Osmotic and osmotic-loop diuresis in brain surgery

Effects on plasma and CSF electrolytes and ion excretion

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In 22 patients to be operated on for brain tumors or cerebal aneurysms, the effect of osmotic diuresis was compared with that of osmotic-loop diuresis on plasma and cerebrospinal fluid (CSF) electrolytes, and water and ion excretion. Mannitol or mannitol plus furosemide were used to reduce brain bulk. After treatment with thiopental and hyperventilation, patients received randomly a rapid infusion of mannitol (1.4 gm/kg), or mannitol (1.4 gm/kg) plus furosemide (0.3 mg/kg). Brain shrinkage was considerably greater and more consistent with mannitol plus furosemide than with mannitol alone. However, hyponatremia, hypokalemia, hypochloremia, and hyperosmolality were also more marked (p < 0.05) with mannitol plus furosemide than with mannitol. The rate of water and ion excretion was even more striking. At 30 minutes after absorption of mannitol alone, water excretion peaked at 17 ml/min, and gradually decreased to 3.8 ml/min 70 minutes later. With mannitol plus furosemide, during an identical time course, initial water excretion was 30 ml/min, followed by a further rise to 42 ml/min and then a decline to 17 ml/min. At peak diuresis after mannitol, Na⁺ and Cl⁻ excretion averaged 0.57 and 0.62 mEq/min, respectively. This compares with mean values of 3.7 and 4.12 mEq/min for Na⁺ and Cl⁻, respectively, after mannitol plus furosemide. Although optimum brain shrinkage is achieved with osmotic-loop diuresis, the rapid electrolyte depletion (Na⁺ and Cl⁻) must be corrected to avoid altered sensorium during the patients' postoperative course.

KEY WORDS • osmotic-loop diuresis • electrolyte imbalance • water and ion excretion • combined diuretic therapy

The diuretics mannitol and furosemide are used in neurosurgery to reduce brain bulk. The amount of reduction in brain water content is proportional to the percentage of total loss of body water. Theoretically, within certain limits, the greater the diuresis, the greater will be the percentage of brain water loss.

Diuresis can be enhanced by the combined use of mannitol and furosemide. The rationale for combining the two diuretics is based upon two sound pharmacotherapeutic concepts. First, if two drugs act on different receptor systems, maximum therapeutic efficacy is increased by combining the two drugs. Second, by combining the two drugs, the therapeutic dose of the individual drug can be reduced without reducing the maximum therapeutic efficacy.

Enhanced diuresis, however, causes electrolyte imbalance which may result in undesirable side effects. If the electrolyte imbalance is identified and corrected, we can achieve optimum brain shrinkage without harm to the patient. The present study compares the effect of osmotic diuresis with osmotic-loop diuresis on plasma electrolytes and water and ion excretion.

Materials and Methods

This study included 22 patients (40 to 70 years of age), with normal renal function and normal or clinically asymptomatic intracranial pressure (ICP) elevation, who were scheduled for brain surgery. The majority of the patients had received corticosteroids preoperatively. Indication for surgery was excision of brain tumors (including meningiomas, gliomas, intraventricular tumors, and metastatic lesions) in 18 patients, and clipping of cerebral aneurysm in four...
The diuretics were administered to facilitate access for brain surgery.

Before induction of anesthesia, indwelling catheters were placed in a radial artery, the right atrium, and a peripheral vein, and an infusion of 0.45% NaCl solution was given at an average rate of 100 ml/hr. Patients were anesthetized with thiopental, N2O/O2, and intermittent doses of fentanyl; they were paralyzed and hyperventilated mechanically. The bladder was then catheterized, and in randomized fashion, 20% mannitol (1.4 gm/kg) or mannitol (1.4 gm/kg) plus furosemide (0.3 mg/kg) was given as a rapid infusion over 20 minutes. Furosemide was given after the first 100 ml of 20% mannitol was absorbed.

Simultaneous arterial blood and urine samples were drawn to measure blood gas tensions, pH, osmolality, Na+, K+, Cl−, and water and electrolyte excretion. The measurements were made at the following intervals: 1) before diuretic administration (pre-diuresis); 2) at the onset of diuresis, approximately 30 minutes after diuretic absorption; 3) at peak diuresis, about 60 minutes after diuretic absorption; and 4) at low diuresis, about 2 hours after diuretic absorption. In the mannitol-furosemide group, two additional measurements were made about 3 and 4 hours after onset of diuresis, respectively (Tables 2 and 5). In this same group of patients, clear ventricular cerebrospinal fluid (CSF) was also drawn at the time of low diuresis, to calculate the CSF:plasma ratio for Na+, K+, and Cl−.

