Intracranial and systemic effects of osmotic and oncotic therapy in experimental cerebral edema

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Experiments were carried out to compare the effectiveness of oncotic and osmotic therapy in dogs with experimental cerebral edema caused by a left parietal cold lesion. Animals were divided into five groups and treated for 6 hours with either crystalloid (control group), or mannitol, albumin, furosemide, or albumin/furosemide (treatment groups). The cerebral effects of therapy were evaluated by intracranial pressure (ICP) measurements and by postmortem evaluations of water content, using computerized tomography (CT) density measurements and wet-dry weight measurements. The ICP was significantly reduced by all treatments except albumin alone, and was reduced equally by mannitol, furosemide, and albumin/furosemide. The CT density of the lesion area was significantly increased by all treatments. The density of the contralateral nonlesioned hemisphere was significantly increased by all treatments except albumin. The water content of the lesion area was significantly decreased by all treatments; water content of the opposite hemisphere was not significantly reduced. The systemic effects of therapy were evaluated by measuring net fluid balance, wedge pressures, hematocrits, free water clearance, and vasopressin. Negative fluid balance without an increase in hematocrit or in vasopressin secretion occurred only in dogs treated with albumin/furosemide. Such oncodiuretic therapy seems to cause normovolemic dehydration and to have cerebral effects similar to mannitol and furosemide, without their undesirable systemic effects.

KEY WORDS • cerebral edema • albumin • furosemide • mannitol • head injury

Osmotic diuretics are often used to lower intracranial pressure (ICP). Their effect depends partly on the creation of an osmotic gradient across an intact blood-brain barrier to dehydrate normal brain, and on the rapid diuresis of water drawn into the vascular compartment by osmotically active particles. Osmotic therapy rapidly lowers ICP, but within a few hours the osmotic gradients diminish as the solutes are excreted, metabolized, or reach an equilibrium concentration in the brain, and the ICP rises. Osmotic therapy may cause undesired side effects such as electrolyte imbalance, hypovolemia, and hyperosmolarity, especially if used repeatedly. Because brain water is withdrawn slowly, drugs used to lower ICP should ideally create more prolonged gradients, similar to the oncotic gradient that continually retains water within the vascular space.

The intravascular volume is normally regulated by the effective osmotic pressure of plasma proteins, the colloid oncotic pressure. Without this pressure, the hydrostatic pressure imposed by the heart would rapidly drive plasma fluid into the interstitial space. The plasma protein that contributes most (80%) of the oncotic pressure is albumin. Physiologists and nephrologists have shown that increasing the serum albumin concentration increases the oncotic pressure, withdraws extravascular water, and increases the plasma volume. General surgeons have infused albumin to treat shock, burns, and pulmonary contusions.

Can albumin infusions dehydrate cerebral tissue? Albumin has several characteristics that suggest its theoretical usefulness for cerebral dehydration: it does not equilibrate across the normal blood-brain barrier into the interstitial space, it has a long (14-day) half-life, and it is not excreted in urine. Albumin should be retained within cerebral capillaries even better than within systemic capillaries because the apparent pore size of cerebral capillaries (8 Å) is substantially smaller than that of systemic capillaries (65 Å).

During the 1930’s, several investigators reported that albumin infusions improved patients’ neurological status and lowered lumbar cerebrospinal fluid (CSF) pressures, but no instruments were available then to measure the oncotic pressure. Subsequent clinical studies showed no reduction in lumbar CSF pressures after albumin infusions, and animal studies demonstrated...
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blanket.

