

MANNITOL INDUCED CENTRAL NERVOUS SYSTEM TOXICITY IN RENAL FAILURE

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ABSTRACT

Large doses of mannitol in the face of uremic acidosis have resulted in severe central nervous system toxicity that cannot be explained simply by uremia. In this study, a rate limited blood-brain barrier to mannitol is demonstrated in dogs. The mechanisms which normally maintain a stable cerebrospinal fluid pH are broken down when the cerebrospinal fluid barrier to mannitol is exceeded.

The use of mannitol has been advocated by some for protection against acute tubular necrosis following major vascular operations, trauma, shock, and transfusion reactions (1, 2). The known adverse effects are hyponatremia and circulatory overload. Because three of our patients developed unexplained central nervous system symptoms after receiving mannitol in large doses for acute renal failure, laboratory investigation was undertaken (N. W. Thompson and W. J. Fry, unpublished observations).

METHOD

Forty-eight healthy mongrel dogs, weighing between 25 and 38 pounds, were divided into two groups. Sixteen dogs were in Group 1 and 32 were in Group 2. All were housed in the animal care unit for at least 2 weeks prior to experimentation.

Group 1. Uremia was produced in 16 dogs by bilateral ligation of the ureters through a midline abdominal incision under Pentobarbital sodium anesthesia. Because the volume of cerebrospinal fluid (CSF) in the dog is limited and since we desired to run a number of laboratory determinations on the CSF, it was necessary to divide the 16 dogs into two subgroups of eight each. Urea nitrogen, osmolality, and mannitol levels were performed on blood and CSF from one subgroup and pH and electrolytes were performed on blood and CSF from the other subgroup. These samples were obtained every 12 hr after ureteral ligation until death.

Four dogs in each subgroup of eight were given mannitol, $\frac{2}{3}$ g per kg iv every 12 hr until death. The other four dogs in each subgroup served as controls and were not given mannitol. Mannitol levels were determined by the method of Corcoran and Page (3). Osmolalities were determined by freezing point depression.

Group 2. The ureters of 32 dogs were ligated as in Group 1. Of these dogs 16 were given mannitol according to the aforementioned dosage schedule. The ties were removed 36 hr after ureteral ligation and ureteral patency was reestablished. Surviving animals received long term clinical follow-up.

RESULTS

Group 1

Urea, osmolality, and mannitol. The findings in these dogs are summarized in Figures 1 to 3. Figure 1 shows that during the various stages of increasing uremia following ureteral ligation the blood urea nitrogen and CSF urea nitrogen rose equally. This was identical in dogs that were and were not given mannitol.

Figure 2 shows that the serum and CSF osmolality also rose equally both in dogs that were and were not given mannitol.

Figure 3 reveals that in dogs given mannitol there was a sharp rise in blood mannitol levels every 12 hr. There was no such rise seen in the CSF, however, until after 36 hr; even then, although the CSF mannitol eventually came to rise at a rate nearly equivalent to that in the blood, there remained throughout a marked disparity between CSF and blood mannitol levels. The osmolality contributed by urea in blood and CSF approximately equalled the total osmolality increase in blood and CSF. The sum of the blood urea and mannitol contribution to osmolality is thus greater than is the total increase in blood osmolality computed by freezing point depression.

Group I

pH and electrolytes. The findings in these dogs are summarized in Figures 4 and 5. In dogs with

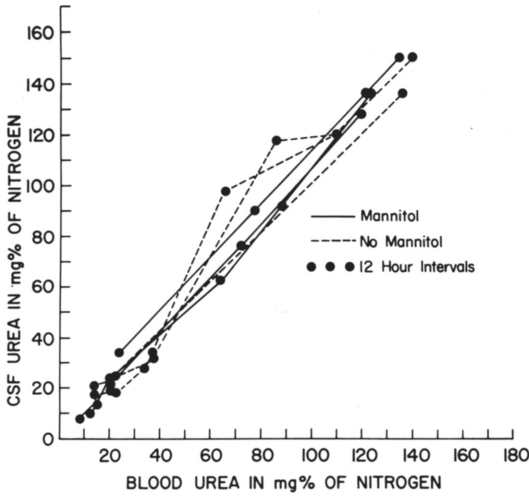


FIG. 1. Urea concentration in blood and CSF are equal at all stages of azotemia in dogs given mannitol and those not given mannitol.

