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Mannitol Treatment in Experimental *Haemophilus influenzae* Type b Meningitis[1]

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ABSTRACT. A study was undertaken to evaluate hypertonic mannitol treatment in experimental lapin *Haemophilus influenzae* type b meningitis and to compare these results with those in normal rabbits. Increased intracranial pressure, brain water content, and concentrations of lactate and hypoxanthine in cerebrospinal fluid (CSF) were measured as a reflection of altered cerebral perfusion and hypoxia and potential brain injury associated with meningitis. A single dose of mannitol reduced transiently the CSF pressure of uninfected rabbits from 2.15 ± 0.20 to 1.34 ± 0.10 mm Hg (maximum reduction 34.9 ± 8.4%; $p < 0.005$). The time to the lowest pressure was 38.7 ± 2.7 min after initiation of the infusion and the time to return of CSF pressure to initial values was 76.7 ± 5.6 min. In infected mannitol-treated animals the CSF pressure was reduced from 4.78 ± 0.53 to 2.61 ± 0.55 mm Hg (maximum reduction 42.0 ± 7.7%; $p < 0.005$). Time to maximum pressure decrease was 44.0 ± 5.6 min. CSF pressure returned to the initial level after 178.5 ± 25.2 min. Four h after initiation of mannitol infusion the mean brain water content in infected mannitol-treated animals was 412 ± 4 g H_2O/100 g dry weight and in infected untreated animals it was 415 ± 3 g H_2O/100 g dry weight ($p > 0.05$). CSF lactate and hypoxanthine concentrations were significantly increased during the 20 h of meningeal inflammation ($p < 0.005$). The mean percentage change from baseline values for lactate concentrations at the end of the experiment (24 h) in infected mannitol-treated rabbits was significantly smaller than that in infected untreated animals ($p = 0.035$). A single dose of mannitol reduced the CSF hypoxanthine concentrations of infected animals, but this reduction was not statistically significant. (*Pediatr Res* 22: 118–122, 1987)

Abbreviations

cfu, colony-forming units
$CMRO_2$, cerebral metabolic rate of oxygen
CSF, cerebrospinal fluid
WBC, white blood cells
LDH, lactate dehydrogenase
HPLC, high-pressure liquid chromatography

Meningitis caused by *Haemophilus influenzae* is associated with a case-fatality rate of approximately 5% and with neurological sequelae in about 30% of survivors (1). The advent of more potent antimicrobial agents is unlikely to improve significantly the outcome from Haemophilus meningitis (2–5) and only little progress has been made in elucidating the mechanisms that contribute to brain damage in patients with meningitis. Brain edema, increased intracranial pressure, and the diminished cerebral blood flow have been considered important factors in the pathogenesis of the brain injury (6–8).

The present study was undertaken to evaluate hypertonic mannitol treatment in experimental lapin *H. influenzae* type b meningitis and to compare these results with those in normal animals. Increased intracranial pressure, brain water content, and brain lactate and hypoxanthine production, the latter being reflected by concentrations of lactate and hypoxanthine in CSF, were assessed as a reflection of altered cerebral perfusion and hypoxia and potential brain injury associated with meningitis.

METHODS

Animal model. A model of experimental meningitis originally described by Dacey and Sande (9) was used in a modified form (10). New Zealand White male rabbits (2–3 kg) were used.

Anesthesia. Anesthesia was induced using pentobarbital 20 mg/kg intravenously for all experimental procedures. In the case that a continuous recording of CSF pressure was required, steady anesthesia was maintained by means of a constant iv infusion of pentobarbital 5 mg/kg/h, which was started 60 min after the initial dose of pentobarbital. Preliminary studies carried out in normal uninfected animals showed that with the above regimen, CSF pressure was steady over a period of 4 h with a coefficient of variation of 9%.

Production of meningitis. The anesthetized animals were immobilized in a stereotactic frame. A spinal needle (3½ in, 20 gauge) was introduced into the cisterna magna.

Meningitis was induced by intracisternal injection of 0.2 ml of an inoculum of 10^8–10^9 cfu of *H. influenzae* type b/ml, originally isolated from the CSF of an infant with meningitis. The organism produced β-lactamase.

