuously. Saline (0.9%) was infused intravenously throughout each experiment at a rate sufficient to maintain a high output of urine, which was collected by an indwelling catheter. Experimental procedures were carried out in two stages:

Measurement of CSF Absorption

The atlanto-occipital membrane was exposed and approximately 25 μc of indium ¹¹¹DTPA in 0.6 ml of saline were injected into the cisterna magna through a 27-gauge needle. Venous blood and urine (2-ml samples) were collected prior to injection and at 30-minute intervals thereafter for 4 hours. At the end of the experiment the radioactivity in each sample was measured with a well-counter, and the total radioactivity in the blood and urine at each half-hour period calculated using the estimated blood volume and the measured urine volume. Results were expressed as a percentage of the radioactivity in the initial injection using a standard equal to the injected dose to correct for radioactive decay. Photoscans were carried out immediately after injection and at hourly intervals thereafter using a Picker Magnascanner.*

Measurement of Resistance to CSF Flow

After completion of the first stage, indwelling cannulae were inserted into the cisterna magna and the superior sagittal sinus. CSF and sagittal sinus pressures were then measured continuously using strain-gauge transducers and a paper chart recorder. After stable conditions had been established, pressure measurements were continued for approximately 30 minutes to give baseline levels. A bottle of warmed Ringer's lactate solution was then connected by a 3-way tap to the cisterna magna cannula and a continuous infusion started. Monitoring of CSF (infusion) pressure and sagittal sinus pressure was continued throughout. The height of the bottle was adjusted to give successive infusion (CSF) pressures of approximately 10, 25, 50, 75, and 100 mm Hg; at each level the rate of infusion was determined over three separate 2-minute intervals and a mean rate calculated. Infusion pressure was plotted against infusion rate for each experiment and the resistance to flow calculated from the slope of the curve.

At the end of each experiment the animal was killed, the brain removed and weighed in the fresh state and then fixed in 10% formol-saline for several weeks. The brains were then cut and an index of ventricular size obtained from the product of the maximum anteroposterior length and the depth, at the midpoint, of the right lateral ventricle. Three groups of animals were studied:

Group 1. Six control dogs.

Group 2. Six steroid-treated dogs. These were given 125 mg cortisone acetate per day, in divided doses, for 4 weeks prior to the experiment. Immediately before anesthesia each dog was also given 100 mg hydrocortisone hemisuccinate intravenously.

Group 3. Six dogs on steroid withdrawal. These animals were also given a 4-week course of cortisone acetate (125 mg/day) which was stopped abruptly at the end of the fourth week. Each dog was then studied 6 to 8 days from the last steroid dose.

Results

CSF Absorption

The mean recovery of indium ¹¹¹DTPA from the CSF in control animals was 42.7% of the injected dose over 4 hours (Fig. 1, Table 1). The rate of recovery was initially relatively constant but fell during the fourth hour (Fig. 2). In another group of four dogs 78% of the mean 24-hour recovery occurred during the first 4 hours (Fig. 3). Steroid-treated (Group 2) dogs showed a slower rate of recovery of isotope than controls although the difference was not significant at 4 hours. Mean values in this group were somewhat biased by one animal with very low isotope recovery which may have been partly artifactual due to a poor injection.

After acute steroid withdrawal (Group 3 dogs) isotope recovery was significantly less

*Picker Magnascanner made by Picker Röntgen, 4992 Espelkamp, West Germany.
than control levels over 4 hours, 21.7% compared to 42.7%, and also less than in the steroid-treated group although in this case the difference was significant only over the first 2 hours.

All animals on steroids and after steroid withdrawal showed an increased rate of isotope recovery during the latter part of the 4-hour measurement period, although this was more pronounced after steroid withdrawal (Fig. 2).

Patterns of isotope distribution on the photoscans were similar in all three groups, namely, initial concentration in the cisterna magna, followed by passage along the basal cisterns and then over the posterior aspects of the cerebral hemispheres. Little isotope appeared to pass over the convexities of the cerebral hemispheres or down the spinal canal. The rate of isotope clearance from the cisterna magna and its subsequent passage through the subarachnoid space was noticeably slower in Group 3.