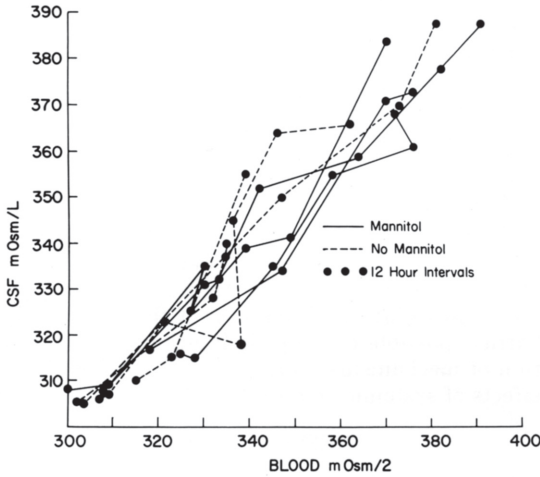


FIG. 2. Osmolality of blood and CSF are equal at all stages of azotemia in dogs given mannitol and those not given mannitol.

their ureters ligated but not given mannitol, the CSF pH remained within a normal range (7.38 to 7.42) until the death of the animal despite a progressive drop in blood pH to as low as 7.10. A progressive rise in serum potassium occurred, reaching as high as 8 mEq per liter prior to death, but no such change occurred in CSF potassium (normal range, 2.4 to 3.5 mEq per liter). By contrast, in the dogs given mannitol, the pH of the CSF fell progressively and corresponded to the low blood pH. A less consistent rise in CSF potassium occurred also in these animals, coincident with the rise in serum potassium.

Serum hyponatremia developed in all dogs but was more marked in those given mannitol. There was no such change in the CSF.

Group II

Of the 16 dogs not given mannitol, 15 survived without sequelae. One dog died 24 hr following removal of the ureteral ties. No animal demonstrated an increased sensitivity to Pentobarbital sodium administered prior to removal of ureteral ties at 36 hr.

Of the 16 dogs given mannitol, eight died immediately following minimal pentobarbital administration (doses as low as one-third normal). Three died within 9 hr of removal of the ureteral ties. Four survived and suffered long term central nervous system injury. Three of these dogs devel-

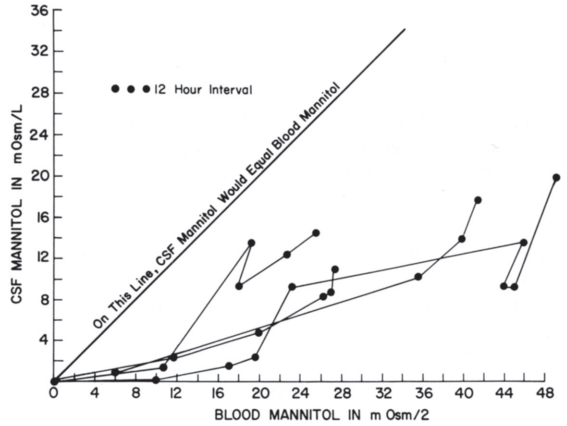


FIG. 3. CSF mannitol levels are very low despite high blood levels until a saturation threshold is reached between 14 and 20 osmoles per liter in blood. After this point CSF mannitol levels rise with blood levels but still not proportionately.

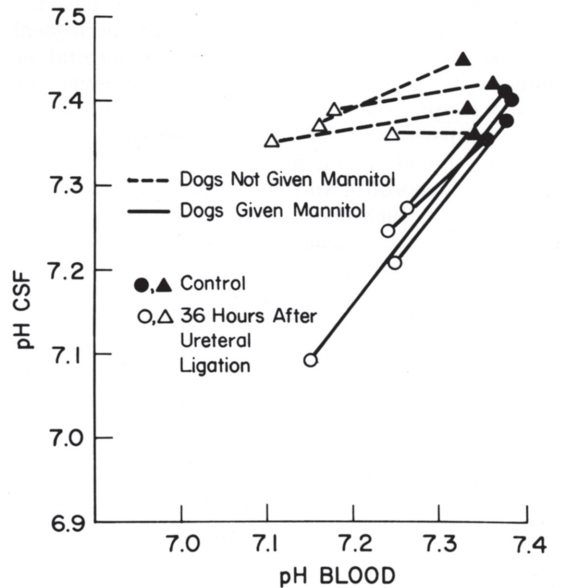


FIG. 4. CSF pH is stable despite falling blood pH in dogs not given mannitol. In those given mannitol CSF pH declines with blood pH.