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until the experiments began. Anesthesia was induced
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experimental studies have combined oncotic therapy
of the intravascular volume, the cerebral blood volume,
edema were treated with enough mannitol and albumin
did not produce the desired gradients and the results
were inconclusive.¹

In the current study, dogs with experimental cerebral
edema were treated with enough mannitol and albumin
to create the desired gradients, and albumin was com-
bined with a diuretic, furosemide. Water withdrawn by
either an osmotic or an oncotic gradient will increase
the intravascular volume, the cerebral blood volume,
and the ICP, unless diuresis takes place. No previous
experimental studies have combined oncotic therapy
with a diuretic, although a clinical report based on this
combination has just been published.¹⁵ The present
study 1) tested the hypothesis that oncodiuretic therapy
would lower ICP and dehydrate cerebral tissue; 2) com-
pared the effects of oncotic and osmotic therapy on
ICP and cerebral dehydration; and 3) compared the
effects of oncotic and osmotic therapy on systemic fluid
balance and vasopressin secretion.

Materials and Methods

Adult mongrel dogs weighing approximately 20 kg
each were used. The dogs were allowed to drink water
until the experiments began. Anesthesia was induced
with thiopental and maintained with Innovar (fentanyl
and droperidol) and pancuronium. An endotracheal
tube was inserted and was connected to a ventilator
adjusted to maintain a pCO₂ of 35 to 40 torr. Intrave-
nenous, arterial, Swan-Ganz, and urinary catheters were
inserted. Body temperature was measured by a rectal
thermometer and was kept at 36° to 37°C by a warming
blanket.

Each animal’s head was held on a stereotaxic head
holder. A catheter was inserted into the right frontal
subarachnoid space to monitor ICP. A 2.5-cm left
parietal craniotomy was performed, and a cold probe,
2.1 cm in diameter, cooled to −65°C with dry ice-
Hexanes, was applied to the intact dura mater for 10
minutes. The craniectomy defect was closed with
methylmethacrylate.

The 47 dogs were separated into five groups and
therapy was randomized. Group 1, the control group,
received crystalloid solution (Plasmalyte) at two-thirds
maintenance requirement volumes. Therapy in Groups
2 through 5 began 1 hour after the lesion. Group 2 dogs
received mannitol (20% solution, 1.5 gm/kg intrave-
nously over 20 minutes) at 1 and 5 hours after the
lesion, and in the interim received Plasmalyte as in
Group 1. Group 3 dogs were given a 1-mg/kg bolus of
furosemide; at 1 and 5 hours they received a 1-mg/kg bolus
of furosemide at 1 hour, then a constant infusion of 0.5
mg/kg/hr and Plasmalyte at two-thirds maintenance
requirement volumes. Group 4 dogs received albumin
(25% solution, 2 gm/kg intravenously over 20 minutes)
at 1 and 5 hours after the lesion, and Plasmalyte in the
interim. Group 5 dogs received albumin and furose-
mide; at 1 and 5 hours they received a 1-mg/kg bolus of
furosemide and 25% albumin (2 gm/kg over 1 hour).
From Hours 2 to 5, Group 5 dogs received Plasmanate
(human plasma 5% protein fraction), at two-thirds
maintenance requirement volumes, and furosemide
(0.5 mg/kg/hr).

The mean arterial pressure, pulmonary artery pres-
sure, and ICP were continuously recorded on a Model
7 Grass polygraph.* The ICP zero reference level was
the interaural line. Transducers were calibrated hourly
against water-filled manometers. Pulmonary artery
wedge pressures and urinary output were measured
hourly. Blood samples were obtained hourly for mea-
surements of hematocrit, serum osmotic and oncotic
pressures, and sodium, potassium, and vasopressin
levels. Oncotic pressure was measured with an IL 186
Weil oncometer calibrated with human serum albumin
control.† Vasopressin was assayed by the method of
Seif, et al.²⁹ Urinary osmolar and water clearance were
calculated by standard formulas.