Additionally, in one patient undergoing osmotic-loop diuresis, three clear ventricular CSF samples were drawn for analysis, at time of onset of diuresis, peak diuresis, and low diuresis.

Patients who received blood or in whom the fluid infusion rate was increased above the pre-set value were not included in the study. The data were analyzed for statistical significance using Student’s t-test. Values of p < 0.05 or less were considered statistically significant.

### Results

#### Plasma and CSF Electrolytes

Both methods of diuresis lowered plasma Na+, K+, Cl−, and increased plasma osmolality. Hyponatremia, hypochloremia, and hyperosmolality were more significant (p < 0.05) and sustained with combined mannitol-furosemide than with mannitol alone. With mannitol-furosemide therapy, the plasma osmolar gradient (with respect to pre-diuresis measurements) ranged from a maximum of +21 mOsm (at onset of diuresis, respectively (Tables 2 and 5). In this same group of patients, clear ventricular cerebrospinal fluid (CSF) was also drawn at the time of low diuresis, to calculate the CSF:plasma ratio for Na+, K+, and Cl−. Additionally, in one patient undergoing osmotic-loop diuresis, three clear ventricular CSF samples were drawn for analysis, at time of onset of diuresis, peak diuresis, and low diuresis.

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water and electrolyte excretion

Table 5 shows significant differences between the two methods of inducing diuresis. The first striking difference is the magnitude of water loss. Total excretion of urine after mannitol infusion averaged 1266 ml compared to a mean of 3019 ml after combined mannitol-furosemide treatment. The rate of water excretion during active diuresis gives a better insight into the dynamics of water loss with the two methods of diuresis induction. After mannitol administration, a peak diuresis of 17 ml/min was reached within 30 minutes; in the next 70 minutes, water excretion fell to 4 ml/min. By contrast, during an identical time course, combined mannitol-furosemide infusion yielded an initial water excretion rate of 30 ml/min, followed by a further increase to 42 ml/min, and then declined to 17 ml/min, the maximum water excretion rate with mannitol alone.

Clinical observations

Brain relaxation. About 30 minutes after mannitol-furosemide infusion, brain shrinkage was readily discerned. Shrinkage was more pronounced, sustained, and more consistent with diuresis induced with mannitol-furosemide than with mannitol alone. This, however, was a clinical impression and was not quantitated.

Arterial blood pressure. A moderate increase (30 mm Hg) in mean arterial blood pressure (MABP) was observed prior to onset of diuresis with mannitol. In contrast, a consistent rise in MABP was seen after mannitol-furosemide infusion at the time of low diuresis (42 to 17 ml/min). This rise was an increment of 30 to 40 mm Hg in four patients, 50 to 60 mm Hg in three, and 70 to 80 mm Hg in two. In all cases, however, the magnitude of the arterial pressure rise was blunted with incremental doses of thiopental (50 to 100 mm Hg).

The second striking difference is the magnitude of Na⁺ and Cl⁻ loss with osmotic-loop diuresis. During peak diuretic activity, Na⁺ and Cl⁻ loss after combined mannitol-furosemide administration was disproportionate to the loss of these ions after mannitol alone by a factor of 6.5. This huge Na⁺ and Cl⁻ loss diminished considerably when active diuresis subsided (Table 5). The third difference concerns Cl⁻ excretion. This was evaluated by calculating Cl⁻ ratio (Cl⁻/Na⁺ + K⁺). A ratio greater than 0.73 indicates preferential Cl⁻ excretion. During active diuresis, both groups of patients showed a preferential Cl⁻ excretion, with the distinction that it was transient with mannitol diuresis, and more pronounced and sustained after mannitol-furosemide treatment (Table 5).

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Patients' consciousness improved dramatically. When the Na\(^+\) and Cl\(^-\) loss was replaced (0.45% NaCl), the state of the patients' consciousness improved dramatically.

**Discussion**

Combined osmotic-loop diuresis caused optimal brain shrinkage, marked diuresis, and a huge (albeit transient) loss of Na\(^+\) and Cl\(^-\) ions. With osmotic diuresis, loss of water and ions was moderate and brain shrinkage was less prominent and inconsistent. We can assume that the degree of brain shrinkage after osmotic-loop diuresis was somehow related to the marked loss in H\(_2\)O, Na\(^+\), and Cl\(^-\). Although we did not measure ICP, it has already been proven that loop diuretics (that is, ethacrynic acid and furosemide), when used in conjunction with mannitol, enhance mannitol's beneficial effect on ICP and brain edema. Tornheim, *et al.*, proposed that, while mannitol dehydrated the normal brain, furosemide dehydrated the edematous brain. Wilkinson, *et al.*, observed that, in experimental brain edema, mannitol combined with ethacrylic acid lowered an elevated ICP by 60%, as opposed to a 40% reduction with mannitol alone. Recently, Millson, *et al.*, found that furosemide was even more potent in enhancing mannitol action, since it lowered the elevated ICP by 74%, as compared to a 53% reduction after mannitol or furosemide alone.

