Effects of Infusion of Hypertonic Mannitol on Electrolyte Balance and on Osmolarity of Serum and Cerebrospinal Fluid*

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Intravenous infusion of hypertonic solution of mannitol has been shown to be effective in lowering cerebrospinal-fluid pressure and decreasing the mass of brain,11,17,18 as well as lowering intraocular pressure.13 In addition, mannitol is said to be effective in preventing renal damage2,2,9 and treating dilutional hyponatremia.5 Because of the increasing use of this substance, it is important to understand its effect on fluid and electrolyte balance, particularly in the postoperative patient.

The studies of osmolarities were done to elucidate the mechanism of action of mannitol in lowering cerebrospinal-fluid pressure.

Methods

The concentrations of sodium and potassium in serum and urine were determined by flame photometry with a lithium internal standard. The preoperative blood sample was drawn on the day prior to operation, or on the morning of the first postoperative day. An indwelling urinary catheter was inserted immediately after the induction of anesthesia; urine from the bladder was discarded then and urine was collected during the next 24-hour period (“operative day”). Osmolarity was determined by the method of freezing-point depression.†

The amount and type of intravenous fluids administered to these patients varied, since the surgeon in charge of each case determined the intake of fluid. Most neurosurgical patients at this hospital receive at least 75 mEq. of sodium on the operative day.16

Results

In 18 patients who received hypertonic solution of mannitol (1.1 to 3.6 gm./kg.) during operation the mean urinary volume

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† Advanced Instruments model 31-L osmometer.

on the operative day was 2840 ± 863† mm. per 24 hours. In 17 of these, the mean urinary output of sodium was 94 ± 56 mEq.; excluding patients with pituitary or hypothalamic lesions there were 12 patients with a mean output of sodium of 77 ± 37 mEq. (Fig. 1). (The patients with pituitary or hypothalamic lesions received gluco-corticoid supplementation.) Six patients who did not receive mannitol had a mean operative-day excretion of sodium of 44 ± 17 mEq.

In 16 patients who received mannitol the mean operative-day urinary excretion of potassium was 80 ± 30 mEq. Excluding pituitary and hypothalamic lesions the mean excretion of potassium was 74 ± 31 mEq. The mean value for 3 patients who did not receive mannitol was 55 mEq.

Both preoperative and postoperative concentration of serum sodium was determined in 17 patients who received mannitol during the operative procedure (Fig. 2). Mean preoperative concentration of serum sodium was 141.3 ± 4.2 mEq. per l.; mean postoperative concentration of serum sodium was 144.1 ± 6.7 mEq. per l. Excluding patients with lesions of the pituitary and hypothalamus, the respective mean concentrations were 139.9 ± 2.7 mEq. per l., and 142.1 ± 5.2 mEq. per l. in 12 patients. In 8 additional patients the preoperative concentration of serum sodium had not been determined, but the mean postoperative concentration of serum sodium was 140 ± 3 mEq. per l. In 10 patients who did not receive mannitol the preoperative and postoperative concentrations of serum sodium were respectively 139.5 ± 3.4, and 137.9 ± 2.7 mEq. per l.

Concentration of serum potassium

† Standard deviation.
dropped slightly postoperatively whether or not mannitol was administered (Fig. 2).

Osmolarity Studies

In 4 patients simultaneous measurements of cerebrospinal-fluid pressure and serum and determinations of osmolarity of cerebrospinal fluid were performed before, during and after infusion of mannitol. (Some in-accuracy was introduced necessarily in the measurements of pressure by the need to remove samples of cerebrospinal fluid periodically for determinations of osmolarity.) Two patients had malignant gliomata and had undergone craniotomy 3 and 5 weeks previously. In the first patient (Fig. 3) infusion of 8 gm./kg. of mannitol in 65 min. increased osmolarity of serum 33 mOsm. and osmolar-
ity of cerebrospinal fluid 6 mOsm. At this point, concentration of serum sodium had dropped from 138 to 122 mEq. per l. Eighty min. after infusion osmolality of serum was still 30 mOsm. above the start, concentration of serum sodium was 129 mEq. per l. and osmolality of cerebrospinal fluid was 18 mOsm. above the start. In the second patient (Fig. 4) 3.6 gm./kg. of mannitol in 45 min. increased osmolality of serum 42 mOsm., with no significant change in osmolality of cerebrospinal fluid. Fifty min. later the osmolarities of serum and cerebrospinal fluid were respectively 34 and 4 mOsm. above the base-line values.