Animals were killed 6 hours after the lesions were

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Scans</th>
<th>Parietal (lesion area) Left Hemisphere</th>
<th>Frontal</th>
<th>Parietal Right Hemisphere</th>
<th>Frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>9</td>
<td>28.82 ± 0.10</td>
<td>27.98 ± 0.19</td>
<td>33.39 ± 0.13</td>
<td>28.07 ± 0.27</td>
</tr>
<tr>
<td>mannitol</td>
<td>10</td>
<td>30.23 ± 0.23†</td>
<td>29.49 ± 0.32†</td>
<td>36.32 ± 0.17†</td>
<td>29.48 ± 0.31†</td>
</tr>
<tr>
<td>furosemide</td>
<td>9</td>
<td>30.40 ± 0.15†</td>
<td>27.80 ± 0.14</td>
<td>34.13 ± 0.10†</td>
<td>27.18 ± 0.16</td>
</tr>
<tr>
<td>albumin</td>
<td>10</td>
<td>31.67 ± 0.10†</td>
<td>28.09 ± 0.23</td>
<td>33.76 ± 0.15</td>
<td>27.05 ± 0.24</td>
</tr>
<tr>
<td>albumin/furosemide</td>
<td>9</td>
<td>31.07 ± 0.16†</td>
<td>27.96 ± 0.18</td>
<td>34.57 ± 0.15†</td>
<td>31.71 ± 0.22†</td>
</tr>
</tbody>
</table>

*Values are given in Hounsfield units. Each measurement listed is the mean value of 720 to 800 pixels ± standard error of the mean (80 pixels/
dog x the number of dogs in each group).
†Density measurements significantly greater than in the control group of the same area (p < 0.01). The density of the lesion area was sig-
nificantly increased, indicating reduced water content, by all treatments, and density of the contralateral hemisphere was significantly increased
by mannitol and albumin/furosemide.

A. L. Albright, R. E. Latchaw and A. G. Robinson

J. Neurosurg. / Volume 60 / March, 1984
Therapy of experimental cerebral edema

FIG. 1. Intracranial pressure (ICP) measurements of the five treatment groups. The mean ICP's of groups receiving mannitol, furosemide, and albumin/furosemide (alb/furos) were significantly lower than the control group and were not significantly different from each other.

made. The brains were immediately removed, placed in a container of cold 0.9% saline solution, and scanned within 1 hour on an EMI 1010 computerized tomography (CT) scanner with a 160 × 160 matrix, using pixels of $1 \times 1 \times 10$ mm. The scans were obtained at the level of the centrum semiovale. Circular areas containing 80 pixels were outlined in white matter of the left and right parietal and frontal areas, and the mean CT density and standard error of the mean were computed for those areas (Table 1). After the scans, the brains were sectioned, and samples of white matter were taken from the parietal and frontal areas, corresponding approximately to the areas of CT density measurements. Brain samples were weighed, dried at 60° to a constant weight, and reweighed, and the water content was calculated.

The ICP data were analyzed by analysis of variance of repeated measures. Depending on the outcome of significance of the appropriate F-test, a Student Newman-Keul test for pair-wise comparisons was employed. The CT density measurements, water content determinations, and clearances were compared with the control group by a Student t-test. Statistical differences of $p < 0.05$ were considered to be significant.

Results

Intracranial Effects

Intracranial Pressure. Measurements of ICP in the five groups are depicted in Fig. 1. The mean ICP of the control group was 20.2 torr, but was significantly lowered by all treatments except albumin alone. The mean ICP values of dogs receiving mannitol, furosemide, and albumin/furosemide were not significantly different from each other. The differences were statistically significant, whether the analysis was done with ICP data for all 6 hours of the experiment or with data for the first 5 hours (excluding the effects of the second dose of therapy). In Group 4, without furosemide, ICP often increased 3 to 8 torr for several minutes after the albumin was injected. This did not occur in the albumin/furosemide group.

We elected to compare mean ICP values of the groups even though the analysis of variance indicated significant differences in the temporal relationships (patterns) of hourly ICP values among the groups. This statistical difference could be attributed to the sensitivity of the analysis of variance test; the large F value and large number of degrees of freedom made it almost certain to indicate a statistically significant difference among hourly ICP patterns.