The same procedure of immobilization and cisternal puncture, which was performed at the beginning of the experiment (T_o), was repeated at 20 and 24 h after induction of meningitis, to measure intracisternal pressure and to obtain CSF for WBC count, number of bacterial cells, and lactate and hypoxanthine concentrations. All experiments took place at a room temperature of 18.3 to 21.1° C.

Treatment. Twenty h after induction of infection rabbits received either no therapy or 25% mannitol given as a 1 g/kg dose by constant intravenous infusion in 20 min. Additionally six uninfected control animals received the same regimen of mannitol.

Enumeration of WBC and bacteria in CSF. CSF WBC were counted in a Neubaur hematocytometer. The number of bacteria in CSF was quantified by preparing 10-fold dilutions and inoc-

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ulating chocolate agar plates, which were incubated for 16 h at 37° C in 5% CO_2.

CSF lactate and hypoxanthine measurements. The CSF specimens were centrifuged in a microcentrifuge for 1 min within 30 s of collection. The supernatant was stored immediately at −70° C. Samples were analyzed at various intervals after collection and storage.

Lactate was measured by a kinetic enzymatic method, which utilized the reaction of lactate with β-NAD^+ in the presence of LDH to produce NADH and pyruvate (11). The NADH production was quantitatively monitored at 340 nm absorbance on a 2600 Gilford spectrophotometer utilizing a UV deterium source. Precision of the method was assessed by testing a known standard of 40 mg of lactate/dl (no. 826-10, Sigma Chem. Co., St. Louis, MO) 10 times during the course of one day. The coefficient of variation was 2.2%.

Hypoxanthine concentrations were measured by HPLC (12) using a Waters liquid chromatograph (Waters Associates, Inc., Milford, MA), equipped with a high-pressure delivery pump (M-45) and a variable-wave length detector (M-450) set at 254 nm. Separation was achieved with a reverse-phase Techsphere-C18 column [particle size, 5 μm; 25 cm (length) by 4.6 mm (inside diameter); Chromanetics Corp., Kensington, MD]. The mobile phase contained 0.02 M KH_4PO_4 buffer solution, pH to 3.0 with phosphoric acid (degassed and filtered before each analysis). Hypoxanthine standards were prepared in HPLC mobile phase solution to a concentration range of 0.5 to 20 μM/liter. Hypoxanthine was well separated from endogenous CSF compounds with retention time of 6.5 min. CSF samples were prepared for HPLC by filtration through Millex-HV_4 filter units (0.45 μm pore size, Millipore Corp., Bedford, MA).

Identification of hypoxanthine was confirmed by enzymatic degradation of the hypoxanthine peak through catalysis with xanthine oxidase to produce xanthine, which has a different peak retention time. Precision of the method was evaluated by measuring a 10 μM/liter standard extracted and analyzed 10 times in the course of a day. The coefficient of variation was 2.4%.

All specimens collected from individual rabbits were assayed at the same time. Because of the relatively large interassay variability, the percentage change rather than the absolute differences from baseline values was considered to be a more appropriate parameter for comparison purposes.

Intracisternal pressure measurement. Intracisternal pressure was measured at T_o and 20 and 24 h later. After initiation of mannitol therapy at 20 h a continuous recording of cerebrospinal pressure was obtained until the end of the experiment at 24 h. As soon as free flow was established through the spinal needle, and before removing or adding fluid, the spinal needle was connected with a water-filled mechanical pressure transducer (Gould Statham P 23 ID; Gould Inc., Oxnard, CA). The pressure was recorded on a multichannel polygraph (R611 Dynograph Recorder; Beckman Instruments Inc., Schiller Park, IL). The transducer was referenced to the level of the cisterna magna, while the animal was lying in a prone position. The CSF pressure was obtained by electronic integration of the respective transducer signals. Before each measurement the transducer was calibrated with a mercury manometer. Measurements of pressure were considered accurate when 1) average pressure was stable for 15 s, 2) respiration was associated with measurable change in pressure, and 3) compression of the jugular vein induced elevation of pressure. Intracisternal pressure is expressed in mm Hg (1 mm Hg = 13.6 mm H_2O).

