

Mannitol crosses the blood-brain barrier in Reye's syndrome

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Although cerebral edema was noted at autopsy in the first reported victims of Reye's syndrome¹ (RS) in 1963, it was not until 1975 that the morbid role of intracranial hypertension in this syndrome became clear^{2,3} and that survival depends on its control.⁴

Monitoring intracranial pressure (ICP) is now standard in the management of moderate and severe cases of RS,⁵ with mannitol the osmotic diuretic of choice.²⁻¹⁴ However, studies of the serum and cerebrospinal fluid (CSF) concentrations of mannitol in RS therapy raise serious questions about the prolonged and indiscriminate use of this drug.

Materials and methods

Four patients with RS confirmed by liver biopsy were treated by a standard protocol.⁶ Each patient fulfilled the clinical and laboratory diagnostic criteria for RS,¹⁵ and both light and electron microscopy findings in the liver biopsy specimens were consistent with RS.

Once the patient reached clinical Stage II,¹⁶ aggressive, definitive therapy was commenced consisting of nasotracheal intubation, neuromuscular paralysis with pancuronium bromide, controlled ventilation to maintain a PaCO₂ of 25 ± 2 mm Hg

and a PaO_2 of 100–150 mm Hg, sedation with morphine sulfate, placement of an intraventricular catheter to monitor ICP and sample CSF, arterial and Swan-Ganz catheterization, and induced hypothermia to 31 C.⁵ An EEG was obtained as soon as possible after the start of therapy and repeated daily. Fluid intake was restricted to 1200–1400 cc/m²/day. Intracranial hypertension was managed initially by manual hyperventilation whenever the ICP exceeded 20 mm Hg as a plateau wave; if 2–3 minutes of hyperventilation failed to lower the ICP to less than 20 mm Hg, the patient was given 0.5–1.0 g/kg of mannitol. All patients received dexamethasone, 0.5–1.0 mg/kg/day; vitamin K, 10 mg/day; and oxacillin, 50 mg/kg/day.

Mannitol levels in CSF and blood were determined by the microcolorimetric method of Bailey.¹⁷

