Management of raised intracranial pressure and hyperosmolar therapy

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ABSTRACT

The management of raised intracranial pressure is undergoing rapid change. The choice of medical treatments to reduce intracranial pressure varies between institutions and regions of the world. The mainstay of therapy, however, continues to be the infusion of a hyperosmolar solution to achieve an osmotic gradient to force the exit of water from the brain. This review introduces the basic concepts of raised intracranial pressure, summarises several recent studies that have challenged dogma in the field, and provides practical advice on hyperosmolar treatment, based on personal experience and a critical reading of the literature.

Forty years after the inception of the specialty of neurological critical care, its central tenets regarding the treatment of raised intracranial pressure (ICP) have been challenged. Recent clinical trials have dashed many closely held notions about ICP monitoring and the use of hyperosmolar agents to reduce ICP.[1] The deconstruction of our ideas regarding ICP measurement and treatment are interesting but leave a gap that requires guidance. What follows is applicable to most of the commonly encountered causes of intracranial hypertension, including intracerebral haemorrhage, brain swelling from cerebral infarction, traumatic brain injury, intracerebral and extracerebral haematoma, brain tumour and acute hydrocephalus. Figure 1 gives an imaging example of such a mass. This review provides advice on the main methods for reducing ICP, with emphasis on the use of hyperosmolar solutions to reduce the volume of the brain.

Any recommendations on this subject first require an explanation of the reasoning behind the treatment of elevated ICP. The fundamentals are:

1. As intracerebral volume expands, ICP increases at a greater than linear rate, approximating an exponential function.
2. The skull and its underlying inelastic dura restrict the expansion of its contents (brain, intravascular blood and cerebrospinal fluid). Any increase in the volume of one component occurs only at the expense of a reduction in the volume of the others.
3. As ICP rises, it opposes cerebral blood flow sufficiently to cause global brain ischaemia and brain death. This is reflected in cerebral perfusion pressure, which approximates blood pressure minus ICP.
4. Medical and surgical treatments that lower ICP act either by reducing the volume of one of the components listed in no. 2 above, removing a mass, or by opening the closed cranium to the atmosphere.
5. Except for headache, vomiting, and papilloedema, the signs of an intracranial mass are due to secondary tissue shifts induced by the mass, and not to raised ICP. Clinical signs only approximately reflect the level of ICP.

In counterpoint, several problems limit the clinical application of these axioms. A relationship between elevated ICP and poor outcome is supported mainly by retrospective studies of patients with traumatic brain injury. While seemingly self-evident, there is sparse confirmation that reducing ICP improves clinical outcome. Furthermore, several clinical trials have shown no benefit from monitoring ICP as a means of directing treatment.

TO BE OR NOT TO BE MONITORED

A central foundation of neurological intensive care has been the direct measurement of ICP in order to predict clinical deterioration and guide treatment. This is similar to using pulmonary capillary wedge pressure to manage congestive heart failure or haemodynamic shock. To virtually everyone's surprise, clinical trials have been unable to show clear value to pulmonary artery pressure measurements over clinical and X-ray evaluation. The

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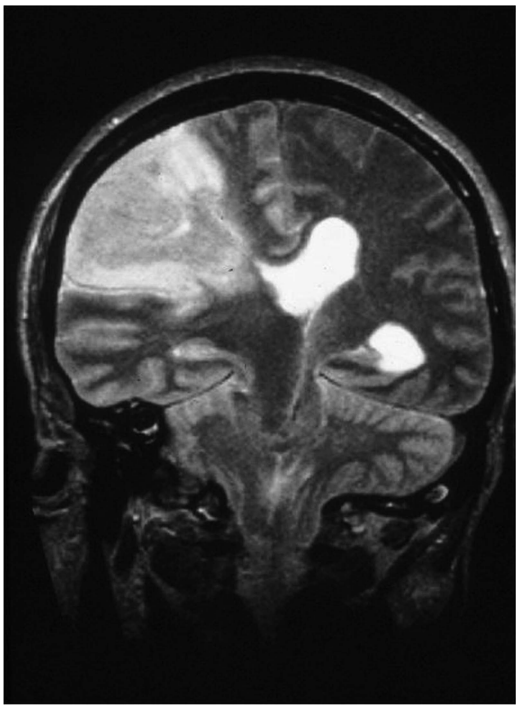

Figure 1 MRI showing a large right middle cerebral artery stroke with brain swelling that rerquired treatment with hyperosmolar therapy.

approach of direct measurement of ICP originated in the studies of brain trauma conducted decades ago by Lundberg, Becker, and Marshall as summarised in a contemporary review.[2] Lundberg *et al* showed that ICP could be measured for clinical purposes continuously and safely rather than intermittently by lumbar puncture. They used intraventricular catheters for this purpose and demonstrated that a patient's clinical state deteriorated at high pressures. The results from almost every subsequent study have suggested that this type of pressure monitoring helped to guide treatment, at least for traumatic brain injury.