The other 2 patients were considered to have increased intracranial pressure of undetermined cause ("pseudotumor cerebri"). Both patients were fully alert and were allowed to drink and eat during the rather prolonged studies. In the first patient (Fig. 5) infusion of 8 gm./kg. of mannitol in 60 min. increased osmolality of serum 28 mOsm. and osmolality of cerebrospinal fluid 6 mOsm. Seventy min. later osmolality of serum was 9 mOsm. above base line and cerebrospinal fluid, 4. At 130 min. osmolality of serum and cerebrospinal fluid were respectively 6 and 4 mOsm. above base line. Four hours after the completion of the infusion osmolality of serum was 6 mOsm. below base line and osmolality of cerebrospinal fluid 26 mOsm. above.

The other patient with "pseudotumor cerebri" received 3 gm./kg. of mannitol in 90 min. with increase in osmolality of serum and cerebrospinal fluid of 33 and 8 mOsm. respectively (Fig. 6). At 90 min. osmolality of serum and cerebrospinal fluid were respectively 18 and 1 mOsm. above base line; at 150 min. 22 and 14 above base line; and at 4 hrs. 18 and 16 mOsm. above base line.

In 5 patients with ocular disease, reported elsewhere, hypertonic solution of mannitol, 1.3 to 2.2 gm./kg., in 25–105 min., raised osmolality of serum 12 to 30 mOsm. per l.

Discussion

These results indicate that the intravenous infusion of hypertonic solution of mannitol during operative procedures causes a moderate increase of the 24-hour urinary excretion of sodium, and to a lesser extent, potassium, during the operative day. (Statistical comparison of the means was not done because of variation in the dosage of mannitol and variation of amounts and types of other fluids given to these patients.) This natriuretic action of mannitol has been recognized before, and may vary with the intake of sodium. However, in its current use, the mean 24-hour loss of sodium is not very high, and if some salt-containing fluids are admin-

![Fig. 3. Effect of mannitol on osmolality (dashed lines with open circles and triangles), concentration of sodium (solid line with open circles and triangles), and cerebrospinal-fluid pressure (solid line and solid dots). The dashed portions of the line of cerebrospinal-fluid pressure represent periods when cerebrospinal fluid was removed for analysis.](image-url)

![Fig. 4. Effect of mannitol as in Fig. 3.](image-url)
istered during the operative day, the net flux of sodium usually is negligible. In patients with pituitary or hypothalamic lesions, output of sodium may be greater in spite of glucocorticoid supplements.

The diuretic effect of mannitol appears to counteract the antiuresis which often occurs on the operative day. The net result is that, although concentration of serum sodium may be lowered transiently at the conclusion of the infusion of mannitol, the concentration of serum sodium (and presumably osmolarity of serum) on the first postoperative day is altered very little (or raised slightly) from the preoperative value.

There was also slight augmentation of excretion of potassium after mannitol, but little effect on concentration of serum potassium.

The results of the studies of osmolarity were somewhat similar to those of Langfitt7 with urea. At the conclusion of infusion of mannitol (3 to 3.6 gm./kg. in 45 to 90 min.) osmolarity of serum was increased 28 to 42 mOsm. and the osmotic gradient between cerebrospinal fluid and serum was 16 to 35 mOsm. Lowest levels of pressure of cerebrospinal fluid were reached shortly after these determinations. Fifty to 90 min. later osmolarity of serum was still 9 to 34 mOsm. above base line and osmotic gradients were 1 to 22 mOsm. These gradients were 13 and 22 mOsm. in the patients who had no intake of fluid during the recording, and 1 and 8 mOsm. in the 2 who were allowed to take oral fluids. Intake of salt-free fluid would, of course, tend to lower osmolarity of serum.

In these 2 latter patients, osmolarities of serum and cerebrospinal fluid were equal at 130 and 150 min. during the rising phase of

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Fig. 5. Effect of mannitol as in Fig. 3. In addition, periodic blood-pressure readings and cumulative crude fluid-balance are indicated. Arrows at bottom of figure indicate points when samples of cerebrospinal fluid were removed.

Fig. 6. Effect of mannitol as in Fig. 5.
cerebrospinal-fluid pressure and the osmotic gradient was reversed at 240 min. although no “overshoot” of pressure occurred.

The results of these limited studies seem to be in agreement with the conclusions of others studying mannitol and urea, i.e., there is a rough correlation between the osmotic gradient produced and the change in cerebrospinal-fluid pressure, particularly during the phase of falling pressure.\textsuperscript{4,7,11}

In the clinical use of an osmotic agent, several variables may affect the osmotic gradient produced and the degree and duration of lowering of cerebrospinal-fluid pressure. These variables include the amount and type of fluid and electrolyte administered with or following the osmotic agent, as demonstrated in these 4 cases, as well as the total amount and speed of administration of the osmotic agent.\textsuperscript{11}

**Summary**

Intravenous infusion of hypertonic solution of mannitol during neurosurgical operative procedures caused a moderate increase in urinary excretion of sodium during the operative day, as compared to patients who did not receive mannitol. However, excretion of water also was increased by infusion of mannitol so that the net result was a slight increase of the concentration of serum sodium on the first postoperative day. It appears that if some sodium-containing intravenous fluids (75–100 mEq.) are administered on the operative day, the net flux of sodium from the body after infusion of mannitol will be insignificant in most cases.

