THE VALUE OF HYPERTONIC MANNITOL SOLUTION IN DECREASING BRAIN MASS AND LOWERING CEREBROSPINAL-FLUID PRESSURE*

BURTON L. WISE, M.D., AND NORMAN CHATER, M.D.
Division of Neurological Surgery, University of California
School of Medicine, San Francisco, California

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The value of a chemical or pharmacological agent that temporarily would lower cerebrospinal-fluid pressure and decrease the mass of the brain is apparent to neurosurgeons. Since Weed and McKibben demonstrated that various hypertonic solutions could accomplish these effects, many agents have been tested. Each of these substances has been found to have certain disadvantages or toxic effects.

The use of hypertonic urea for these purposes originally was proposed by Fremont-Smith and Forbes, and Wolf and Forbes, and was restudied by Fremont-Smith et al., Smythe et al., and Javid and Settlage. This material was difficult to prepare for sterile intravenous injection, but when lyophilized urea and invert sugar became available it found wide acceptance.

While hypertonic urea frequently is effective in lowering cerebrospinal-fluid pressure and decreasing the mass of the brain, there are certain theoretical and practical objections to its use. Urea is distributed throughout total body water, although it does equilibrate relatively slowly with brain water and cerebrospinal fluid. Thus, unless the urea administered were excreted fairly rapidly, one would expect dissipation of its osmotic gradient as equilibration of urea with brain water and cerebrospinal fluid occurred, and secondary "rebound overshoot" of pressure and brain mass. This effect indeed has been reported in studies in animals and in the human.

There also have been reports of experimental and clinical evidence of toxicity of urea, particularly at high concentrations. These include weakness, anorexia, nausea and vomiting, and diarrhea, as well as seizure discharges in the electrocorticogram, changes in the electrocardiogram, occasional hemoglobinuria, and abnormalities of prothrombin time. Necrosis of tissue and sloughs have been reported if hypertonic urea escapes into the subcutaneous tissue and thrombosis has occurred in the vein through which the urea was administered.

An additional disadvantage has been the time necessary to make up the solution prior to administration. If the solution is mixed and not used, it may have to be discarded because of the instability of urea solutions.

On theoretical grounds it appeared to us that mannitol, a 6-carbon hexahydric alcohol with a molecular weight of 182, would be a safe and effective hypertonic agent for lowering cerebrospinal-fluid pressure and reducing the mass of the brain. Extensive use of mannitol in animals and humans in the past has established its inertness and lack of toxicity. Previous studies had established that mannitol is confined mainly to the extracellular space and is excreted fairly rapidly. There is some disagreement as to whether mannitol may be metabolized to a small extent in man but this appears to be insignificant in its present use.
Hypertonic solutions of mannitol are prepared easily for intravenous injection by standard methods of heat sterilization, are stable, and are relatively inexpensive.

Consequently, a series of experiments utilizing hypertonic mannitol solution were carried out in animals. These studies established that hypertonic mannitol solutions lowered cerebrospinal-fluid pressure without secondary "rebound overshoot". Osmotically equivalent amounts of mannitol were at least as effective as hypertonic urea, and appeared to have a more prolonged effect. When renal excretion was prevented, it appeared that hypertonic mannitol solution caused more prolonged lowering of cerebrospinal-fluid pressure and less secondary elevation of pressure than urea.

Following these studies, hypertonic mannitol solutions were administered to humans. A preliminary report of our experiences with use of mannitol in 24 patients has been presented. The first 3 patients studied were in terminal condition because of inoperable or recurrent gliomas. In these patients, continuous recording of cerebrospinal-fluid pressure was done with a Statham strain gauge and a Grass polygraph. Thus, the cerebrospinal-fluid space was kept closed, and a permanent continuous recording of cerebrospinal-fluid pressure was obtained. After initial base-line recording for 20 to 30 min., during which time pressure did not vary significantly, intravenous infusion of hypertonic mannitol solution, 1.5 to 2 gm./kg., was administered. In these cases, the cerebrospinal-fluid pressure was lowered 50 to 90 per cent with return to initial levels in 5.5 to 8 hours, and no secondary rebound above control levels (Figs. 1, 2 and 3). It was noted on polygraph records, although not shown in the accompanying figures which chart the mean levels of these recordings, that the initial effect of mannitol, before any drop in mean pressure, was a decrease in the amplitude of "arterial" pulsations of the cerebrospinal fluid.

Hypertonic mannitol solution has been administered to 70 patients with intracranial lesions. In most instances, it has been admin-
istered during operative procedures to decrease the mass of the brain. The patients have included 23 with gliomata, 11 with intracranial aneurysms (with and without hypothermia), 9 with meningiomas, 7 with pituitary tumors and craniopharyngiomas, 5 with metastatic carcinoma to the brain, 5 undergoing hypophysectomy, 2 with "pseudotumor 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 very satisfactory. There has been no apparent incompatibility between mannitol and hypothermia. Recently Shenkin and Goluboff\(^7\) have confirmed our results, although they used smaller doses than we.

We feel that hypertonic mannitol solution is useful whenever lowering of cerebrospinal-fluid pressure and decrease of brain mass are required. Some specific situations in which mannitol has proved, or might be expected to prove, useful are as follows:

1. To prevent damage to the brain when intracranial tension is high and the dura mater is about to be opened.

2. To facilitate retraction of the brain in the approach to deep structures, i.e., exposure of the pituitary, exposure of a carotid aneurysm, etc.