CT Density Measurements. Density measurements are listed in Table 1. The density of the left parietal lesion area was significantly increased in all treatment groups compared to the control group. Density in the right parietal non-lesion area was significantly increased by all treatments except albumin alone. Density in the right frontal non-lesion area was increased significantly more in the albumin/furosemide group than in the group with furosemide alone. No CT scan demonstrated a contusion or hemorrhagic infarction at the level of the centrum semiovale; either would have increased density values with a decreased water content.

Water Content Determinations. The water content percentages are listed in Table 2. The water content of the left parietal lesion area was significantly lower in all treatment groups than in the control group. The water
content of the right parietal area was usually 1% to 2% less in the treatment groups than in the control group; the difference is statistically insignificant.

**Systemic Effects**

The mean blood pressures of the groups ranged from 104.4 to 109.4 torr and were not significantly different by comparison of multiple-means analysis. Osmotic and oncotic pressures are shown in Figs. 2 and 3. The desired oncotic and osmotic gradients were present. The mean oncotic pressure was significantly increased in the group receiving albumin/furosemide. Although the mean osmotic pressures were not significantly different, the 6-hour osmotic pressure in the mannitol group was significantly higher than in the other treatment groups.

**TABLE 2**

Percent water content determined in each treatment group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Dogs</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parietal (lesion area)</td>
<td>Frontal</td>
</tr>
<tr>
<td>control</td>
<td>9</td>
<td>80.25 ± 1.95</td>
<td>73.16 ± 2.21</td>
</tr>
<tr>
<td>mannitol</td>
<td>10</td>
<td>77.28 ± 3.12†</td>
<td>71.71 ± 2.82</td>
</tr>
<tr>
<td>furosemide</td>
<td>9</td>
<td>78.16 ± 2.58†</td>
<td>73.49 ± 2.28</td>
</tr>
<tr>
<td>albumin</td>
<td>10</td>
<td>77.71 ± 2.24†</td>
<td>72.11 ± 2.97</td>
</tr>
<tr>
<td>albumin/furosemide</td>
<td>9</td>
<td>77.88 ± 2.57†</td>
<td>72.13 ± 2.22</td>
</tr>
</tbody>
</table>

*Water content was calculated by the formula: % water content = (wet weight − dry weight) × 100/wet weight. Mean values ± standard deviations are given.

†Water content significantly less than in the control group of the same region, p < 0.05. Water content of the lesion area was significantly decreased by all treatments, but was not significantly reduced in the contralateral hemisphere.

**TABLE 3**

Effects of therapy on fluid balance in each treatment group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mean Net Fluid Balance (ml)</th>
<th>Mean Change in PAWP (torr)</th>
<th>Mean Change in Hematocrit</th>
<th>Osmolar Clearance (ml/min)</th>
<th>Free Water Clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>590 ± 425</td>
<td>−1.1</td>
<td>−2.3</td>
<td>2.41 ± 1.39</td>
<td>−1.32 ± 1.04</td>
</tr>
<tr>
<td>mannitol</td>
<td>−55 ± 277</td>
<td>−3.2</td>
<td>−0.6</td>
<td>5.19 ± 2.86†</td>
<td>−2.33 ± 1.15†</td>
</tr>
<tr>
<td>furosemide</td>
<td>−758 ± 299</td>
<td>−1.9</td>
<td>11.5</td>
<td>3.33 ± 1.36†</td>
<td>0.58 ± 0.37†</td>
</tr>
<tr>
<td>albumin</td>
<td>456 ± 378</td>
<td>3.4</td>
<td>−6.0</td>
<td>2.28 ± 1.15</td>
<td>−0.95 ± 0.44</td>
</tr>
<tr>
<td>albumin/furosemide</td>
<td>−656 ± 407</td>
<td>−0.3</td>
<td>−0.7</td>
<td>3.14 ± 1.86†</td>
<td>−0.17 ± 0.35†</td>
</tr>
</tbody>
</table>

*Osmolar clearance is defined as the milliliters of plasma cleared per minute of osmotically active solutes. Osmolar clearance was calculated as follows: Cosm = Uosm × V/Posm, where Uosm and Posm represent the osmolarities of urine and plasma, respectively, in Osm/ml, and V = urine flow in ml/min. Free water clearance is defined as the solute-free water excreted (+) or reabsorbed (−) in ml/min, and is calculated as follows: CH₂O = V − Cosm. Values are means ± standard deviations. PAWP = pulmonary artery wedge pressure.

