The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients

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The effect of mannitol on serum and urine electrolytes and osmolality was investigated intraoperatively in neurosurgical patients. Patients in Group A (n = 7) received 1 gm·kg^{-1} of 20 per cent mannitol ("low"-dose) and in Group B, (n = 7) 2 gm·kg^{-1} ("high"-dose). There was a significant decrease in serum sodium and bicarbonate, and a significant increase in serum osmolality in both groups after mannitol administration. The decrease in serum sodium and the increase in serum osmolality were significantly greater in patients receiving the larger dose of mannitol. The infusion of low-dose mannitol resulted in a slight decrease in serum potassium. In contrast, after high-dose mannitol there was a significant rise in serum potassium reaching a maximum mean increase of 1.5 mmol·l^{-1}. Urine electrolyte concentration and osmolality showed a similar decrease in both groups. The significant changes that occurred with the administration of mannitol were of short duration in these patients with normal cardiac and renal function. The clinically most important change is the increase in serum potassium with high-dose manitol. The exact mechanism of this increase remains unclear.

Osmotic diuretics are used to reduce intracranial pressure and decrease brain bulk in neurosurgical patients.[1,2] Intraoperatively, mannitol is most frequently administered in dose ranges of 0.25–1 gm·kg^{-1}. More recently, high-dose mannitol (2 gm·kg^{-1}) has been shown to have a protective effect in acute focal cerebral ischaemia.[3,4] Accordingly, high-dose mannitol may be given prior to temporary or permanent occlusion of a major cerebral artery, which is frequently necessary during the clipping of a giant cerebral aneurysm. Previous investigators have examined the influence of low-dose mannitol on serum electrolytes and osmolality, but the effects of high dose mannitol in man have not been fully investigated.[5,6] Therefore, the purpose of this study was to compare the intraoperative effects of 1 gm·kg^{-1} (referred to as "low"-dose in this study) and 2 gm·kg^{-1} ("high"-dose) of mannitol on the serum and urine electrolytes and osmolality in neurosurgical patients.

Key words

ANAESTHESIA: neurosurgical; PHARMACOLOGY: mannitol; FLUID BALANCE: electrolytes.

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Methods

This study was approved by the Health Sciences Committee on Human Research of the University of Western Ontario. Informed consent was obtained from each subject. Fourteen patients scheduled for clipping of a cerebral aneurysm were studied. None had cardiac or renal disease. Patients in whom temporary or permanent occlusion of a major artery was anticipated were given high-dose mannitol. Group A (seven patients) received 1 gm·kg^{-1} of 20 per cent mannitol and Group B (seven patients) received 2 gm·kg^{-1} of 20 per cent mannitol.

Patients were unpremedicated. Anaesthesia was induced with thiopentone 5–6 mg·kg^{-1}, fentanyl 2–3 μg·kg^{-1} and lidocaine 1 mg·kg^{-1}. Succinylcholine 1 mg·kg^{-1} was used to facilitate tracheal intubation. Patients were mechanically ventilated to maintain a $PaCO_2$ of 28–32 mmHg. Anaesthesia was maintained with 50 per cent nitrous oxide, 50 per cent oxygen, isoflurane and pancuronium. Intraoperative monitors included a standard lead II electrocardiogram, intra-arterial catheter, central venous or pulmonary artery catheter, urinary catheter, nasopharyngeal temperature probe and an end-tidal capnometer. A lumbar subarachnoid catheter was inserted for drainage of cerebral spinal fluid. During stable anaesthesia mannitol was infused at a rate of 15 ml·min^{-1} through a large-bore intravenous cannula. Blood was obtained for serum osmolality, electrolytes, BUN, creatinine, glucose, haemoglobin and haematocrit. A free flowing urine sample was collected for osmolality

and electrolytes. All samples were obtained at the following times: (1) preoperatively, (2) after induction of anaesthesia, (3) after $\frac{1}{3}$ mannitol dose infused, (4) after $\frac{2}{3}$ mannitol dose infused, (5) at the completion of mannitol infusion, (6) 15 minutes postinfusion, (7) 30 minutes postinfusion, (8) 60 minutes postinfusion, (9) in the Recovery Room, and (10) postoperative day one.