Marked reduction in ICP and marked brain shrinkage from osmotic-loop diuresis is believed to be the result of a synergistic action of the two diuretics. This involves several mechanisms: 1) by causing a high and sustained osmotic gradient between circulating blood and brain-tissue extracellular fluid; 2) by a direct action of furosemide on CSF formation and brain Na\(^+\) uptake; and 3) by inhibition by furosemide of Na\(^+\), Cl\(^-\), and H\(_2\)O reabsorption at renal tubules, resulting in marked H\(_2\)O, Na\(^+\), and Cl\(^-\) depletion.

When hypertonic solutions (such as 20% mannitol) are rapidly infused, a significant osmotic gradient may develop between circulating blood and brain tissue. This osmotic force draws water out of the brain tissue, thereby causing brain shrinkage. The amount of water withdrawn along the osmotic gradient depends upon the magnitude of the osmotic gradient, the total time during which the osmotic gradient exists, and the proportional integrity of the blood-brain barrier.

Assuming that this latter factor was equal between our two groups of patients, our data clearly show that the first two factors are greater with osmotic-loop diuresis than with mannitol alone. When the osmotic gradient is large and sustained, the brain loses water as well as Na\(^+\) and Cl\(^-\). Van Harreveld, *et al.*, studied the effect of a continuous hypertonic infusion (50% glucose) on brain cortical impedance, brain water, and ions in rabbits. The first 20 to 30 minutes of infusion produced profound diuresis and visible brain shrinkage, but no change in brain impedance. As the infusion continued, brain shrinkage increased and brain impedance gradually rose, reaching a peak of 36% above control, at which time the animal died. In the first 20 to 30 minutes of profuse diuresis, the brain lost only water; as brain dehydration progressed, water loss was accompanied by Na\(^+\) and Cl\(^-\) outflow. When dehydration was pushed to the extreme, and the animal died, the loss in brain-tissue H\(_2\)O content averaged 25%, while the loss in brain Na\(^+\) and Cl\(^-\) content was 50 and 46 mm/kg dry weight, respectively. These experiments indicate that the osmotic gradient is a powerful mechanism in creating brain dehydration.

**Table 5**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Diuretic Agent</th>
<th>Pre-Diuresis</th>
<th>Onset of Diuresis</th>
<th>Peak Diuresis</th>
<th>Low Diuresis</th>
<th>Recovery Room</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st Hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd Hr</td>
</tr>
<tr>
<td>real time (min)</td>
<td>M</td>
<td>to absorption</td>
<td>28 ± 3</td>
<td>63 ± 4</td>
<td>105 ± 5</td>
<td>220 ± 10</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td>to absorption</td>
<td>25 ± 3</td>
<td>53 ± 4</td>
<td>116 ± 8</td>
<td>174 ± 9</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 ± 20</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>365 ± 47</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>254 ± 32</td>
</tr>
<tr>
<td>urine total output (ml)</td>
<td>M</td>
<td></td>
<td>495 ± 53</td>
<td>451 ± 68</td>
<td>170 ± 28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>860 ± 54</td>
<td>940 ± 30</td>
<td>600 ± 71</td>
<td></td>
</tr>
<tr>
<td>H(_2)O (ml/min)</td>
<td>M</td>
<td></td>
<td>17 ± 1.5</td>
<td>12.6 ± 2.0</td>
<td>3.8 ± 0.4</td>
<td>2.8 ± 0.2</td>
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<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>30.3 ± 3.8</td>
<td>42 ± 7</td>
<td>17 ± 3.6</td>
<td>10 ± 2.1</td>
</tr>
<tr>
<td>Na (mEq/min)</td>
<td>M</td>
<td></td>
<td>0.77 ± 0.1</td>
<td>0.57 ± 0.1</td>
<td>0.17 ± 0.03</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>2.70 ± 0.4</td>
<td>3.70 ± 0.9</td>
<td>1.01 ± 0.2</td>
<td>0.46 ± 0.1</td>
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<tr>
<td>K (mEq/min)</td>
<td>M</td>
<td></td>
<td>0.14 ± 0.02</td>
<td>0.13 ± 0.02</td>
<td>0.06 ± 0.01</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>0.38 ± 0.08</td>
<td>0.35 ± 0.05</td>
<td>0.25 ± 0.07</td>
<td>0.20 ± 0.07</td>
</tr>
<tr>
<td>Cl (mEq/min)</td>
<td>M</td>
<td></td>
<td>0.72 ± 0.10</td>
<td>0.62 ± 0.09</td>
<td>0.19 ± 0.03</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>2.90 ± 0.45</td>
<td>4.12 ± 0.83</td>
<td>1.30 ± 0.30</td>
<td>0.60 ± 0.16</td>
</tr>
<tr>
<td>1Cl(^-) ratio† (Cl/Na + K)</td>
<td>M</td>
<td></td>
<td>0.87 ± 0.05</td>
<td>0.88 ± 0.03</td>
<td>0.87 ± 0.04</td>
<td>0.77 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>M + F</td>
<td></td>
<td>0.92 ± 0.05</td>
<td>0.96 ± 0.04</td>
<td>1.02 ± 0.06</td>
<td>0.88 ± 0.06</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the mean for 11 samples for each measurement period.
† 1Cl\(^-\) ratio calculated from mEq/liter for each sampling period.