†Treatment groups significantly different from the control group, p < 0.05.
Therapy of experimental cerebral edema

The effects of therapy on fluid balance are listed in Table 3 and Figs. 4 and 5. Furosemide alone caused a markedly negative fluid balance and hemoconcentration; when combined with albumin, furosemide caused a negative fluid balance with virtually no change in hematocrit. Osmolar clearance and free water clearance were increased by mannitol and by furosemide either alone or in combination with albumin. Free water clearance was closest to zero (indicating isotonic urine) in the group receiving albumin/furosemide. Vasopressin secretion increased 1 hour after the lesion in most animals, and was sporadically increased to high levels thereafter except in the albumin/furosemide group, where it was normal (Fig. 5). Dogs with markedly increased vasopressin levels did not have unusually high ICP's.

Discussion

We evaluated both the intracranial and the systemic effects of the treatments. Intracranial effects were studied by ICP monitoring, CT scan density measurements, and water content determinations. Systemic effects were studied by measuring fluid balance, hematocrits, wedge pressures, urinary water clearance, and vasopressin levels. Both intracranial and systemic effects must be evaluated to interpret the experiments.

Of the methods used to study intracranial effects, ICP monitoring was probably the most clinically relevant. The ICP values were reduced by all treatments except albumin alone. Although albumin/furosemide reduced ICP, the reduction was primarily due to the furosemide, not to the albumin.

The CT density of the lesion area was increased by
all treatments. The density of the contralateral frontal and parietal areas was increased by mannitol and albumin/furosemide. We attributed the increased CT density of white matter to a reduction in cerebral water content. The correlation between water content and CT density has been documented previously.\(^6\,31\) The ICP and CT density measurements correlated well; ICP was decreased and the density correspondingly increased in one or more areas in all groups except the group treated with albumin alone, the only group with no reduction in ICP.

Water content was reduced in the lesion area by all treatments but was not significantly decreased in the opposite hemisphere. The estimations of water content by wet-dry calculations indicated 1.6\% to 2.1\% less water in the treated groups than in the control group. Similar reductions, not reaching statistical significance, have been documented by others.\(^1\,18\,22\) Although the reductions may not be statistically significant, they should have considerable clinical significance: Cascino, et al.,\(^4\) recently reported that a 1.6\% reduction in water content would decrease human brain volume by approximately 90 ml, and increase CT brain density by approximately 1.5 Hounsfield units. Thus, in summary, the intracranial effects indicate that an oncotic gradient plus furosemide significantly lowers ICP (although no better than furosemide alone), increases white matter density (better than furosemide and comparable to mannitol), and decreases water content of the lesion area although not in the opposite hemisphere.

The systemic treatment effects are easier to interpret. A positive fluid balance (intake greater than output) was seen in animals receiving crystalloid or albumin therapy alone. A markedly negative fluid balance occurred in dogs receiving furosemide, either alone or in combination with albumin. Furosemide alone caused marked hemoconcentration, which probably increased viscosity, but if furosemide was combined with albumin, the hematocrit was unaffected. None of the treatments altered serum sodium concentration more than 2.2 mEq from the basal value; larger changes may have occurred if the experiments had been longer.