THE BENEFITS OF ICP TREATMENT BROUGHT INTO QUESTION

The only modern randomised-controlled trial assessing the validity of monitoring to guide treatment compared a management protocol based on direct ICP measurement with a clinical approach based on neurological signs and CT; there was no advantage to pressure measurements.[3] Both groups were treated with the same methods to reduce ICP, including hyperosmolar therapy. That trial was criticised on a number of points but it had the advantage of using a utilitarian end point of death and severe disability, rather than an intermediate goal of simply reducing ICP. Another recent trial indirectly addressed the same question by studying the use of a bifrontal craniectomy to lower raised ICP after traumatic brain injury. The surgical procedure failed to improve outcome even though ICP was greatly reduced (to atmospheric pressure by opening the skull).[4] Many neurosurgeons objected to the limited extent of the decompressive operation but this does not negate the fact that ICP was successfully reduced. Other studies are being undertaken to address some of the shortcomings of these completed trials, particularly the relatively low level of ICP at which medical or surgical treatment was instituted.

THERAPEUTIC PROGRAMMES TO REDUCE INTRACRANIAL PRESSURE

Treatments to reduce ICP work in a narrow therapeutic window, perhaps because compression of venous structures by brain displacements rapidly elevates ICP in a self-regenerating cycle. Although this review emphasises hyperosmolar therapies, these comprise but one component of an ensemble of interventions that are undertaken in parallel. One obvious solution to reducing pressure and minimising clinical deterioration from brain compression is to remove a mass surgically. This is feasible only in certain circumstances, mainly of a discrete clot in the subdural or extradural space, and for some tumours. Contused brain tissue, swollen cerebral infarctions, oedema surrounding a tumour and deep haemorrhages are not amenable to removal. Furthermore, in keeping with the earlier-mentioned clinical trials, a study of surgical removal of cerebral haemorrhages gave generally negative results.[5] A recently completed follow-up trial by the same investigators did not alter this conclusion.

A reduction in the volume of the intracerebral contents can also be accomplished by removing cerebrospinal fluid from the ventricles but this requires the insertion of a catheter and the effects are only temporising in most cases. The remaining available treatments may be considered to be 'medical'. Foremost among these is the maintenance of normal body temperature, as fever greatly increases cerebral blood flow and volume, thereby raising ICP. Although several trials have failed to show that hypothermia improves outcome in patients with raised ICP, lowering body temperature does lower pressure, the problem being that rewarming results in a return to elevated levels. Sedation and pharmacological paralysis are part of the regimen for managing critically ill patients with brain masses; there may be a direct effect of some of the drugs used that lowers ICP but their ability to facilitate mechanical ventilation and avoid 'bucking' the ventilator are more important. Hyperventilation quickly lowers ICP through the mechanism of alkalosis in the CSF that causes cerebral vasoconstriction and reduces cerebral blood volume but the effect is transient because homoeostatic production of ammonium ions by the choroid plexus rapidly returns the pH of cerebrospinal fluid (CSF) towards normal (which is 7.37, not 7.40 as in blood). Finally, corticosteroids have a beneficial effect on peritumoural oedema but do not affect other forms of brain

swelling and are no longer used except in the situation of brain tumours.

This leaves hyperosmolar treatment, or osmotherapy, as the main means of lowering ICP over long periods of time. All hyperosmolar agents shrink the brain and reduce ICP by creating a gradient for water extraction from the interstitial fluid to the vascular compartment. The agents used in clinical practice have differing capacities to remain on the vascular side of the blood–brain barrier, a characteristic summarised as the reflection coefficient of each substance. Hyperosmolar substances that rapidly cross the barrier, such as glucose, are therefore not effective dehydrating agents for the brain. It follows that solutions such as D5/W (5% dextrose in water) and D5/0.5% normal saline (dextrose 5% in 0.5% normal saline) are also ineffective and have the deleterious effect of forcing water into the brain and raising ICP. Table 1 shows the osmolarities and reflection coefficients of the main agents used for osmotherapy. Those with both an osmolarity above the normal serum value of approximately 287 mOsm/L and a high reflection coefficient have the ability to reduce brain volume and to lower ICP.