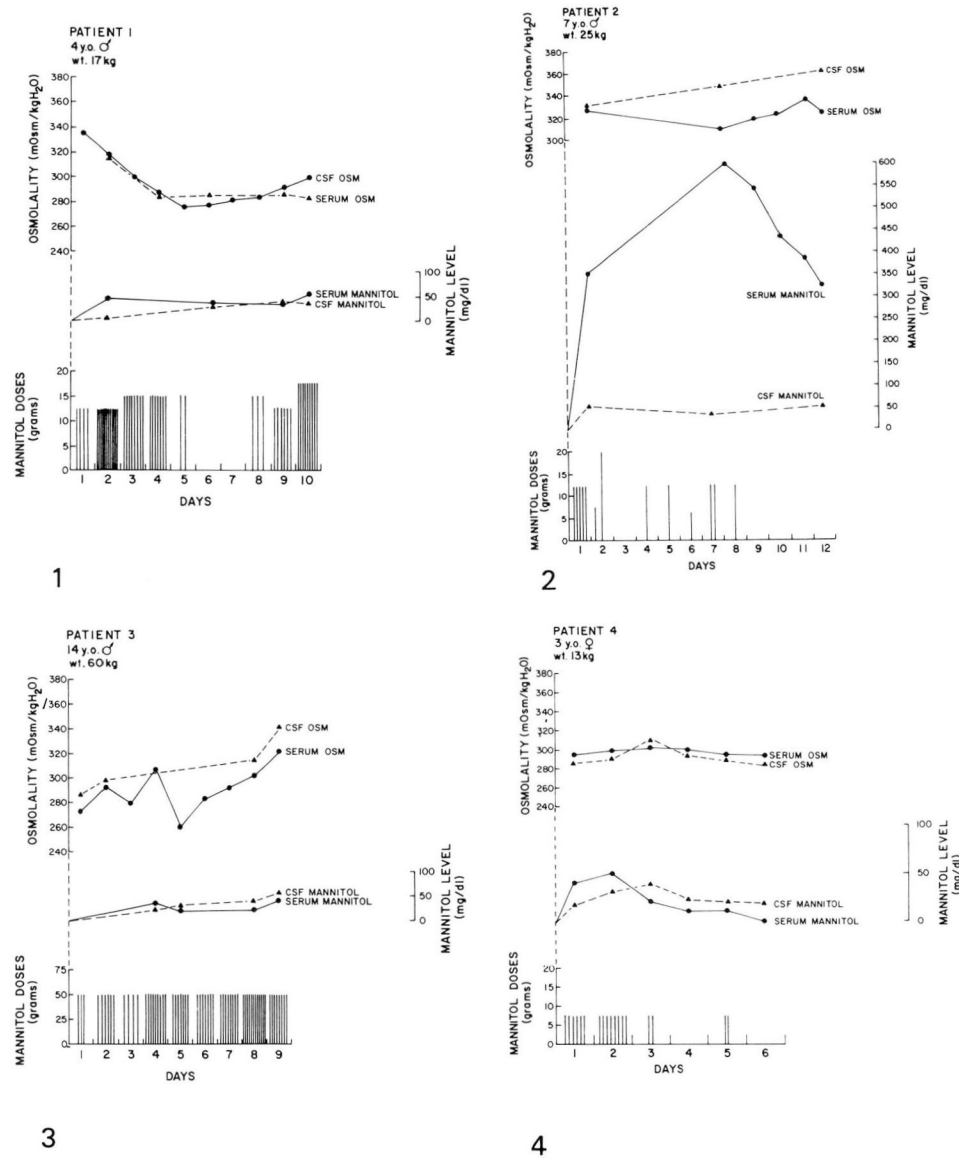
Results

Case 1 (Fig. 1). A 4-year-old boy with RS was transferred to the ICU from a community hospital 24 hours after neurologic deterioration necessitated intubation and mechanical ventilation. He had received four doses of mannitol prior to transfer and was hyperosmolar and dehydrated from vomiting, hyperglycemia, and mannitol therapy. Serum osmolality was 336 mOsm/kg H₂O prior to transfer. He was treated with insulin to lower the blood sugar, and with cautious rehydration, but multiple ICP plateau waves greater than 20 mm Hg necessitated several doses of mannitol over the next three days. Initial mannitol levels were 45 mg/dl in the serum and 7 mg/dl in the CSF. The initial CSF osmolality was 316 mOsm with a simultaneous serum osmolality of 318 mOsm. The CSF and serum osmolalities returned to normal with hydration and control of blood glucose over two days. Serum mannitol levels were stable at 30–50 mg/dl and CSF mannitol levels increased to 28 mg/dl on day 6

and 40 mg/dl on day 9. The child required only occasional doses of mannitol for ICP control from days 5 through 8, but required frequent doses on days 9 and 10 for ICP elevations after extubation. Despite the prolonged course and the hyperosmolality, the child did well and recovered fully.

Case 2 (Fig. 2). A 7-year-old boy presented with Stage III RS with the unusual but reported complication of oliguric acute renal failure.^{18,19} He had received five doses of mannitol prior to transfer from a community hospital and on admission his serum mannitol level was 350 mg/dl and his CSF mannitol level was 56 mg/dl. Intracranial hypertension was a serious problem, and despite induced hypothermia and barbiturates, occasional acute ICP plateau waves > 25 mm Hg were noted and he was given 0.5 g/kg doses of mannitol. The serum mannitol level increased to a high of 600 mg/dl before it began to fall and CSF mannitol levels ranged from 35 to 55 mg/dl. The peak blood urea nitrogen (BUN) was 75 mg/dl and the creatinine level was 2.5 mg/dl. Hemodialysis was instituted to reduce hyperosmolality and fluid overload, but he died of a malignant rise of ICP >60 mm Hg with a fall in cerebral perfusion pressure to <40 mm Hg. The EEG became isoelectric and the pupils fixed. A comparison of his measured and calculated osmolalities (Table) suggested the generation of idiogenic osmoles in the brain^{20,21} in response to the serum hyperosmolality and possibly the presence of mannitol in the CSF.¹⁹