Brain water content measurement. A standard procedure for the estimation of brain edema was used. This involves sampling brain tissue (10, 13, 14) and expressing the respective brain water content as g of water per 100 g of dry weight (10, 14). The brain water content was calculated employing the formula:

$$\text{brain water content} = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100$$

At the end of the experiment (*i.e.* 24 h) the animals were sacrificed by an overdose (150 mg/animal) of pentobarbital given intravenously. Immediately after death a craniotomy was performed and the brain without the cerebellum and medulla was removed and weighed in glass dishes. The brain was then dried to stable weight (approximately 1 wk) in a vacuum oven (Precision Scientific Group, Chicago, IL) at a temperature of 105° C and a vacuum of −50KPa. For comparison purposes, 18 rabbits without meningitis were sacrificed and brain water content measured.

Statistical analysis. Values are expressed as mean ± 1 SEM. Comparison of a single parameter between two groups was performed by two-tailed Student's *t* test. Animals were compared within a treatment group using one way repeated measures analysis of variance followed by Student-Neuman-Keuls pairwise multiple comparisons (15). A p value < 0.05 was considered significant.

RESULTS

At 20 h the infected rabbits were febrile (≥ 39.5° C) and lethargic or comatose. The mean bacterial counts were 3.4 ± 0.2 and 3.8 ± 0.2 $\log_{10}$ cfu/ml at 20 h, and 3.9 ± 0.3 and 4.2 ± 0.3 $\log_{10}$ cfu/ml at 24 h in the mannitol-treated and untreated infected animals, respectively (Table 1).

Cerebrospinal fluid WBC counts, expressed in 10^3 cells/μl, were 6.1 ± 1.7 and 9.6 ± 2.4 at 20 h ($p > 0.05$ between the two groups) and 5.7 ± 1.6 and 9.1 ± 2.0 at 24 h ($p > 0.05$ between the two groups) in the mannitol-treated and untreated infected animals, respectively.

In the uninfected animals (control group) the CSF remained sterile throughout the experiment and no CSF pleocytosis was noted.

CSF pressure. Twenty hours after initiation of the experiment there was a significant increase in CSF pressure in the two groups of infected animals ($p < 0.005$; Table 2). By contrast, there were no significant changes in CSF pressure in the uninfected rabbits.

A single dose of mannitol reduced transiently the CSF pressure of uninfected rabbits (Fig. 1). The maximum reduction in CSF pressure was 34.9 ± 8.4%. The intracisternal pressure was reduced from 2.15 ± 0.20 to 1.34 ± 0.10 mm Hg ($p < 0.005$). The time to the lowest pressure was 38.7 ± 2.7 min after initiation of the infusion and the time to return of CSF pressure to initial values was 76.7 ± 5.6 min.

In infected animals with increased CSF pressure, a transient further increase in CSF pressure was recorded during the infusion of mannitol in all but one animal (Fig. 1). This was followed by a maximum reduction in CSF pressure of 42.0 ± 7.7%. The intracisternal pressure was reduced from 4.78 ± 0.53 to 2.61 ± 0.55 mm Hg ($p < 0.005$). Time to maximum pressure decrease was 44.0 ± 5.6 min. CSF pressure returned to the initial level after 178.5 ± 25.2 min.

A rebound increase in intracranial pressure following mannitol treatment was not recorded in any of the treated animals.

Table 1. *CSF bacterial counts in rabbits with H. influenzae type b meningitis*

Group	Mean ± 1 SEM no. bacteria as $\log_{10}$ cfu/ml		
	0 H	20 H	24 H
I. Uninfected rabbits treated†	ND*	Sterile	Sterile
II. Infected rabbits treated†	ND	3.4 ± 0.2 (12)‡	3.9 ± 0.3 (12)
III. Infected rabbits untreated	ND	3.8 ± 0.2 (9)	4.2 ± 0.3 (9)

* Not determined.

† 20-min intravenous infusion of 25% mannitol given to groups I and II.

‡ Numbers in parentheses represents number of animals.