Infusion of mannitol increased excretion of potassium slightly with very little change in concentration of serum potassium.

Osmolarity of serum was increased 28 to 42 mOsm. and serum/cerebrospinal-fluid osmotic gradient was 16–35 mOsm., after the infusion of 3 to 3.6 gm./kg. of mannitol in 45 to 90 min. Osmolarity of serum then gradually fell towards normal while in 2 patients osmolarity of cerebrospinal fluid was increased moderately at 4 hrs.

Several of the factors affecting the osmotic gradients produced and the degree of lowering of cerebrospinal-fluid pressure are discussed.

Some of the determinations of electrolytes were done by Tillie Leake, Betty Halliday and Carol Knight. Some of the patients on whom these studies were performed were under the care of Drs. John E. Adams, Edwin B. Boldrey and Joseph A. Witt, who kindly used mannitol and permitted these studies. The studies of the 2 patients with “pseudotumor cerebri” were performed by Dr. Leatham Flanagan.

**References**


14. West, C. D., and Bayless, R. K. Relation of the saluresis of urea and mannitol loading to the normal

**Discussion**

Dr. Henry A. Sluckin: I feel that we should all be grateful for another thoughtful contribution from Dr. Wise.

It is reassuring from this work that the natureuse known to be induced by infusion of mannitol is blunted in the operative state, because of the natural holding back of excretion of salt at that time. Our clinical experience confirms that no electrolyte imbalance does occur with the use of mannitol as a cerebral decompressing agent during operation.

[Slide] Our own data confirm Dr. Wise's inference that there is no direct relationship between change in osmolarity of serum induced by infusion of mannitol and fall in pressure of cerebrospinal fluid.

I think the difference in osmolarity of serum has no direct relation to the magnitude of the fall of cerebrospinal-fluid pressure, contrary to our original impression communicated to this Society last year. It might be inferred, however, from Dr. Wise's data this afternoon that an important factor in the fall in pressure of cerebrospinal fluid is the gradient of osmolarity established between blood and the reservoir of cerebrospinal fluid.

Mannitol usually is thought to diffuse into the extracellular compartments and the fact that an osmolar gradient does exist between blood and cerebrospinal fluid indicates that the latter is not an ordinary extracellular compartment and if mannitol does enter it, it must do so slowly and then reverses the osmolar gradient, as shown by Dr. Wise. Serial determinations of concentrations of mannitol in the cerebrospinal fluid would prove this. If mannitol did not enter the cerebrospinal fluid, the implication would be that the fall in pressure of cerebrospinal fluid primarily is caused by loss of water from this extracellular compartment.

Current work in our laboratory in an effort to elucidate the mechanism of action of infusion of mannitol in lowering pressure of cerebrospinal fluid has disclosed the curious phenomenon that during infusion of osmotic agents in some patients, the pressure of cerebrospinal fluid falls exponentially with time.

[Slide] The significance of this is as yet unclear. Whereas mannitol produced a single slope, urea produces a fall in cerebrospinal-fluid pressure which was a compound exponential function consisting of two slopes.

From a clinical point of view, I can only reiterate that mannitol has many advantages over urea, among which are the fact it can be used in patients with poor kidneys, it hasn't as yet caused a slough, and it has less tendency to rebound. Further, I have the impression that hypothermia which I personally believe is not a useful technique as an adjunct for surgery, does not mix very well with urea, but it probably would not be adversely affected by mannitol.

Dr. Manucher Javid*: Because of our mutual concern for the problem of electrolyte balance after the use of hypertonic solutions, we found Dr. Wise's paper to be very interesting.

We have a paper in press concerning electrolytes following administration of urea. There is no significant difference in the trend of serum sodium and potassium of surgical patients after urea or mannitol. Patients receiving mannitol do appear to excrete significantly more water and sodium. Urea gives no increase in excretion of potassium compared to the controls while mannitol appears to have given a 35–50 per cent increase in excretion of potassium. Similar augmentation of loss of potassium has been reported by Moore and co-workers when 5 per cent mannitol and 4 per cent urea were compared. The excess excretion of potassium introduces a potential hazard, particularly if mannitol has to be used repeatedly subsequent to operation.