**Postoperative State of Consciousness.** Early in the postoperative hours, patients subjected to osmotic-loop diuresis appeared lethargic and exhibited hypnagogia and hypochrome, and a mean osmotic gradient of +12 to +14 mOsm/liter. When the Na\(^+\) and Cl\(^-\) loss was replaced (0.45% NaCl), the state of the patients' consciousness improved dramatically.
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The H₂O, Na⁺, and Cl⁻ loss combined with the large osmotic gradient in osmotic-loop diuresis leads us to suspect that under these circumstances brain extracellular space loses both H₂O and ions. Supportive evidence is provided by recent studies of Millson, et al., in a complex model of cytotoxic-vasogenic edema, in which combined mannitol-furosemide therapy caused a loss of brain H₂O and Na⁺. Brain Cl⁻, although not measured, presumably followed the Na⁺ pattern. When mannitol or furosemide was used separately, these authors found no change in brain H₂O or Na⁺ content. This suggests a synergistic action between mannitol and furosemide, at least for the edematous brain. If this occurred also in our osmotic-loop diuresis group of patients, it must have been a transient phenomenon, limited to the phase of marked diuresis, and was reflected in the low Na⁺ value in the CSF and the high RCSF for Cl⁻ (Table 4). The values reported here approached those that have been reported in dogs with acute salt depletion.

Of course, a decreased Na⁺ value in CSF could be due to a central action of furosemide by depressing Na⁺ and CSF secretion by the choroid plexus, and by inhibiting Na⁺ uptake by the brain cortex, thereby reducing Na⁺ flux in the CSF. This central action is the second mechanism by which furosemide enhances mannitol-induced diuresis. The major argument against this mechanism acting in our patients is that the dosage required to inhibit CSF formation and Na⁺ secretion, and to inhibit Na⁺ uptake by the brain cortex, is considerably larger than the one we used here.

A more plausible explanation is that the low Na⁺ value in CSF and the high RCSF for Cl⁻ reflect a phase of acute salt depletion, induced by the combined diuretics, which reversed, in part, as Na⁺ and Cl⁻ excretion diminished. Furosemide enhances mannitol-induced diuresis by blocking Na⁺, Cl⁻, and H₂O reabsorption at renal tubules, the third mechanism. This is less affected by mannitol alone (Table 5). The major action of furosemide is to inhibit Cl⁻ transport in the thick ascending limb of Henle's loop. This, in turn, affects Na⁺, K⁺, and H₂O transport. The net consequences are disproportionate loss in H₂O, Na⁺, Cl⁻, and K⁺, excessive contraction of the extracellular space, and electrolyte imbalance. If the extracellular space of the total body becomes contracted, obviously brain extracellular space is also proportionally contracted. By the time of low diuresis, Na⁺ and Cl⁻ depletion drastically diminishes, while the osmotic gradient between brain and circulating blood is becoming smaller. Brain is increasing its osmolality as the result of the relative increase in brain Na⁺, K⁺, and Cl⁻, secondary to water loss, and slow mannitol diffusion in the brain.

The marked loss of Na⁺ and Cl⁻, albeit transient, causes some problems that cannot be overlooked. The first is a moderate arterial hypertension as diuresis decreases. This can be misinterpreted as light anesthe-

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