Resistance to CSF Flow

Resistance values in the control and steroid-treated animals corresponded closely with mean values of 42.7 and 40.2 mm Hg/ml/min, respectively (Fig. 4, Table 2). After acute steroid withdrawal there was a marked increase in resistance to CSF flow, with values ranging from 65 to 94 mm Hg/ml/min in five of the six animals, the remaining animal having a level within the control range. Statistically there was a significant difference in resistance values between Group 3 and Groups 1 and 2 (p < 0.05), but no difference between the latter two groups. In all groups flow rates fell off as higher infusion pressures were reached (Fig. 4).
Effect of steroids on CSF absorption

### TABLE 1

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Group 1 (Control)</th>
<th>Group 2 (On Steroids)</th>
<th>Group 3 (After Steroid Withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43.8</td>
<td>42.3</td>
<td>39.5</td>
</tr>
<tr>
<td>2</td>
<td>55.2</td>
<td>28.4</td>
<td>21.7</td>
</tr>
<tr>
<td>3</td>
<td>26.8</td>
<td>25.9</td>
<td>18.8</td>
</tr>
<tr>
<td>4</td>
<td>37.8</td>
<td>14.0</td>
<td>22.3</td>
</tr>
<tr>
<td>5</td>
<td>46.4</td>
<td>34.0</td>
<td>16.1</td>
</tr>
<tr>
<td>6</td>
<td>46.3</td>
<td>43.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Mean</td>
<td>42.7</td>
<td>31.3</td>
<td>21.7</td>
</tr>
<tr>
<td>SD</td>
<td>9.6</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Values expressed are percentages of injected isotope dose recovered over 4 hours. SD=standard deviation; NS=not significant.

### Intracranial Pressure and Other Parameters

Mean values for intracranial pressure corresponded closely in the control and steroid-withdrawal groups (Groups 1 and 3); these were 8.3 and 8.2 mm Hg, respectively (Table 3). No Group 3 animals had frank intracranial hypertension, although two animals did have intracranial pressure levels of 15 mm Hg. The steroid-treated animals (Group 2) had a lower mean intracranial pressure level, 5.3 mm Hg. Sagittal sinus pressures were similar in all three groups, although slightly lower in Group 3. The mean pressure gradient between CSF and superior sagittal sinus was similar in Groups 1 and 3 but was lower in Group 2.

Mean PaCO₂ levels and brain weights did not differ significantly between the three groups. None of the animals had hydrocephalus. The calculated ventricular index was slightly lower in Group 3 compared with the other two groups.

### Discussion

The primary factors controlling CSF absorption are the pressure differential between cortical subarachnoid space and superior sagittal sinus and the resistance to CSF flow across the absorptive channels. Secondary factors such as the rate of CSF production, the patency of the subarachnoid space and the chemical composition of the CSF may also be important although their effects may be partly attributable to their influence on the two primary factors.

### TABLE 2

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Group 1 (Control)</th>
<th>Group 2 (On Steroids)</th>
<th>Group 3 (After Steroid Withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>34</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>31</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Mean</td>
<td>42.7</td>
<td>40.2</td>
<td>71.7</td>
</tr>
<tr>
<td>SD</td>
<td>9.6</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Values expressed are mm Hg/ml/min. SD=standard deviation; NS=not significant.

Both chronic steroid administration as well as acute withdrawal of steroids after chronic administration cause a reduction in CSF absorption in our experiments; however, the effect was more marked after steroid withdrawal; furthermore, the mechanism behind the reduced absorption appeared to differ in the two groups. Thus, chronic steroid administration caused only a slight reduction in the CSF-sagittal sinus pressure gradient and no change whatever in the measured resistance to CSF flow. This suggests an

### TABLE 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (Control)</th>
<th>Group 2 (On Steroids)</th>
<th>Group 3 (After Steroid Withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP (mm Hg)</td>
<td>(≈ 3.9)</td>
<td>(≈ 3.2)</td>
<td>(≈ 5.5)</td>
</tr>
<tr>
<td>SSP (mm Hg)</td>
<td>(≈ 1.9)</td>
<td>(≈ 3.4)</td>
<td>3.4</td>
</tr>
<tr>
<td>gradient (ICP-SSP)</td>
<td>(≈ 2.5)</td>
<td>(≈ 1.1)</td>
<td>4.8</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>(≈ 3.4)</td>
<td>(≈ 3.1)</td>
<td>33.6</td>
</tr>
<tr>
<td>brain wt. (gm)</td>
<td>(≈ 2.0)</td>
<td>(≈ 6.2)</td>
<td>81.3</td>
</tr>
<tr>
<td>ventricular index</td>
<td>(≈ 0.25)</td>
<td>(≈ 0.28)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* There were no statistically significant differences between the groups for any parameter. ICP=intracranial pressure; SSP=sagittal sinus pressure.
I. Johnston, D. L. Gilday and E. B. Hendrick

I. Johnston, D. L. Gilday and E. B. Hendrick

Effect on one, or more, of the secondary factors referred to above. On the other hand, acute steroid withdrawal caused a marked increase in resistance to CSF flow but did not alter the CSF-sagittal sinus pressure gradient.

