Hyponatremia and natriuresis following subarachnoid hemorrhage in a monkey model

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A monkey model of subarachnoid hemorrhage (SAH) was used to study both the incidence of hyponatremia and natriuresis and the associated changes in antidiuretic hormone (ADH) secretion and salt and water balance. Following SAH, seven of nine monkeys became natriuretic and hyponatremic. The natriuretic period lasted an average of 4.4 ± 0.4 days. The mean nadir of serum sodium content was 125.7 ± 1.6 mEq/liter, and occurred on the average on the 5th day following SAH. The sodium balance after SAH was negative as compared to the preoperative positive sodium balance (p < 0.001). The plasma vasopressin level was usually elevated for a day following surgery, but there was no significant difference in the levels during the preoperative period and during the period of natriuresis following SAH. The daily urine output and aldosterone levels were not significantly different, and the plasma volume was slightly, but not significantly, decreased after SAH. Four of the animals that had a hyponatremic and natriuretic response following SAH showed a normal regulation of vasopressin in response to both a water challenge and hypertonic saline challenge. The three monkeys that underwent sham procedures did not become hyponatremic and natriuretic postoperatively. The sham-operated monkeys did not show significant differences in their plasma vasopressin levels, urine volume, plasma volume, and aldosterone levels following surgery. These observations are more consistent with primary natriuresis as the cause of hyponatremia rather than the syndrome of inappropriate secretion of ADH. The cause of the renal loss of sodium is not known, but the possibility of a brain natriuretic factor or an alteration in the neural control of the kidney should be considered.

KEY WORDS • hyponatremia • natriuresis • subarachnoid hemorrhage • vasopressin • syndrome of inappropriate antidiuretic hormone • sodium level

Hyponatremia and natriuresis form a common metabolic disorder in neurosurgical patients. Originally, this abnormality was referred to as cerebral salt wasting, and the primary defect was thought to be the renal loss of sodium, but more recently the problem has been thought to be secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). It has been difficult to perform detailed balance studies of this problem clinically because of the difficulty of carefully controlling salt and water balance in hospitalized patients and because of the impossibility of obtaining pre-morbid data in patients with intracranial disorders. Therefore, an animal model of subarachnoid hemorrhage (SAH) was used to study both the incidence of hyponatremia and natriuresis following SAH and the associated changes in antidiuretic hormone (ADH) secretion and salt and water balance.

Materials and Methods

Male cynomolgus monkeys, each weighing 4.5 to 5 kg, were trained to sit in a primate chair. An infant feeding tube was placed nasogastrically for feeding. The femoral vein was cannulated for chronic blood sampling. The animals were given a fixed diet of 150 cc volume/kg, 150 calories/kg, and 2 mEq sodium/kg. Each animal’s hematocrit, serum sodium, and plasma vasopressin and aldosterone levels were measured daily in the morning, and the animal’s 24-hour urine was measured for volume and sodium concentration. The vasopressin and aldosterone levels were determined using highly specific radioimmunoassays. The sodium determinations were made using a flame photometer. Plasma volume was determined before and after SAH at the nadir of the serum sodium using iodine-131-labeled serum albumin. The animals were weighed any
TABLE 1
Sodium balance in experimental and control monkeys*

<table>
<thead>
<tr>
<th>Group &amp; Test</th>
<th>Na(^+) Balance (mEq/day)</th>
<th>Serum Na(^+) (mEq/liter)</th>
<th>Vasopressin (µU/ml)</th>
<th>Urinary Volume (cc/day)</th>
<th>Plasma Volume (cc)</th>
<th>Plasma Aldosterone (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop</td>
<td>2.5 ± 0.6 (35)</td>
<td>134.8 ± 1.3 (7)</td>
<td>3.4 ± 0.2 (30)</td>
<td>452 ± 30 (35)</td>
<td>261 ± 23 (7)</td>
<td>40.6 ± 3.2 (14)</td>
</tr>
<tr>
<td>postop</td>
<td>−4.9 ± 0.8 (31)</td>
<td>125.7 ± 1.6 (7)</td>
<td>4.0 ± 0.3 (33)</td>
<td>486 ± 24 (36)</td>
<td>220 ± 11 (7)</td>
<td>30.5 ± 4.2 (23)</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop</td>
<td>1.5 ± 0.7 (21)</td>
<td>141 ± 1 (16)</td>
<td>5.1 ± 0.7 (11)</td>
<td>397 ± 12 (21)</td>
<td>265 ± 28 (3)</td>
<td>37.3 ± 5.0 (16)</td>
</tr>
<tr>
<td>postop</td>
<td>2.5 ± 1.1 (17)</td>
<td>140 ± 1 (14)</td>
<td>6.5 ± 1.4 (19)</td>
<td>415 ± 19 (17)</td>
<td>204 ± 50 (3)</td>
<td>43.8 ± 7.4 (18)</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Group A included seven monkeys that were hyponatremic and natriuretic after subarachnoid hemorrhage; Group B included three sham-operated control monkeys. Values are mean ± standard error of the mean. Numbers in parentheses indicate number of measurements. Significance calculated by the Student t-test. NS = not significant.