Hyperosmolar solutions also induce a rapid but brief change in cerebrovascular tone that results in a transient drop in ICP. Agents such as mannitol that are renally excreted cause a diruresis that raises serum osmolarity and prolongs the favourable effect of an osmotic gradient. Therapy begins with the avoidance of serum hyperosmolarity. This is accomplished by choosing intravenous fluids, typically normal saline, for maintenance and for medication infusions that do not add free water to the circulation. If further reduction in ICP is needed, therapeutic induction of serum hyperosmolarity is required.

MANNITOL

The sugar alcohol mannitol represents the class of hyperosmolar agents. It is given in a 20% solution and, as mentioned, dehydrates tissues including the brain, as well as causing a duiresis.[6] The net result of the diuresis is to reduce the intravascular water content and to cause hyperosmolarity and hypernatraemia. Once a static level of hyperosmolarity has been achieved, further doses of a hyperosmolar agent are required to sustain the water gradient outwards from the brain.

The peak effect of the reduction in brain water occurs 15–35 min after an infusion.[7] However, persistent hyperosmolarity is required to prevent the water gradient from being reversed and for water to reenter the brain. The duration of hyperosmolarity after a single bolus of mannitol is generally several hours but the reduction in ICP is briefer as the sugar leaches into the brain and slowly equilibrates the water gradient. Other factors such as 'idiogenic osmoles'—ions presumed to be produced by the brain as a compensatory response to the hyperosmolarity of interstitial fluid—play a role as well but their nature and origin are not understood.

The typical initial dose of mannitol is a rapid infusion of 0.25–1.0 g/kg body weight, the higher dose being used in extreme circumstances of imminent death from an intracranial mass. In such emergencies, I use approximately 60 g (1 g/kg), of course, not stopping to establish the patient's exact weight. After this initial treatment, I prefer to maintain the elevated osmolarity with hypertonic saline given every 4–12 h or in a continuous infusion as discussed below. The alternative is to infuse further boluses of mannitol at similar intervals or as required in response to measurements of serum osmolarity.

Mannitol can be administered through a peripheral or central intravenous catheter over 10–20 min. If ICP is being directly measured, the interval between doses and the amount of mannitol can be judged based on the measurements, with the usual goal of maintaining pressure below 20 mm Hg. A satisfactory alternative is to assume that sustained hyperosmolarity is required while the effects of an intracranial mass persist, and to use serum sodium or osmolarity to gauge the effects of a hypertonic solution. (In most laboratories osmolality is measured by freezing point depression, the value of which virtually equates with osmolarity). Serum sodium is a surrogate for osmolarity and is more conveniently and rapidly obtained than osmolarity. Serum osmolarity is calculated by=(sodium×2)+potassium+(blood urea nitrogen/3)+(glucose/18); if there is a discrepancy between the calculated and measured values, there is circulating mannitol or another solute that is increasing the measured value but will not produce a sustained effect in shrinking the brain. In order to avoid including the circulating mannitol in the osmolarity measurement, blood should be sampled approximately 40 min after an infusion, preferably longer, at a time when the mannitol has been eliminated by renal excretion.

Table 1 Osmolarity and reflection coefficients of commonly used intravenous solutions

Solution	Effective mOsm/L	Reflection coefficient	Dose range
Saline 0.9%	285	1.0	Maintenance intravenous solution or bolus
Mannitol 20%	1375	0.9	Bolus 0.25–1.0 g/kg body weight
Saline 3%	1026	1.0	Bolus 150 mL
Saline 23.4%	80 081	1.0	Bolus 30 mL
Lactated Ringer's solution	273	0.8	Infusion
Urea		0.59	No longer used
Glycerol 10%	5715	0.48	Oral 50 g; I.V., 250 mL (25 g)

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Deleterious effects of mannitol include skin sloughing from infiltration, hypokalaemia and alkalosis from the diuresis, and a hyperglycaemic hyperosmolar state in patients with diabetes mellitus and the elderly. Mannitol is used in boluses in order to rapidly establish a water gradient from the brain to the vasculature. Extremely high osmotic levels after mannitol may produce renal damage. The mechanism has not been clearly defined but is not attributable simply to a prerenal dehydrating effect and may be through a redistribution of intrarenal blood flow. This complication has generally occurred only if a total of 200 g of mannitol has been given over a day or two. The renal failure is usually self-limited within a few days after stopping the mannitol. The upper limit of serum osmolarity that may be safely attained with mannitol has been stated to be 320 mOsm/L but this level is often exceeded in practice without ill effect.