Both acute and chronic steroid administration causes a marked fall in CSF production, up to 50% in normal animals, and this may lead to secondary changes in CSF flow. Steroids may also reduce brain bulk, at least in states of cerebral edema, although whether they do so under conditions of normal intracranial tension is uncertain. If they do, there may be a compensatory increase in the volume of the CSF compartment with an associated reduction in CSF flow and absorption, although this effect may be masked by the more pronounced effect on CSF production. There was, in fact, no evidence of a direct effect on brain bulk in our experiments. Furthermore, other studies have shown that acute administration of steroids does not alter CSF composition in a way that might influence CSF dynamics. It seems probable, therefore, that decreased CSF absorption after chronic steroid administration reflects predominantly decreased CSF production although reduction in the CSF-sagittal sinus pressure gradient may contribute to this decrease to some extent.

The effect of acute withdrawal of steroids after chronic administration on CSF dynamics has not previously been studied, although it is well known that intracranial hypertension may follow steroid withdrawal in clinical situations after treatment of a variety of conditions. Reduced CSF absorption after acute steroid withdrawal in these experiments was associated with a substantial increase in the resistance to flow of CSF across the absorptive channels, but not with any change in the CSF-sagittal sinus pressure gradient. Attempts to define the mechanism underlying this change in resistance are, however, hampered by lack of agreement on the nature of the absorptive channels. Recent studies have suggested that open channels with a relatively low selectivity in terms of molecular size connect the subarachnoid space with the superior sagittal sinus at the arachnoid villi. Electron microscopic studies, on the other hand, have favored the presence of a discrete continuous cellular membrane dividing the two compartments. This would mean that some type of transcellular transport, active transport, diffusion, pinocytosis, or some other method, is responsible for CSF absorption. Our data do not bear directly on this problem, although one may speculate that steroids might be more likely to act on intact membranes either by altering the physical properties of the membrane directly or by influencing transport mechanisms at the membrane or intracellularly.

Davson, et al., have recently attempted a synthesis of the two opposing views considered above, postulating an absorptive mechanism similar to that described by Tripathi in the eye; that is, the formation, by infolding of the cell membrane, of vacuoles which increase in size until they form complete channels across the cells dividing subarachnoid space from superior sagittal sinus. In the light of Willmer's speculations it seems possible that steroids may be important in such membrane changes. Thus, under normal circumstances, or when steroid levels in the circulation are high during steroid administration, the process may be unimpaired. Acute withdrawal of steroids after chronic administration may lead to low circulating levels and this may adversely affect the cycle of membrane changes.

Whatever the underlying mechanisms, the observed effects of steroids and steroid withdrawal on CSF absorption have important clinical implications. First, they may elucidate the benign intracranial hypertension syndrome which may follow cessation or reduction of steroids after chronic administration. Various theories have been advanced to explain the increase in intracranial pressure in this condition, including an increase in brain bulk, in cerebral blood volume, or in CSF volume. The argument has recently been advanced that intracranial hypertension results from an increase in CSF volume caused by reduced CSF absorption; this may be secondary to either an increase in resistance to flow across the absorptive channels or to a reduction in the CSF-sagittal sinus pressure gradient. Our results support this concept by demonstrating a marked effect on resistance to CSF flow with a corresponding reduction in absorption secondary to one of the established etiological factors of the syndrome.

In addition, steroids are widely used for the control of raised intracranial pressure, yet lit-
Effect of steroids on CSF absorption

te is known of the effects of chronic administration and subsequent withdrawal on CSF dynamics. Our findings agree with earlier work suggesting that the primary effects are on brain bulk and CSF production and not on CSF absorption per se. They do, however, raise questions about possible adverse effects during dose reduction or withdrawal. A better understanding of the quantitative aspects of the observed effects and, in particular, the time course would provide a sounder basis for the use of steroids in the control of intracranial hypertension.

References
5. Foley J: Benign forms of intracranial hypertension—“toxic” and “otitic” hydrocephalus. Brain 78:1–41, 1955

Address reprint requests to: Ian Johnston, Department of Neurosurgery, Royal Alexandra Hospital for Children, Camperdown 2050, Sydney, New South Wales, Australia.