Table 2. *Effect of mannitol* therapy on CSF pressure in experimental H. influenzae type b meningitis*

Group	Mean ± 1 SEM CSF pressure in mm Hg (*n*)		
	0 H	20 H	24 H
I. Uninfected rabbits treated*	2.28 ± 0.24 (6)	2.15 ± 0.20 (6)	2.12 ± 0.34 (6)
II. Infected rabbits treated*	2.02 ± 0.33 (11)	4.78 ± 0.53 (11)†	5.11 ± 0.71 (11)
III. Infected rabbits untreated	2.00 ± 0.29 (10)	5.13 ± 0.59 (10)†	5.49 ± 0.87 (10)

* 20-min intravenous infusion of 25% mannitol given to groups I and II.
† $p < 0.005$ in comparison with preinfection values.

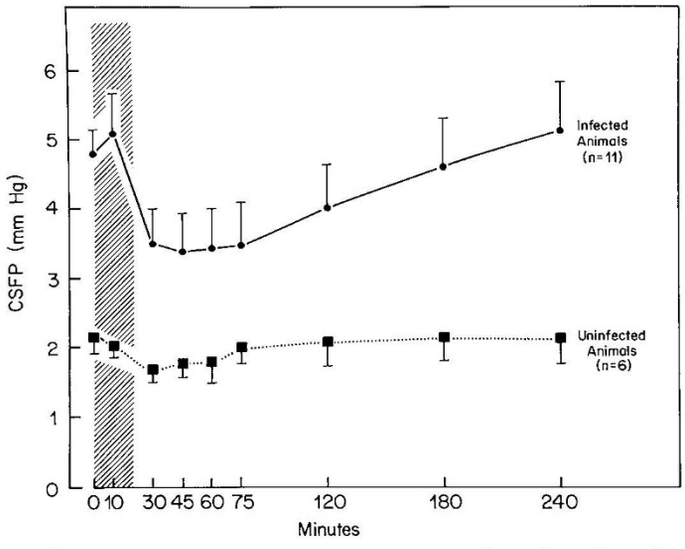

Fig. 1. Mean CSF pressure (± 1 SEM) at various times following mannitol infusion in infected and uninfected rabbits. The time that the maximum pressure occured and the total time that CSF pressure remained at significantly reduced levels varied considerably from animal to animal. See text for the mean ± 1 SEM of the lowest achieved pressures in each group. The *cross-hatched vertical column* represents the infusion time of 20 min.

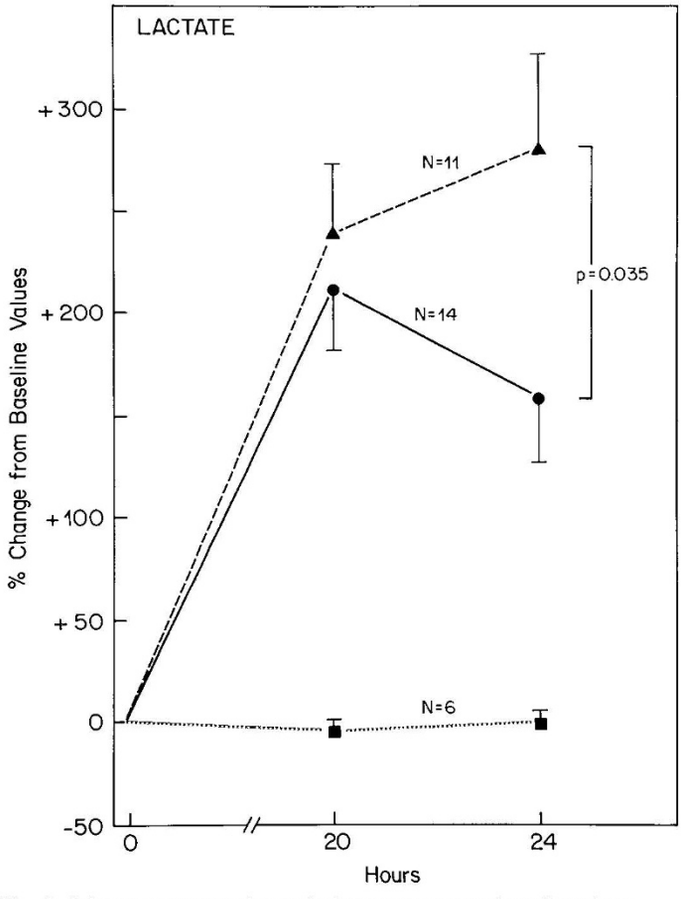

Fig. 2. Mean percentage change in lactate concentrations from baseline values (± 1 SEM) at 20 and 24 h after the initiation of the experiment. Twenty-min intravenous infusion of 25% mannitol was administered at 20 h. Infected rabbits—mannitol treated (●); infected rabbits—untreated (▲); uninfected rabbits treated(■).

