THE USE OF MANNITOL FOR THE REDUCTION OF INTRA-
CRANIAL PRESSURE IN INTRACRANIAL SURGERY*

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The facilitation of intracranial surgery by the use of urea, to reduce brain bulk, has suggested that other osmotic agents might be useful for the same purpose. Wise and Chater1 suggested that mannitol, a hexitol, long used by renologists in order to induce a diuresis, might be useful in this regard. It is readily available and its innocuousness to man has been amply proven. It has a molecular weight triple that of urea, but this osmotic disadvantage of mannitol to urea might well be offset by the fact that mannitol is confined to the extracellular space, for all practical purposes. This exclusion from the intracellular compartment theoretically might be of further advantage in preventing a rebound of intracranial pressure said to be noted on occasions after the use of urea. On the other hand, mannitol is excreted rapidly by the kidney (1 per cent per min. of a loading dose) and its osmotic level in the blood is less prolonged than after urea, used in equivalent dosages and speed of injections. An advantage for mannitol is that renal disease does not appear to be a contraindication for its use; indeed, it has been advocated recently for use in patients with renal disease, in order to prevent urinary shutdown.1

DOSEAGE

In calculating the amount of mannitol to use for optimum clinical advantage, we have been guided by our previous experiences with urea. It has been our impression that urea used in the recommended doses of 1 to 1 1/2 gm. per kg. as a routine before craniotomy has been unnecessary. Smaller doses of approximately 1/2 gm. per kg. given intravenously in 15 min., has been sufficient to relax the brain for most procedures, thus facilitating the turning of the bone flap and preventing herniation of the brain upon opening the dura mater and, when necessary, permitting easy access to the cisterna, the emptying of which completely relaxes the brain for ample exposure of structures beneath the brain. This smaller dose of urea had not caused the venous ooze seen with the use of the recommended larger doses of urea, presumably resulting from the more drastic shrinkage of brain bulk and a concomitant greater increase in intravascular volume.4 Furthermore, these smaller doses have not masked the very occasional state of shock, that we feel has occurred at times, with routine use of 1 to 1 1/2 gm. per kg. doses of urea, particularly in the older patient. Consequently, we have used, on the average, a dose of 1 gm. of mannitol per kg. of body weight given in 20 to 25 per cent solutions intravenously in a period varying from 10 to 15 min. This has achieved a maximum rise in osmolarity of serum amounting to 20 to 30 milliosmols at the termination of the infusion, with a decline in osmoticity to control levels over a period of approximately 3 hours.

We are in the process of determining the effects of variations in the speed of infusion of urea and mannitol upon osmolarity of serum and resulting influences on cerebrospinal-fluid pressure. It is reasonable to assume that the osmotic gradient achieved between blood and brain is the factor that produces a reduction in brain bulk with the

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**TABLE 1**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Dosage (gm./kg.)</th>
<th>Infusion Time</th>
<th>Osmolarity</th>
<th>CSFP Change</th>
<th>Time of Maximum CSFP Fall</th>
<th>Time of Return to Initial CSFP</th>
<th>Time of Return to Initial Osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Maximum Δ osmol.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.M.</td>
<td>1.1</td>
<td>14 min.</td>
<td>283</td>
<td>37</td>
<td>140→100 (20%)</td>
<td>1 hr.</td>
<td>5 hrs.</td>
</tr>
<tr>
<td>A.C.</td>
<td>1.0</td>
<td>10 min.</td>
<td>298</td>
<td>29</td>
<td>836→125 (47%)</td>
<td>1 1/2 hrs.</td>
<td>8 hrs.</td>
</tr>
<tr>
<td>J.K.</td>
<td>0.7</td>
<td>12 min.</td>
<td>290</td>
<td>20</td>
<td>297→210 (39%)</td>
<td>1 hr.</td>
<td>8 hrs.</td>
</tr>
<tr>
<td>C.A.</td>
<td>1.0</td>
<td>10 min.</td>
<td>280</td>
<td>24</td>
<td>440→175 (60%)</td>
<td>1 hr.</td>
<td>8 hrs.</td>
</tr>
<tr>
<td>A.R.</td>
<td>1.1</td>
<td>10 min.</td>
<td>250</td>
<td>27</td>
<td>180→80 (56%)</td>
<td>2 hrs.</td>
<td>*</td>
</tr>
</tbody>
</table>

*This value did not return to base line at end of 6 1/2 hours (Fig. 1).

use of intravenous mannitol or urea. It further is to be assumed that the speed of infusion of these agents, as well as the total dosage used, are important in achieving this osmotic gradient. These provide two variables that are capable of control in achieving an optimum clinical effect.