time they came out of the primate chair. Whenever possible the red blood cells were given back to the animal after plasma was taken for the daily determinations. After the animals' sodium and water balance was equilibrated, they were taken out of the primate chair and an SAH was created. On the day of the SAH, they received 0.2 mg atropine and were anesthetized with 0.5 cc Innovar (droperidol) and 10 mg Flaxedil (gallamine triethiodide). After intubation, the animals were ventilated with a Harvard respirator.* An arterial line was inserted and blood pressures and arterial blood gases were measured serially and maintained in normal ranges throughout the procedure. The left periorbital area was shaved, prepared for surgery, and draped. The left orbital contents were then removed using sterile technique. The optic strut was removed by drilling. Under visualization with an operating microscope, the dura and arachnoid were opened to expose the internal carotid artery and its bifurcation. Subarachnoid hemorrhage was induced by perforating the anterior cerebral artery just distal to the bifurcation using a No. 30 needle. The bleeding was controlled by pressure over the artery. The eyelid was sutured shut and the anesthesia was reversed with intramuscular Robinul (glycopyrrolate), 0.1 mg; Narcan (naloxone), 0.2 mg intravenously and 2 mg intramuscularly; and intravenous Prostigmin (neostigmine), 0.1 cc. The animals were returned to the primate chair and generally recovered in 2 to 3 hours.

Nine animals underwent an SAH. Sham-operated animals consisted of two animals that had their left orbital contents removed, but did not have an SAH, and one animal that underwent an abdominal laparotomy.

After complete recovery from the SAH, four animals underwent testing with water and osmotic challenges to determine if they were capable of normal ADH suppression and stimulation. After an overnight water deprivation, baseline plasma vasopressin levels were obtained. A water load consisting of 2% of the animal's body weight was given by nasogastric tube. Blood samples were withdrawn for vasopressin testing until a stable low level was reached (approximately 60 minutes). For the osmotic challenge, 3% sodium chloride was administered intravenously at 1 cc/min for 60 minutes. Blood samples were obtained every 15 minutes during the 60-minute infusion and for another 60 minutes following the infusion.

Data are expressed as mean ± standard error of the mean, and statistical analysis was performed using the Student t-test for paired or unpaired data as appropriate.

Results
Following SAH, seven of the nine monkeys became natriuretic and hyponatremic (Fig. 1, Table 1). The natriuretic period, which was associated with a negative sodium balance, lasted an average of 4.4 ± 0.4 days. The nadir of serum sodium occurred on the 5th day following SAH on the average. The mean nadir of serum sodium was 125.7 ± 1.6 mEq/liter. There were significant differences in the sodium balance between the preoperative baseline period and the post-SAH natriuretic period (p < 0.001), and of the lowest serum sodium in the two periods (p < 0.01). Plasma vasopressin was usually elevated for a day following surgery, but there was no significant difference in plasma vasopressin during the preoperative period and the period of natriuresis post-SAH. The daily urine output and plasma aldosterone levels were not significantly different following SAH. Plasma volume was slightly, but not significantly, decreased after SAH. Serum creatinine was stable in all animals before and after SAH. Hematocrit decreased 1.4 ± 0.6 points, and the weight 0.1 ± 0.1 kg during the experiment.

Serial determinations of sodium balance, serum sodium, vasopressin, and aldosterone in two of the experimental animals are shown in Fig. 2. The animals became natriuretic with a negative sodium balance immediately after SAH, and natriuresis lasted 4 days. The nadirs of serum sodium were 127 and 119 mEq/liter, and occurred on the 6th and 5th days following SAH. The vasopressin was increased transiently after SAH, but there was no sustained elevation in vasopress-

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No sham-operated animal became hyponatremic or natriuretic (Fig. 3, Table 1). The vasopressin was increased on the 1st day following surgery, as in the experimental group, but overall there was no significant increase in the level of vasopressin following surgery. There was also no significant change in the sham-operated animals’ urine volume, plasma volume, or aldosterone level following surgery.

When the SAH animals that developed hyponatremia and natriuresis were compared to the sham-operated animals (Table 1), significant differences were found in the postoperative sodium balance (p < 0.001) and the serum sodium (p < 0.001). There were no significant differences in the preoperative sodium balance and serum sodium nor in the pre- and postoperative levels of aldosterone. Inexplicably, the control animals had somewhat higher levels of vasopressin both preoperatively (p < 0.01) and postoperatively (p < 0.05).