Case 3 (Fig. 3). A 14-year-old boy with RS had intracranial hypertension exceptionally difficult to control despite hyperventilation, induced hypothermia, and barbiturate coma. Initial serum and CSF osmolalities were normal but both rose steadily over the course of his illness to dangerously high levels and demonstrated the dichotomy between calculated and measured levels of CSF osmolality, as in Case 2. The CSF mannitol levels rose from 22 mg/dl on day 4 to 56



Figs. 1-4. Serum and CSF mannitol levels are plotted against doses of mannitol in each patient, also the serum and CSF osmolalities over the course of treatment. Patient presented with oliguric acute renal failure as a complication of RS.

mg/dl on day 9, and he died of malignant and uncontrollable intracranial hypertension.

Case 4 (Fig. 4). A 3-year-old girl with RS had serum and CSF osmolalities relatively

constant at 285-305 mOsm over the course of her illness. She required only rare doses of mannitol after the first 48 hours, but the CSF mannitol levels increased to a high of 38 mg/dl on day 3 following a peak in serum mannitol of 50 mg/dl on day 2. Mannitol

Table. Comparison of measured and calculated serum and CSF osmolalities late in the course of treatment of each patient with RS*

mOsm	Case 1	Case 2	Case 3	Case 4
Measured serum osm	293	324	322	295
Calculated serum osm	274	314	267	290
Measured CSF osm	287	361	342	286
Calculated CSF osm	274	290	258	280
Δ Serum osm	19	10	55	5
Δ CSF osm	13	71	84	6

* The calculated osmolalities were derived from measured values for sodium (Na), urea nitrogen (UN), glucose and mannitol concentrations in serum and CSF using the formula:

$$\text{Osm} = 2 [\text{Na}] + \frac{[\text{UN}]}{2.8} + \frac{[\text{Glucose}]}{18} + \frac{[\text{Mannitol}]}{18}$$

The large difference (Δ) in CSF osmolalities between measured and calculated values is assumed to reflect the generation of idiogenic osmoles.

was detectable in the CSF at 18 mg/dl on the first day of treatment. She has recovered fully.

The *Table* shows the differences between measured and calculated serum and CSF osmolalities in each patient late in the course of treatment. The survivors had only small differences (<15 mOsm) between calculated and measured values whereas those who died had large differences (>70 mOsm). It is presumed that these large differences might reflect idiogenic osmoles generated by the brain in an attempt to reverse the cellular dehydration iatrogenically created by osmotherapy with mannitol.

Discussion

Reye's syndrome is a distinct clinical and pathologic entity in children characterized by an acute encephalopathy with fatty metamorphosis of the liver.¹ The etiology and pathogenesis of this disease process remain obscure. The sub-cellular insult appears to affect mitochondria in multiple organ systems, especially the liver and brain. Since death is usually related to neurologic deterio-

ration secondary to intracranial hypertension, treatment is directed to its early control with osmotherapy and hyperventilation to reduce morbidity and mortality.^{4, 5, 8-12}

Of the osmotic diuretics available for the treatment of cerebral edema, mannitol is probably the most commonly employed agent. Almost all published protocols for the treatment of RS use mannitol as the osmotic diuretic of choice, sometimes in amounts as high as 2.5-3.0 g/kg/dose.²⁻¹⁴