At the end of the experiment (24 h) CSF pressure in mannitol-treated infected animals returned to values similar to untreated infected animals (Table 2). At 24 h normal uninfected animals had CSF pressure comparable to baseline (T_o) values.

CSF lactate and hypoxanthine concentrations. At 20 h after the beginning of the experiment, CSF lactate concentrations were significantly increased ($p < 0.005$; Fig. 2), in the two groups of infected animals. At 24 h CSF lactate concentrations were significantly reduced from these at 20 h in the infected rabbits treated with mannitol whereas the values were somewhat increased in untreated infected animals.

CSF hypoxanthine concentrations were significantly elevated at 20 h of infection ($p < 0.005$; Fig. 3). At 24 h mannitol-treated infected animals had reduced CSF hypoxanthine concentrations compared with values at 20 h but this reduction was not statistically significant.

Brain water content. At completion of the experiments (24 h) the brain water content of infected animals was similar in both mannitol-treated (412 ± 4 g H_2O)/100 g dry weight) and untreated (415 ± 3 g H_2O/100 g dry weight) animals. Those values were substantially elevated compared with values of uninfected, mannitol-treated animals at 24 h (402 ± 6 g H_2O/100 g dry weight) and of uninfected nontreated animals (405 ± 3 g H_2O/100 g dry weight).

DISCUSSION

In 1961, Wise and Chater (16) first used mannitol for treatment of brain edema and increased intracranial pressure. Although there is extensive experience with use of mannitol in neurosurgical patients with mass lesions (17–20) and in patients with cerebral edema postsurgery or secondary to head trauma (19, 21, 22) or cerebral ischemia (19), use of mannitol in patients with bacterial meningitis has been principally empirical. There is also limited experience with another osmotic agent, urea, in the treatment of bacterial meningitis. Hypertonic urea was administered intravenously to six children with *H. influenzae* meningitis (23). Following urea treatment a prompt neurological improvement occurred in four of the six patients. This improvement was presumably related to a reduction in intracranial pressure although this was not specifically measured.

Brain edema in bacterial meningitis has features of vasogenic, cytotoxic, and interstitial (hydrocephalic) cerebral edema (24–26). Mannitol is considered to have its effect mainly on the vasogenic and cytotoxic forms of edema (25). Mannitol therapy significantly reduced brain edema in patients with brain tumors (20), in cytotoxic edema produced by 6-aminonicotinamide in

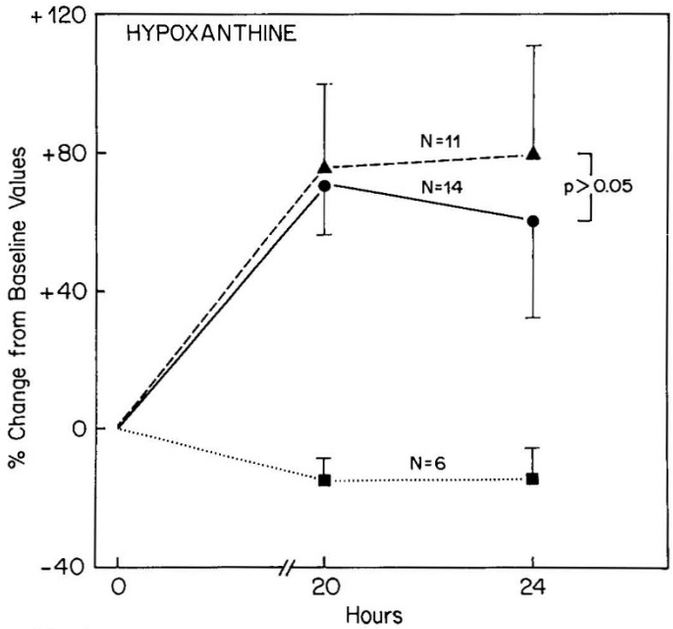

Fig. 3. Mean percentage change in hypoxanthine concentrations from baseline values (± 1 SEM) at 20 and 24 h after initiation of the experiment. Twenty-min intravenous infusion of 25% mannitol was administered at 20 h. Infected rabbits—mannitol treated (●); infected rabbits—untreated (▲); uninfected rabbits treated (■).