The effects of treatment on urinary osmolar clearance and free water clearance were expected. In general, negative free water clearance reflects the excretion of hypertonic urine, positive free water clearance reflects the excretion of hypotonic urine, and neutral clearance reflects the excretion of isotonic urine. Ideally, drugs used to dehydrate cerebral tissue would cause the excretion of isotonic urine. In these experiments, free water clearance in dogs receiving albumin/furosemide was almost neutral (0.17 ml/min), and the urine was, therefore, more isotonic than in dogs receiving mannitol (−2.33 ml/min).

The effects of treatment on serum vasopressin are
Therapy of experimental cerebral edema

consistent with the fluid balance findings. Vasopressin secretion was intensely stimulated by mannitol and furosemide (drugs that caused hypovolemic dehydration), but was virtually normal in dogs receiving albumin/furosemide, indicating that plasma volume was maintained in spite of marked diuresis.

In summary, the systemic treatment effects indicate that albumin/furosemide 1) caused a marked diuresis of isotonic urine; 2) did not increase the hematocrit as furosemide had because extravascular water was retained within the vascular system by albumin; and 3) normalized vasopressin secretion. In short, the goal of normovolemic dehydration (relative to the vascular space) was achieved. Normalizing the vascular volume with albumin/furosemide may also lessen edema-related ischemia by improving tissue perfusion and by reducing viscosity.23

In these six-hour experiments, intravascular volume and serum vasopressin changed markedly in animals receiving mannitol or furosemide. Because albumin/furosemide was as effective in lowering ICP as mannitol or furosemide, but did not cause fluid imbalance, we infer that albumin/furosemide could be used to treat intracranial hypertension for several days, with fewer risks than with mannitol, and perhaps with better baro-stabilization.23

The systemic effects of these treatments are related to the effects of osmotic and oncotic gradients in distributing fluid between the plasma and interstitial spaces. Because the molecular weights of plasma proteins are high, varying from 69,000 for albumin to over 1,000,000 for certain globulins, the osmotic effects of these proteins are small (28 torr), even though their concentrations are relatively large (60 to 70 gm/liter). In comparison with the 5100 torr exerted by crystalloid solutes, the solutes exert no osmotic force across the endothelium and traverse it nearly as readily as does water. On the other hand, capillaries are relatively impermeable to proteins, and nearly the full colloid osmotic effect of plasma protein is exerted across the capillary endothelium, opposing the filtration of fluid from capillaries into the interstitial space and promoting resorption of fluid into the vascular component.28 Thus, the animals receiving colloids maintained their intravascular volume in spite of diuretics.

Oncotic gradients should affect the water content in brain more slowly than in other tissues because of capillary differences. Systemic capillaries are permeated by 60-Å pores that permit rapid influx or efflux of water in response to changes in oncotic pressure.16,28 Cerebral capillaries seem to have 8-Å pores,10 larger than the water molecule (4 Å) but too small to permit bulk flow. Although the hydraulic conductivity of cerebral capillaries is low, increasing the plasma oncotic pressure from 18–20 to 30–35 torr adds a considerable gradient to help withdraw brain water, a gradient that should be additive to the crystalloid osmotic gradient.

The relationship of albumin to cerebral edema is important and perhaps not as clear cut as it seemed when Sundt wrote, "The good news is that it [albumin] improves the microcirculation, the bad news is that it increases the amount of edema."1 He postulated that albumin would cross the damaged blood-brain barrier in ischemic areas, bringing with it a certain amount of fluid, and hold the fluid within the ischemic area. Evans blue dye, bound to albumin, certainly crosses the blood-brain barrier damaged by vasogenic edema, but the evidence is controversial that increasing the serum albumin concentration and oncotic pressure will significantly increase the oncotic pressure of edema fluid or increase edema. Oncotic pressure of the edema fluid does not equilibrate with circulating plasma proteins.5,14

In previous experiments, albumin infusions either have not changed1 or have decreased slightly11 water content in experimental cerebral edema. In the present experiments, neither albumin nor albumin/furosemide increased edema as determined by ICP measurements, by CT density measurements of the edematous area, or by wet-dry determinations of the edematous area; on the contrary, both albumin and albumin/furosemide seemed to decrease edema.