HYPERTONIC SALINE

Saline in concentrations of 3–23% achieves a state of hyperosmolarity by adding solute to the circulation directly rather than by a causing diuresis. It follows that the main difference from mannitol is that the vascular compartment is expanded with saline, instead of contracted, as it is with continued use of mannitol. The net effect of saline infusions is reflected in elevated serum sodium or osmolarity, as it is for mannitol. Either a bolus of high concentration hypertonic saline (7–23%) or a continuous infusion of a 3% solution can be used to sustain the level of hypernatraemia adequate to shrink the brain but the bolus method is more rapid for initial treatment. Lactated Ringer's solution may appear to be a suitable alternative for hyperosmolar therapy based on its calculated osmolarity above 310 mOsm/L but lactate and citrate associate with sodium ions and make the effective osmolarity only 289 mOsm/L.

The concentrations of hypertonic saline used in the USA are typically 3–23.4% as shown in table 1 but 7% and other concentrations are used elsewhere with similar effect. I begin with 3% sodium chloride in boluses of 150 mL or 23% in 30 mL boluses. After the initial treatment with either saline or mannitol, I initiate a constant infusion of 3% to maintain serum hyperosmolarity, checking sodium concentrations every 6–8 h to maintain a level of 145–149 mEq/L. It may also be suitable to follow the first bolus of hypertonic saline with an infusion of normal (0.9%) saline as this solution contains 154 mEq/L of sodium and an effective osmolarity of 285 mOsm/L (although the calculated value is 309 mOsm/L). However, homoeostatic fluid mechanisms reverse the attained hypertonicity and a 3% concentration is usually required to maintain a high serum osmolarity.

A central venous catheter is needed to accommodate 3% sodium chloride if it is used for more than a day or two, or if higher concentrations are needed at any time. Sodium and fluid overload from these infusions may cause congestive heart failure in patients with poor cardiac output, especially if there is diastolic heart failure.

One report, now quite dated, suggested that continuous hypertonic saline infusion did not reduce cerebral swelling and was associated with higher mortality, although the reasons for these findings were not clear.[8] In part based on this retrospective finding, many centres use hypertonic saline in boluses, similar to mannitol, rather than in continuous infusions. Continuous hypertonic saline does not appear to lead to more complications—such as venous thrombosis, renal failure or infection—than does normal saline.[9] Most studies comparing various modes of administering hypertonic saline are selective or retrospective and pertain only to patients with traumatic brain injury, making generalisation difficult.

COMPARISONS BETWEEN MANNITOL AND HYPERTONIC SALINE

The trend in the field of neurological critical care, according to recent surveys, has been to use saline in preference to mannitol.[10] The reasons for this preference are, in my opinion, not entirely clear and may be overstated. Although a few randomised trials have been conducted comparing the two agents, some purportedly provide evidence favouring hypertonic saline, but it is not difficult to find the flaws in the design and implementation of these studies. Meta-analyses have further favoured hypertonic saline[11 12] depending on the models used, some of which are contrived. Several recent articles also express the strong opinion that hypertonic saline, not mannitol, is a better choice and is the 'gold standard'.[13] A summary of the trials and a perspective on hyperosmolar treatment can be found in the article by Hinson *et al*.[14]

Curiously, mannitol has been endorsed in society guidelines to treat adults with intracranial hypertension[15] and hypertonic saline, to treat children.[16] In the elderly or in patients with diabetes, I use hypertonic saline to avoid severe dehydration, whereas, in patients with congestive heart failure, I use mannitol to avoid a sudden intravascular fluid overload from saline. Neither one of these suggestions is absolute, as both agents can cause severe hyperosmolarity and fluid overload.