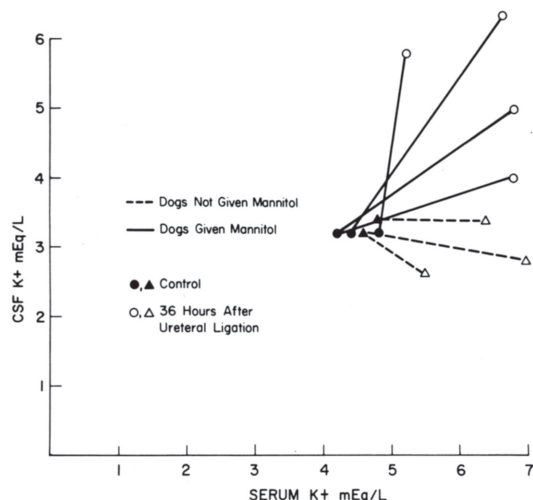


FIG. 5. CSF potassium is stable despite rising serum potassium in dogs not given mannitol; in some of those given mannitol the CSF potassium rises with serum potassium.

oped persistent ataxia and one dog slowly became dehydrated without apparent thirst and subsequently died. Serum creatinine and blood urea nitrogen had returned to normal within 36 hr.

DISCUSSION

This study was initially prompted by three patients in acute renal failure who developed unexplained central nervous system symptoms after treatment with mannitol 25 g every 12 hr, for at least 36 hr. At autopsy diffuse degenerative brain changes were found.

In addition there have been reports of patients with renal failure going into coma from peritoneal dialysis with high concentrations of sorbitol or glucose in the dialysate. Despite the achievement of low serum creatinine and urea levels, these patients lapsed into profound coma with a high serum osmolality and high serum sorbitol or glucose levels (sorbitol and mannitol are merely stereoisomers of each other produced by reduction of glucose). In these cases the same relative blood CSF barrier was found for sorbitol as we have shown for mannitol (4). There is a less striking but similar blood-brain barrier to glucose.

It is thought that the hyperosmotic coma is caused by intracellular dehydration and the formation of an osmotic gradient between vascular and cerebrospinal compartments (5). However, the importance of acid-base balance of the CSF in hyperosmotic states has received little attention.

It is apparent from these studies that mannitol administered in large doses to an anuric animal can, like sorbitol, cause harmful central nervous system changes that do not occur as a result of uremia alone. The blood-brain barrier to mannitol in the dog is shown to maintain its integrity until excessive blood levels have been reached. A sim-

ilar barrier has been demonstrated by Lapides (6) in man. This rate limited blood CSF barrier to mannitol which exists despite osmotic equilibration suggests an active transport mechanism much like that for glucose in the renal tubule. When the threshold is surpassed, a concomitant derangement in CSF acid-base balance occurs.

Of course it is conceivable that breakdown of the CSF buffering mechanism is secondary to brain damage from mannitol rather than a cause of the brain damage, but this is unlikely when one considers the mechanisms for CSF acid-base balance. Carbon dioxide diffuses quickly across the blood-brain barrier and cell membranes; CO_2 tensions in brain tissue, blood, and CSF are equal (7). On the other hand, hydrogen ion and bicarbonate ion move much more slowly across the barrier. It is believed that an active transport mechanism maintains the bicarbonate ion concentration in CSF (7). In systemic metabolic acidosis the bicarbonate ion concentration in CSF becomes substantially higher than in blood to assure a normal CSF pH. Patients have been shown to remain conscious and tolerate this systemic acidosis well if the CSF pH remains normal. When the CSF pH is low, the patients deteriorate rapidly (7). Thus patients with respiratory acidosis are likely to develop a low pH in the CSF from CO_2 diffusion and do poorly, whereas patients with metabolic acidosis can do remarkably well because of a normal CSF pH.

This study may help to explain why patients with acidosis and high mannitol or sorbitol levels (usually with renal shutdown preventing excretion of these sugars) do poorly. High serum levels of mannitol result in penetration of the blood-brain barrier, possible cerebral desiccation, and disruption of mechanisms protecting the brain from the effects of systemic acidosis.

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