Mannitol is an effective agent for reduction of cerebrospinal-fluid pressure and was one of the agents that we compared with urea several years ago. It is a better diuretic than urea; as a consequence, it tends to cause greater loss of water and electrolytes. Mannitol has a more limited solubility and a higher molecular weight, thus approximately 4 to 5 times as much fluid must be administered to achieve an osmotic effect comparable to that obtained with 30 per cent urea. These are the main reasons for our preference for urea. Recently a 70-year-old asthmatic patient with acute glaucoma received 600 cc. of 25 per cent mannitol. The sudden expansion of blood volume precipitated acute pulmonary edema and cardiac insufficiency. The patient died within 48 hours. In another patient we have seen venous thrombosis after administration of mannitol similar to what is occasionally seen after urea.

Dr. Wise's data on the osmolality of serum after administration of mannitol are similar to data obtained after administration of urea. Spinal-fluid osmolality seldom exceeds that of the serum by more than experimental error in the work reported by Dr. Langfitt using urea. The results reported by Dr. Wise concerning solute content of spinal fluid are not consistent and it would be difficult to draw definite conclusions other

* Read by Dr. David Gilboe.
than the fact that mannitol also penetrates the blood-
cerebrospinal-fluid barrier. If this were a factor, it too
could be expected to give some degree of "rebound."
In our experience with 1250 patients and in animal ex-
periments employing urea and mannitol, we have not
seen anything that can be interpreted as "rebound"
after use of either agent. Factors responsible for the
"rebound phenomenon," reported by some in the lit-
erature, will be discussed in a paper to be submitted for
publication shortly.

[Slide]

<table>
<thead>
<tr>
<th>Serum electrolytes</th>
<th>(14) Mannitol (Wise)</th>
<th>(50) Urea (Gilboe &amp; Javid)</th>
<th>(10) Mannitol Control (Wise)</th>
<th>(15) Urea Control (Gilboe &amp; Javid)</th>
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</thead>
<tbody>
<tr>
<td>Na before</td>
<td>139.9</td>
<td>139.0</td>
<td>139.5</td>
<td>138.25</td>
</tr>
<tr>
<td>Na after</td>
<td>142.1</td>
<td>141.2</td>
<td>137.9</td>
<td>137.17</td>
</tr>
<tr>
<td>K before</td>
<td>--</td>
<td>4.41</td>
<td>--</td>
<td>4.48</td>
</tr>
<tr>
<td>K after</td>
<td>--</td>
<td>4.18</td>
<td>--</td>
<td>4.20</td>
</tr>
<tr>
<td>24-hour electrolyte and water excretion</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Na</td>
<td>77 mEq.</td>
<td>60.20 mEq.</td>
<td>44 mEq.</td>
<td>55.69 mEq.</td>
</tr>
<tr>
<td>K</td>
<td>74 mEq.</td>
<td>49.53 mEq.</td>
<td>55 mEq.</td>
<td>51.37 mEq.</td>
</tr>
<tr>
<td>H₂O</td>
<td>2840 ml. (18 pts.)</td>
<td>2148 ml. (3 pts.)</td>
<td></td>
<td>2590 ml.</td>
</tr>
</tbody>
</table>

As far as the entry of mannitol into the brain and the
cerebrospinal fluid is concerned, we are starting some
isotope studies to evaluate this. There have been some
studies done for other purposes, which demonstrated
that mannitol and similar saccharides enter the cerebro-
spinal fluid very slowly and the fraction that does enter
the cerebrospinal fluid passes rapidly back to the blood,
probably through the arachnoid villi. Dr. Brodie and
his associates did this work at the National Heart
Institute.

Regarding the point that Dr. Javid made about urea

Dr. Burton L. Wise: In spite of the way it sounds,
I don't own any stock in "Mannitol, Inc."

I would like to thank the discussers for their com-
ments.

To answer some of Dr. Shenkin's points: this problem of
the relationship between osmolarity and changes in
pressure has been brought up by various people who
studied mannitol and other agents. Dr. Langfitt, study-
ing urea, felt he could find some correlation if he con-
sidered the percentage of drop and the initial pressure.
He thought he saw some correlation during the period
of falling pressure. Admittedly, the correlation I found
was also not exact; it was rather vague during the rising
phase.

and sodium, there have been several studies that had
some bearing on this. Drs. Mason and Raaf studied the
loss of sodium with urea and found, I believe, the op-
erative day loss of sodium was 35 to 55 mEq. Murphy et
al. at Johns Hopkins, studied 15 patients and came up
with a mean postoperative excretion of sodium of 113
mEq. for 24 hours; thus I think there is probably some
variation.

I think the osmotic mechanism is actually similar, and
the difference in change and excretion of electrolytes
is not very great. I did make the point that there will be
some difference depending on the type and amount of
other fluids given during the operative day together
with the osmotic agent.