In patients with cerebral edema, control of ICP and perfusion is probably more important than local edema. Several recent articles suggest that localized edema may exist without impairing neurological function in animals and humans.27,32 Hallenbeck, et al.,17 have shown that the amount of circumscribed edema is not a good predictor of postischemic neuronal recovery.

The albumin/furosemide combination did not cause hypovolemic hemodilution, which has been used to treat focal cerebral ischemia.21,39 Infusing 1 gm of albumin increases plasma volume 18 ml,34 and the increased plasma volume may transiently increase ICP if the albumin is infused rapidly. The addition of furosemide removes water withdrawn by the albumin, in effect dehydrating tissues without causing hypo- or hypervolemia. Normovolemic dehydration may minimize the abrupt fluctuations of autonomic tone that may worsen ICP.15

We gave furosemide in larger dosages (1 mg/kg bolus, with or without a constant infusion of 0.5 mg/kg/hr) than should be given to patients. Some of the results of furosemide treatment may have been due to its effect on oncotic pressure and would be consistent with the slow reduction in ICP noted by Wilkinson and Rosenfeld.37 Mean oncotic pressure in dogs receiving furosemide (21.5 torr) was nearly identical to that of dogs receiving albumin (22.5 torr), and was substantially greater than in dogs receiving crystalloids (16.6 torr). As in our previous experiments,1 crystalloids caused progressive decreases in oncotic pressure, which increased the effect of hydrostatic pressure to increase interstitial fluid and, therefore, increased edema.
Furosemide often decreases systemic blood pressure.\textsuperscript{30} Because hypotension reduces the tissue perfusion gradient and decreases the spread of edema,\textsuperscript{20,22} we minimized hypotension in these experiments by titrating doses of Innovar according to blood pressure, and the mean arterial pressures in dogs receiving furosemide were not significantly different. Mean arterial pressure should be stable in studies evaluating oncotic pressure because a 10-torr increase in arterial pressure increases oncotic pressure by 0.75 torr.\textsuperscript{25}

Several authors have found, as we did, that furosemide significantly decreases ICP in experimental cerebral edema.\textsuperscript{18,24} The effects of furosemide on cerebral water content are less certain, probably because of differences in research methodology. For example, Claßen, \textit{et al.},\textsuperscript{7} gave rhesus monkeys 10 mg/kg of furosemide every 6 hours for 24 hours and found, as we did, that water content was decreased in the lesion hemisphere but not in the contralateral hemisphere. Tornheim, \textit{et al.},\textsuperscript{35} gave cats furosemide, 1 mg/1 gm, every 8 hours for 48 hours, and found specific gravity significantly decreased in the lesion area but not on the opposite side. Millson, \textit{et al.},\textsuperscript{24} gave rabbits 10 mg/kg of furosemide, and Harbaugh, \textit{et al.},\textsuperscript{18} administered 5 mg/kg; 45 minutes after one dose, cerebral water content was not significantly decreased on either side. In our experiments, furosemide decreased the water content 1.7% in the non-lesion hemisphere, a decrease that may have clinical, although not statistical, significance.

Both Harbaugh, \textit{et al.},\textsuperscript{18} and Pappius\textsuperscript{19} have reported that mannitol did not dehydrate edematous tissue. This difference from our results may be due to different mannitol dosages (1.5 gm/kg in the present study, 1.0 gm/kg in the studies of Harbaugh, \textit{et al.}, and Pappius).

Several questions about oncotic therapy remain. Would oncodiuretic therapy have been more effective than furosemide alone if the experiments had been longer? Probably; oncotic gradients remove brain water slowly and the clinical effects of furosemide alone are transient. Would a combination of osmotic and oncotic gradients with mannitol and albumin/furosemide be more effective than either would be alone? Probably; experiments are underway to answer that question.

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References

Therapy of experimental cerebral edema


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