The use of hypertonic nonelectrolyte solutions for the rapid removal of water from brain tissue was introduced by Javid in 1958.²² These agents (urea, glycerol, and mannitol) are powerful adjuncts in the management of intracranial hypertensive states. Not only do they decrease elevated ICP, they can also increase cerebral blood flow, even before their intracranial hypotensive action is recognized.²³ Studies in nephrectomized monkeys have shown that the initial intracranial hypotensive action of hypertonic agents on ICP is independent of diuresis.²⁴ Osmotic diuretics should be impeded by the blood-brain barrier (BBB), be freely filterable by the

glomeruli with limited renal reabsorption, and be pharmacologically inert.²³ Pappius²⁵ has shown that hyperosmotic agents dehydrate the normal brain without removal of sodium and have no direct effect on edematous areas of cerebral tissue within an area of defective BBB. Urea was originally employed as the osmotic agent for regulating ICP, but has been largely replaced by mannitol as urea penetrates the BBB at a much greater rate because of its smaller molecular weight; it has a shorter duration of action, is significantly reabsorbed by the renal tubules, and is more of a vascular irritant.²³ Glycerol therapy is also plagued with problems of rebound phenomenon and reverse osmotic gradient, which limit its usefulness compared with mannitol.²⁶

There is much controversy regarding a rebound or secondary overshoot in ICP following the use of hypertonic agents to reduce intracranial hypertension. Shapiro²³ states that all osmotic diuretics slowly penetrate the BBB even under normal circumstances, and probably enter the brain more rapidly when BBB function is disrupted, although the reference that he cites to support this contention does not address the problem. If osmotic agents do cross the BBB, they could increase the osmolality of the brain and osmotically draw water back into the brain when plasma concentrations of the osmotic agent decrease. Experimentally, ICP rebound can be prevented by limiting volume replacement to a third of that lost during osmotic diuresis and by simultaneous administration of steroids, which appear to preserve the ICP hypotensive effect of mannitol.²⁷ Each patient in this study was fluid-restricted and given dexamethasone.

This study clearly demonstrates that mannitol crosses the BBB in RS. Al-

though CSF cell counts, glucose, and protein are typically normal in RS and one might therefore argue that BBB function is preserved, it is probably safest to assume that BBB integrity is disrupted. Although others have raised concerns about the safety of mannitol osmotherapy in RS,^{28, 29} this is the first study to clearly demonstrate that mannitol osmotherapy could be harmful. It is conceivable that RS cases with refractory intracranial hypertension necessitating craniectomy^{30, 31} resulted from an excess of mannitol crossing the BBB causing a reverse osmotic gradient with increasing intracranial hypertension unresponsive to all measures to lower ICP.

In our Cases 2 and 3, idiogenic osmoles may have protected cell volume at the expense of cell function. Prolonged osmotherapy may not be useful in managing cerebral edema because eventually the idiogenic osmoles would return the brain to its previous abnormal volume despite continued hypertonicity. The generation of idiogenic osmoles could account for the increasing CSF osmolality with a relatively constant CSF mannitol level and the disparity between the measured and calculated CSF osmolalities. It would appear prudent to limit mannitol osmotherapy to stabilization of the patient for immediate transfer to a fully equipped and staffed intensive care unit; to emergent control of ICP in severe acute elevations until other measures to reduce it can be instituted; and to use of the smallest effective dose possible, preferably 0.25–0.50 g/kg/dose. Other measures to control ICP in addition to manual hyperventilation include induced moderate hypothermia to 30–31 C, thiopental at 2.0–2.5 mg/kg/dose, tubular diuretics such as furosemide or ethacrynic acid, and barbiturate coma with pentobarbital or thiopental.

It was originally thought that tubular diuretics had little acute effect on intracranial hypertension,³² but furosemide has recently been shown to reduce the amount of subsequent cerebral edema in cats and monkeys following a cryogenic lesion,³³ and to be an effective agent for lowering ICP during neurosurgery.³⁴ The decrease in ICP with furosemide therapy may be secondary to its diuretic effect or result from a direct reduction of sodium transport into the brain³⁵ independent of any diuretic effect. The potential adverse effects of mannitol osmotherapy including rebound of intracranial pressure, transient increases in cerebral and circulating blood volumes, changes in blood viscosity and coagulation, and increased serum osmolality may make furosemide a more ideal agent for the control of intracranial hypertension.³⁴ If the effects of furosemide on ICP are independent of diuresis, it may be effective for control of ICP even in patients with renal failure.

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