In four animals that had a hyponatremic and natriuretic response to SAH, normal regulation of vasopressin in response to both a water and a hypertonic saline challenge (Fig. 4) was proven after recovery. The vasopressin decreased in response to a water load from 3.5 ± 0.4 to 1.8 ± 0.3 µU/ml and then increased from 2.1 ± 0.5 to 7.5 ± 0.5 µU/ml in response to the hypertonic saline challenge.

Discussion

Hyponatremia associated with natriuresis is a common finding in patients with intracranial disorders, and the recent literature has described this as secondary to SIADH. In our monkey model, SAH produced hyponatremia and natriuresis in seven of nine animals, but the levels of vasopressin were not elevated over those before SAH (Fig. 1, Table 1). It might be argued that the modest levels of vasopressin that were found (about 4 µU/ml) were sufficient to cause SIADH, especially as we were only able to measure the level of...
vasopressin on a daily basis. Several observations in our study do not support this interpretation, however. The studies of administered water load in the monkey demonstrated that the background for unextracted monkey plasma was somewhat greater than we have previously found in the human (1.0 μU/ml) and in the rat (0.74 μU/ml). In each monkey tested, maximum suppression of vasopressin secretion with a water load produced basal levels of vasopressin of about 2 μU/ml, which can be considered the background for the assay in this particular study (Fig. 4). There was a good response above this background when hypertonic saline was administered confirming that the assay will measure changes of vasopressin within the physiological range. Taken in context, then, the levels of 4 μU/ml are consistent with a normal state of hydration, and the similar levels before and after SAH are valid, supporting data that the levels of vasopressin after SAH were not elevated.

Another observation that does not support the occurrence of SIADH in these monkeys is that there was no association between the levels of vasopressin and the degree of natriuresis. In individual monkeys there was no correlation between levels of vasopressin and degree of natriuresis, and in sham-operated monkeys the levels of vasopressin were similar but there was no natriuresis (Table 1). In all of the monkeys there was some elevation of the vasopressin as an immediate response to surgery, and it might be argued that this short elevation of vasopressin set in motion the train of events that led to natriuresis. That observation is not supported by the sham-operated monkeys, in which the levels of vasopressin were even higher in the immediate postoperative period but there was no natriuresis (Figs. 1 and 3).

The mechanism of the natriuresis in SIADH is not completely understood, but is thought to be a response to volume expansion. The measured volumes in our monkeys were not expanded during the time of natriuresis and, in fact, were lower than before SAH. Again, one might argue that the volume expansion occurred early after SAH, and could have been missed in a study in which volume could not be determined on a day-to-day basis. The levels of aldosterone do not support this supposition. There was no suppression of the levels of aldosterone as would be expected with volume expansion. Rather, after natriuresis there was a modest increase in the levels of aldosterone consistent with the somewhat lower plasma volume which was measured at that time. Similarly, the slight decrease in body weight at the end of the study would indicate volume contraction rather than volume expansion. Experimental studies of SIADH have demonstrated weight gain during the syndrome.

All of the above observations led us to consider primary natriuresis as a cause of the hyponatremia rather than SIADH as classically described with second-

![Graph](image-url)

**Fig. 3.** Mean sodium balance, serum sodium, plasma arginine-vasopressin (AVP), and plasma aldosterone in three monkeys that underwent sham procedures.

![Graph](image-url)

**Fig. 4.** Mean plasma vasopressin levels in four monkeys that received a water challenge and a hypertonic saline challenge after they recovered from subarachnoid hemorrhage.
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ary volume expansion. The cause of the renal loss of sodium in these monkeys is not known. One must consider the possibility of a brain natriuretic factor which was released or an alteration of neural control of the kidney as possible causes and each of these areas must be investigated further.\textsuperscript{15,16,18} Caution must be exercised in extrapolating from these animal studies to human clinical situations in which many varied disease processes may coexist with SAH; however, it is of interest that in our previous report of neurological patients with laboratory criteria for SIADH we also found a decreased blood volume.\textsuperscript{24,25} Thus, in the clinical situation after SAH the brain may participate in some way in decreasing the renal reabsorption of sodium. It may be useful to obtain measurements of blood volumes in patients with hyponatremia in an attempt to distinguish between a syndrome of excess natriuresis and a true SIADH with volume expansion. Therapeutically, patients with primary salt wasting are given salt and volume replacement rather than the traditional fluid restriction that is used for patients who are thought to have the syndrome of inappropriate secretion of vasopressin (SIADH).

References


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