DO WHAT I DO, NOT WHAT I SAY

In summary, in an emergent situation, I begin mannitol 0.5–1.0 g/kg, not stopping to obtain the patient's exact weight but estimating it. Figure 2 gives a summary of my subsequent methods, most of which is alluded to above. A central venous catheter is not needed for mannitol or for an initial dose of 3% saline but a Foley catheter should be inserted when feasible in order to be

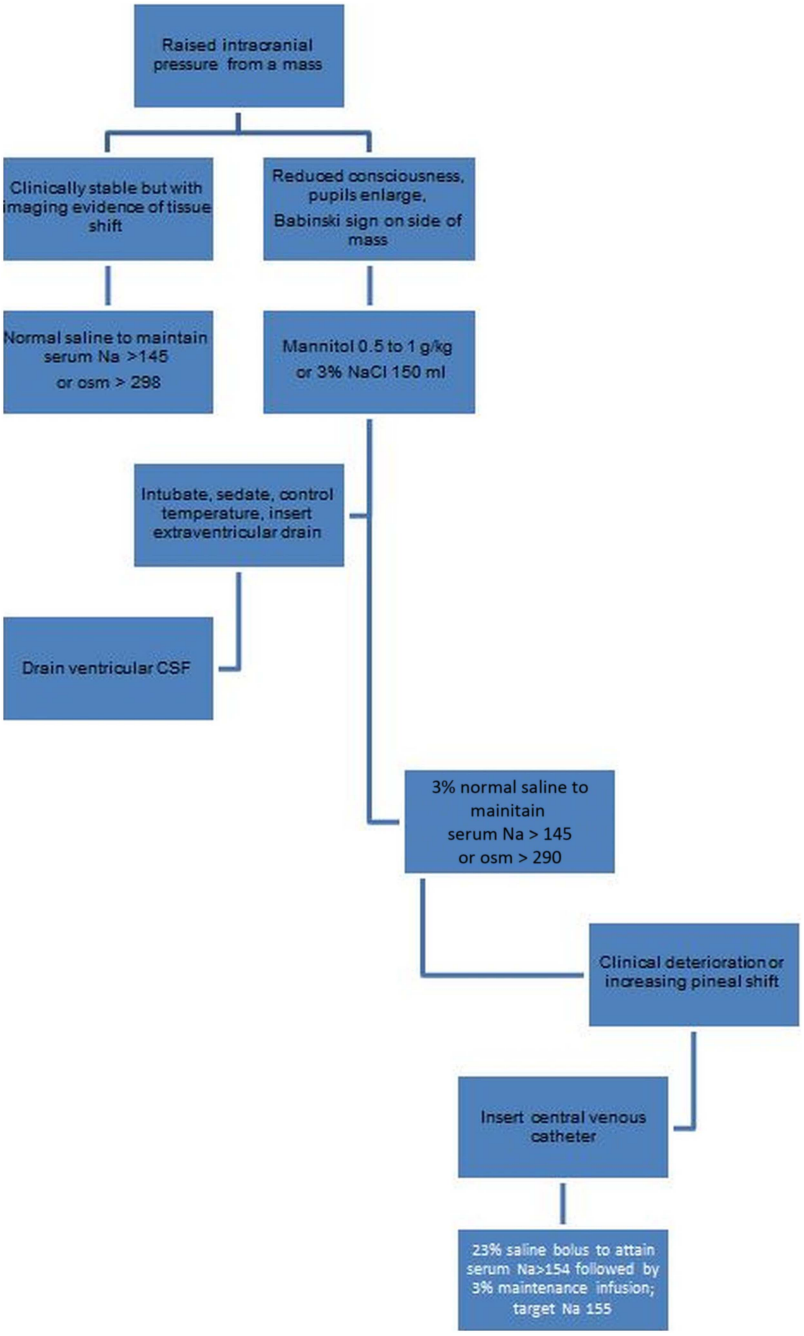

Figure 2 Schematic approach to the use of osmotherapy for raised intracranial pressure.

certain there is a diuresis and to obviate urinary tract obstruction in men.