In 5 experiments (Table 1) approximately 1 gm. of mannitol per kg. of body weight was administered over a period of between 10 to 14 min. by means of a constant-infusion pump. This achieved a maximum increase in osmolarity of serum of between 20 to 37 miliosmols and reduced the cerebrospinal-fluid pressure by 29 to 60 per cent for a period of 2 to 3 1/2 hours or longer (Fig. 1). Although the initial spinal-fluid pressure, as noted previously by others, seems to be an important factor in determining the amount of decrease in pressure achieved, our data (Table 1) indicate a relationship to the magnitude of the osmotic change created. Of course, our data are still quite limited and this point does bear further elucidation.

**RESULTS**

Mannitol was used as an operative preparation for 54 patients. Of these, 21 had supratentorial tumors, 4 of which were meningiomas. There were 2 with posterior-fossa tumors and 4 patients had a retrogasserian rhizotomy. Five patients had aneurysms, 3

![Fig. 1. Chart of effect of intravenous infusion of mannitol upon cerebrospinal-fluid pressure measured over period of 5 1/2 to 6 1/2 hours in 5 patients from Table 1.](image-url)
of the circle of Willis and 2 on the middle cerebral artery. Two patients had a cranioplastie repair of a cranial defect. The patients averaged 45 years of age with a range of 8 to 72 years and 20 of the 34 patients had clear evidences of increased intracranial pressure preoperatively. In all instances, adequate relaxation of the brain was achieved. For instance, the retrogasserian rhizotomies for tic douloureux were all done transtemporally in the upright position and the procedure could be carried out with ease in all instances without the use of a lighted retractor, even before the release of the spinal fluid. In exposure of the circle of Willis, we were impressed with the fact that adequate relaxation of the brain, for operative purposes, did not seem achievable with this dose until the spinal-fluid cisterns were emptied. In each patient, a prompt diuresis developed, ranging from 200 to 400 cc. per hour, during the operative period; which varied from 1 hour to 4½ hours. No observable effects were created upon the blood pressure or pulse or central venous pressure and in no instance was any unexpected vascular reaction encountered.

**DISCUSSION**

The purpose of this presentation is two-fold. First, to confirm the recommendation for the use of mannitol as another osmotic agent for control of brain bulk during intracranial surgery as being safe and effective. Second, to suggest that the method of administration of these osmotic agents (urea and mannitol) as to dosage and speed of infusion needs further investigation. Empirically, in our hands, smaller than recommended doses appear to be effective and create less difficulties. So far, our studies in the laboratory on mannitol given in doses of 1 gm. per kg. (Table 1) appear to correlate with previously reported studies of Javid and Settlage, Langfitt, and Wise and Chater to indicate that there is a relationship between dosage used and increase in osmolarity of serum achieved, when measured, and percentage decrease of cerebrospinal-fluid pressure produced and the length of time this decrease persisted. Wise and Chater, in 3 patients with increased intracranial pressure given 1.5 to 2 gm. of mannitol per kg., found cerebrospinal-fluid pressure lowered 50, 60 and 90 per cent with return to initial pressure in 3½ to 8 hours. Langfitt, using doses of 0.5 to 1.4 gm. of urea per kg., achieved changes ranging from an increase of 19 to 82 milliosmols in the serum of 5 patients and reduced the cerebrospinal-fluid pressure by 62 to 204 per cent. Javid and Settlage gave 23 patients incrementing doses of urea, from 0.1 to 1 gm. per kg. intravenously. If one calculates their data according to percentage decrease in cerebrospinal-fluid pressure achieved against the variable dosages used, a distinct relationship appears, namely, that the percentage decrease in spinal-fluid pressure varies proportionately to the dose used (Table 2).

The salient question in the use of these agents appears, to us, to be the determination of the proper osmotic change that should be produced to yield the optimum reduction of brain bulk during surgery or in treatment of cerebral edema. It does not seem difficult to determine what dosage of an osmotic agent should be used for maximum reduction of brain bulk, but the criteria for the optimum dosage to use leave room for further investigation.

**SUMMARY**

In summary, our experience corroborates the findings of others as to safety and efficacy of mannitol as an osmotic agent for reduction of brain bulk during intracranial surgery.

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**TABLE 2**

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Dosage (gm./kg.)</th>
<th>Average Decrease in CSFP (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.1</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
<td>87</td>
</tr>
<tr>
<td>1</td>
<td>0.7</td>
<td>93</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>72</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>76</td>
</tr>
</tbody>
</table>

* Modified from Table 1 of Javid and Settlage.
Infusion and preoperatively. In all, adequate exposure and relaxation of the brain occurred. This was achieved despite the fact that smaller than recommended doses were utilized.