3. The temporary reversal of evidence of decompensating increased intracranial pressure and herniation of the brain, especially just prior to or during diagnostic studies. We have had 3 instances in which progressive unilateral dilatation of the pupil, rising blood pressure, and slowing pulse were reversed temporarily by rapid intravenous infusion of hypertonic mannitol solution, permitting completion of diagnostic studies and orderly planning of further procedures.

4. Head injuries: We have had little experience with the use of hypertonic mannitol in the treatment of head injuries, but on theoretical grounds it should prove efficacious in those instances in which an osmotic agent would be indicated. It appears that the value of a hypertonic solution is relatively limited in most instances of head injury.\(^44\)

5. On theoretical grounds, mannitol should prove useful to treat "brain swelling" coming on several days after craniotomy. It is likely that some of these cases are caused by mild dilutional hyponatremia,\(^51\) and mannitol has been utilized to treat this in general surgical patients.\(^20\) Of course, caution must be exercised in making the differential diagnosis between cerebral edema and dilutional hyponatremia on the one hand, and postoperative intracranial clot on the other.\(^51\)

6. "Pseudotumor cerebri": 3 gm./kg. of hypertonic mannitol has been administered to 2 patients with this condition. Temporary striking drop in cerebrospinal-fluid pressure has occurred with return to the original levels of pressure, but without "overshoot", in 3 to 4 hours.

7. We have not had the opportunity to use mannitol to treat increased intracranial pressure from other causes, such as lead intoxication. Hypertonic mannitol would be expected to be effective, as urea has been.\(^15,26\)

We currently are using 20 per cent mannitol solution in distilled water. If some of the mannitol has crystallized, it redissolves quickly after heating. The usual dosage is 2.5 to 3 gm./kg., although we have used as much as 4.25 gm./kg. Although we have administered 1 liter of 20 per cent mannitol solution within 30 min., in general we take 1 to 1.5 hours for the complete infusion. However, Shenkin and Goluboff\(^7\) have reported good results with a dose of mannitol of 1 gm./kg., administered in 10 to 15 min.

In many instances there has been transient elevation of blood pressure of 10 to 20 mm. Hg, but no clinical evidence of cardiocirculatory insufficiency. Hypertonic mannitol infusion has been shown to cause transient increase in plasma volume, but it did not cause cardiocirculatory overload in any of 150 patients, some of whom had cardiac disease.\(^1\) In 1 instance in which mannitol solution infiltrated in subcutaneous tissue inadvertently, there was no subsequent evidence of necrosis of tissue or slough.\(^48\) Venous throm-
bosis has not been an apparent problem except in patients who have had indwelling venous catheters left in for a prolonged period. When mannitol has been administered rapidly to conscious patients, several have complained of transient headache, blurring of vision, dizziness, and a chilly feeling, as well as mild pain in the arm into which the mannitol was being infused. These symptoms are similar to those reported in patients receiving urea infusions.9,24,48

We have had 1 instance of postoperative hypovolemia in a patient whose urinary output following mannitol infusion was 3,200 cc. with an input of only 1,300 cc., and no blood transfusion during craniotomy. During the first postoperative day, hypotension and tachycardia developed, as well as laboratory evidence of hemoconcentration. The symptoms were reversed quickly by the rapid infusion of 1 liter of 5 per cent dextrose in water. Of course, this situation may occur following the use of any diuretic agent that causes negative water balance.24 Repeated use of such an agent may result in severe hyperosmolality.50

We are not aware of any contraindication to the use of mannitol in the face of mild to moderate renal disease and, in fact, it has been used as a diuretic in patients with cardiac, renal, and hepatic disease.1,2,5 It should be used cautiously in patients with cardiac disease or cardiac failure. It probably would be unwise to use mannitol in patients with active intracranial bleeding, except during craniotomy. We have used mannitol concurrently with and following hyperventilation.21 In 2 instances, mannitol resulted in decrease in brain mass after there was no apparent effect from 20 min. of continuous hyperventilation.

Our initial studies suggest that there is a slight augmentation of urinary excretion of sodium when mannitol is used during craniotomy, but that excretion of water is augmented to a greater degree. As a result, the serum-sodium concentration is less likely to fall in mannitol-treated patients than in those not so treated. Studies of serum-electrolyte concentrations, urine-electrolyte excretion, and osmolarities after mannitol infusions will be described in a separate article.

Finally, mannitol has been found to be effective in lowering intraocular pressure in patients with glaucoma and other ocular disease. These studies have been described elsewhere.48

SUMMARY

Experimental and clinical studies have established that hypertonic mannitol solution is safe and effective as an agent to lower intracranial pressure and decrease the mass of the brain. It has been administered in 70 patients with various intracranial lesions. Charts of continuous recordings of cerebrospinal-fluid pressure in 3 patients with increased intracranial pressure given hypertonic mannitol are shown in this article. The indications, value, and side effects of the use of this substance are discussed.

Drs. John E. Adams, Edwin B. Boldrey and Joseph A. Witt kindly permitted the use of mannitol solutions in patients under their care, as well as reported their visual observations of the effect of mannitol on mass of the brain during operative procedures.

REFERENCES

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