rabbits (27), and in cryogenic lesion in dogs (28). In those studies the brain water content was measured either by using CT density assessment (20, 28) or by weighing brain samples (27, 28) within 1 h from the initiation of mannitol infusion. Harbaugh *et al.* (29) found that mannitol did not significantly reduce the edematous tissue in cryogenic lesions in rabbits despite the fact that the brain water content was measured during the time of maximal reduction of intracranial pressure.

We did not find a significant reduction in brain water content in animals treated with mannitol compared with values in untreated animals. This observation is possibly attributed to the fact that the brain water content was measured 3 h and 40 min after completion of the mannitol infusion, at a time when CSF pressure had returned to pretreatment values.

In all animals mannitol consistently reduced intracisternal pressure. Factors modulating the response to mannitol include the dose and duration of mannitol infusion, the frequency of the doses (30), and the underlying central nervous system process for which therapy is given. The maximal reduction in CSF pressure recorded by other investigators has been from 27% (31) to 107.8% (29). An accurate dose-response relation in different clinical situations has not been well defined (32).

The initial increase in CSF pressure after beginning mannitol therapy was observed only in the infected rabbits and was most likely caused by an increase in cardiac output (stroke volume) with a resultant increase in cerebral blood flow (31–37). The increased cerebral blood flow is associated with a concomitant reduction in cerebrovascular resistance and a change in $CMRO_2$.

Improvement of cerebral blood flow might be a beneficial effect of mannitol treatment in acute bacterial meningitis because it is known that cerebral blood flow is diminished during meningitis (38, 39). In animals with cerebral ischemia, administration of mannitol resulted in improvement of cerebral blood flow and in protection from further ischemic changes (40, 41). Furthermore, it has been proposed that mannitol may protect against or improve ischemia by acting as a free radical scavenger (42). Oxygen-derived free radicals induce cellular injury to the brain and cause edema as well as changes in vascular permeability (43–45).

Brain edema and increased intracranial pressure with decreased perfusion can cause abnormal cerebral metabolism. Increased lactate is presumed to be a product of brain tissue hypoxia (39, 46). At the same time brain tissue hypoxia leads to increased ATP breakdown, products of which are hypoxanthine, xanthine, and inosine (47–50).

The concentrations of lactate that were increased at 20 h after induction of *H. influenzae* meningitis were significantly reduced after the 20-min infusion of mannitol (at 24 h). It is possible that this finding can be attributed to improved intracranial hemodynamics, increased cerebral perfusion, and increased oxygen availability to the brain tissue, resulting in improved glucose utilization. A significant reduction of CSF lactate concentrations after one 20-min infusion of mannitol is surprising considering that diminution in CSF lactate concentrations in CNS infections after initiation of appropriate treatment is known to be slow. A single dose of mannitol reduced the CSF hypoxanthine concentrations of infected animals, but this reduction was not statistically significant. This may not necessarily be related to persistent increased hypoxanthine production by the brain tissue, but may represent delayed clearance of hypoxanthine from CSF. Mannitol had no effect on the WBC or on the bacterial counts in CSF.

CONCLUSION

A single dose of hypertonic mannitol reduced transiently the CSF pressure in all animals, especially those with experimental meningitis caused by *H. influenzae* type b. Although the mean brain water content of mannitol-treated animals 220 min after completion of mannitol therapy was similar to that of untreated animals, CSF lactate concentrations in infected animals were significantly reduced after treatment. The latter finding might be a result of improved cerebral blood flow and restoration of aerobic cerebral glucose metabolism.

It is not possible to apply directly results from these animal studies to patients with Haemophilus meningitis. Because meningeal inflammation and edema can result in reduced cerebral perfusion pressure in children with meningitis, additional studies in humans should be undertaken in order to assess different therapeutic modalities that might modulate the effects of the cerebral inflammatory reaction and improve blood flow and eventual outcome.

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