Our data from controlled studies indicate that the magnitude of decrease in cerebrospinal-fluid pressure was related to the osmotic gradient achieved at the termination of infusion. In turn, this osmotic gradient can be varied not only by the total dosage used, but also by the speed of injection. The combination of these several factors in order to achieve an optimum result is being investigated currently in our laboratory.

REFERENCES

DISCUSSION

Dr. Burton L. Wise:* We are gratified that Dr. Shenkin and his associates have confirmed our findings that hypertonic mannitol solutions are effective in lowering cerebrospinal-fluid pressure and decreasing brain mass. We began to look for another osmotic agent because of certain theoretical and practical objections to the use of urea. The distribution of urea throughout total body water may cause "rebound overshoot" of cerebrospinal-fluid pressure. Reports of toxicity of urea include changes in the electrocorticogram and electrocardiogram; occasional hemoglobinuria; venous thrombosis; and necrosis of tissue and sloughs in case of evanescent extravasation of urea. Another disadvantage of urea has been its instability, which necessitates making the solution from the lyophilized preparation, and the fact that, if not used, it may have to be discarded.

On theoretical grounds, it appeared to us that hypertonic mannitol solution would be a safe and effective agent to lower cerebrospinal-fluid pressure and decrease brain mass. Extensive use of mannitol in the past had established its lack of toxicity and inertness. Preparation of the hypertonic solution is by simple heat sterilization and the solution is relatively inexpensive and stable. In previous reports, we have emphasized the fact that because of its extracellular distribution and rapid excretion it seemed that mannitol would be less likely to cause secondary "rebound overshoot" than a substance like urea, which eventually is distributed throughout total body water, even if its entry into the brain and cerebrospinal fluid is relatively slow.

We have administered hypertonic mannitol solution to 67 patients. These have included 22 with glioma, 11 with intracranial aneurysms, 8 with meningiomas, 7 with pituitary tumors and cranioopharyngiomas, 5 with metastatic carcinoma to the brain, 4 undergoing hypophysectomy, 2 with "pseudo-tumor cerebri," 1 with a frontal arteriovenous malformation and intracerebral hemorrhage, 1 with brain abscess, 1 undergoing section of the trigeminal nerve in the posterior fossa, and 5 miscellaneous cases. In almost all instances, decrease in intracranial pressure and brain mass has been satisfactory as judged by the various neurosurgeons at our Center who have used it.

Some of the situations in which hypertonic mannitol has proved useful are: (1) when the dura mater is to be opened and intracranial tension is high, (2) to facilitate retraction of the brain in the approach to deep structures, (3) to facilitate dural closure when intracranial tension remains elevated, (4) temporary reversal of evidence of decompensating increased intracranial pressure and brain herniation, and (5) the treatment of "brain swelling" coming on several days after craniotomy.

We currently use a 20 per cent solution of mannitol in distilled water. We generally have used a higher dosage than Dr. Shenkin, namely 2.5 to 3 gm. per kg, and occasionally have given as much as 4.25 gm. per kg. If the infusion is started after the bone flap is turned, decrease in intracranial tension usually is apparent in 15 to 30 min. We have administered the solution as rapidly as 1 l. in 30 min., although generally 60 to 90 min. are taken for the complete infusion. There may be transient elevations of blood pressure of 10 to 20 mm. Hg and other evidence has been reported that hypertonic mannitol solution, as well as urea, causes a transient increase in volume of plasma. However, we have not seen evidence of cardiac circulatory overload. Venous thrombosis has not been a problem and in 1 instance in which mannitol solution inadvertently infiltrated into the subcutaneous tissue, there was no subsequent necrosis of tissue or slough. As Dr. Shenkin pointed out, we are not aware of any contraindication to the use of mannitol in the presence of renal, hepatic, or cardiac disease except
for the possibility of sudden expansion of circulatory volume. We have used mannitol concurrent with hypothermia and found no incompatibility. We have also used mannitol with and following hyperventilation. In 3 instances mannitol resulted in a decrease in brain mass after there was no apparent effect on brain mass from 20 to 30 min. of continuous hyperventilation under anesthesia. In 1 instance, the decrease in brain mass that followed ventricular drainage was augmented by subsequent administration of mannitol. Our initial studies on osmolarities are fairly similar to those reported by Dr. Shenkin.

As might be expected from the similarity of aqueous humor and cerebrospinal fluid, hypertonic mannitol solution has been shown to lower ocular pressure and in preliminary studies has been found to be effective in lowering ocular pressure in patients with glaucoma.

Dr. Henry A. Shenkin: I think that the doses used at the University of California are not really very different from what we are using, if you consider that we infuse mannitol more rapidly than they do. I think it will turn out that the osmotic gradient created is the critical factor. This is the point, I think, that has to be investigated in the use of these osmotic agents for cerebral decompression.