In addition to a decreasing level of alertness, I look for the emergence of a Babinski sign on the same side as a mass as an early sign of increasing brain tissue shifts; this often precedes enlargement of a pupil but cannot be depended upon as a sentinel for deterioration.[17] If one or both pupils become light fixed or enlarge, the situation may be considered hyperemergent but my response is the same. If it is not possible to have an ICP device, I use the serum sodium as a guide to the degree of dehydration and try to obtain serial CT to gauge the mass effect and ventricular size. I take care actually to measure midline brain displacement at the pineal calcification with the computer graticule (and not to estimate it), as this measurement corresponds best to the effect of a mass on the level of consciousness (figure 3).[18] In my experience, 'midline shift', typically referred to in publications, is used to signify displacement of the septum pellucidum and does not correlate well with the clinical state. Compression of the perimesencephalic cisterns is also useful as a surrogate for substantial tissue distortion and raised ICP, as shown in figure 1.

In a less acute situation, such as a slowly declining level of consciousness coupled with increasing mass

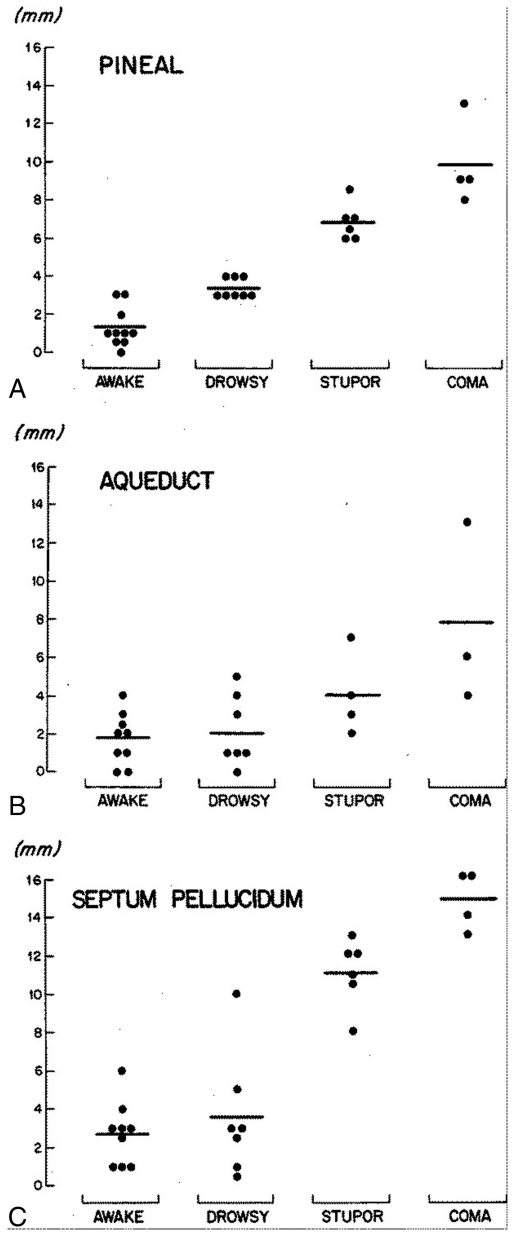

Figure 3 Shift of midline structures on CT as related to level of consciousness in patients with an acute intracerebral mass. Adapted from Ropper.[18]

effect on an imaging test, I use a smaller bolus of mannitol, 0.25 mg/kg. The same holds if ICP is being measured and becomes elevated above 15–20 mm Hg and is sustained for more than a few minutes. If a ventricular catheter is in place, I drain CSF while administering this dose of mannitol.

As mentioned, I set an initial goal of serum hypersosmolarity reflected by serum sodium above 145 mEq/L. If there are further clinical crises or imaging indications of an enlarging mass requiring more hyperosmolar therapy, I set a higher goal for serum sodium, 152–155 mEq/L and may resort to small amounts of higher concentrations of sodium chloride. In extreme circumstances, I will try for a higher serum sodium concentration but most such patients are on the brink of brain death. I do not change these goals if there is non-convulsive status epilepticus. Figure 2 summarises this approach.

The combination of the initial dehydrating effect of mannitol and the subsequent volume repleting effect of sodium chloride often work well to maintain hyperosmolarity and fluid balance. I do not resort to furosemide or other renal loop diuretics unless sodium infusions have caused clinical or X-ray signs of congestive heart failure. I attempt to obtain chest X-rays on alternate days, daily weight and daily glucose concentrations to detect the hyperglycaemic hyperosmolar state. If the syndrome of excess antidiuretic hormone occurs—it is difficult to discern its presence in patients receiving mannitol and saline—that may call for a diuretic to avoid excessive intravascular volume.

I hope this provides guidance in a field that is currently subject to anecdote and strong opinions that could leave the practitioner in a state of uncertainty.

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