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

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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\textsuperscript{46,47} demonstrated that various hypertonic solutions could accomplish these effects, many agents have been tested.\textsuperscript{5,14,17,28,29,46,49,56} 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,\textsuperscript{15} and Wolf and Forbes,\textsuperscript{54} and was restudied by Fremont-Smith et al.,\textsuperscript{23} Smythe et al.,\textsuperscript{29} and Javid and Settlage.\textsuperscript{55} This material was difficult to prepare for sterile intravenous injection, but when lyophilized urea and invert sugar became available it found wide acceptance.\textsuperscript{51,42,44}

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,\textsuperscript{51,40} although it does equilibrate relatively slowly with brain water and cerebrospinal fluid.\textsuperscript{8,53} 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\textsuperscript{4} and in the human.\textsuperscript{13,27,43}

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,\textsuperscript{19} as well as seizure discharges in the electrocorticogram,\textsuperscript{41} changes in the electrocardiogram,\textsuperscript{4} occasional hemoglobinuria,\textsuperscript{25,27} and abnormalities of prothrombin time.\textsuperscript{28} Necrosis of tissue and sloughs have been reported if hypertonic urea escapes into the subcutaneous tissue,\textsuperscript{9,28,44} and thrombosis has occurred in the vein through which the urea was administered.\textsuperscript{8,36,44}

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.\textsuperscript{24}

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.\textsuperscript{1,5,12,16,20,38} Previous studies had established that mannitol is confined mainly to the extracellular space and is excreted fairly rapidly.\textsuperscript{10,11,30,32,35} There is some disagreement as to whether mannitol may be metabolized to a small extent in man\textsuperscript{8,7,34} 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 admini-