Statistical analysis within each group was performed with one-way analysis of variance for repeated measures and where significance was observed ($p \leq 0.05$), Dunnett's Test was used for comparison with the control values. The control was the preoperative value (sample time one) for all measurements except for osmolality where the control was the postinduction value (sample time two). Results between Group A and Group B were analyzed with two-way analysis of variance for repeated measures.

Results

Patient characteristics and duration of mannitol infusion are shown in Table I. The study was completed in all patients and no complications were noted in Group A. In Group B, that is, high-dose mannitol, in two patients it was noted by the surgeon that the brain had collapsed and was "too slack".

During mannitol infusion in both groups there was a significant decrease in serum sodium, chloride, bicarbonate, haemoglobin and haematocrit from preoperative measurement (Figures 1, 2). There was a significant increase in serum osmolality (Figure 3). The duration of infusion was different for each group (Table I) and thus the absolute sampling times were also different between Group A and B. The decrease in serum sodium and chloride and the increase in serum osmolality was significantly greater in group B (Table II). There was no significant difference in serum bicarbonate and haemoglobin and haematocrit between Group A and Group B. In all patients these changes had returned to their preoperative level in the Recovery Room. BUN, creatinine and glucose showed no appreciable changes during this study in either group.

TABLE I Patient characteristics

	Group A Mannitol 1 gm·kg⁻¹	*Group B Mannitol 2 gm·kg⁻¹*
Sex (F:M)	6:1	5:2
Age (years) (mean ± SD)	41.6 ± 12	43.3 ± 15
Weight (kg) (Mean ± SD)	64.6 ± 10	66.6 ± 16
Duration of infusion minutes (mean ± SD)	18.7 ± 6.6	36.4 ± 10.8

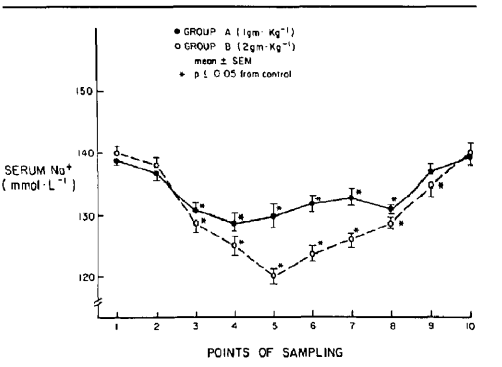

FIGURE 1 Changes in serum sodium during and after mannitol infusion. Within each group the control value is sampling point 1. The decrease was significantly greater in Group B compared to Group A ($p \leq 0.05$). Points of sampling are: (1) preoperatively, (2) after induction of anaesthesia, (3) after $\frac{1}{3}$ mannitol dose infused, (4) after $\frac{2}{3}$ mannitol dose infused, (5) at completion of mannitol infusion, (6) 15 minutes postinfusion, (7) 30 minutes postinfusion, (8) 60 minutes postinfusion, (9) in the Recovery Room, and (10) postoperative day one.

The most striking finding in our study was the change in serum potassium. In Group A there was a slight decrease during the infusion of mannitol, which did not reach statistical significance (Figure 4). In Group B there was a statistically significant increase in serum potassium occurring 15 minutes after the infusion of mannitol. The mean value (± SEM) was 5.1 ± 0.83 mmol·L^{-1}, and in fact in one patient this value reached 6.2 mmol·L^{-1}.

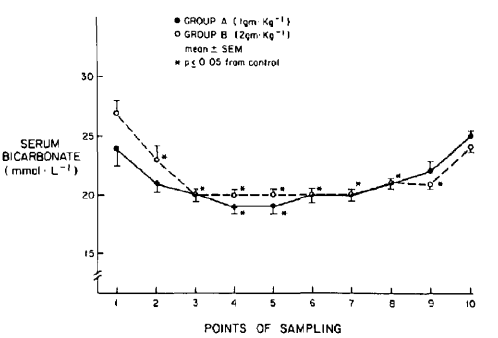

FIGURE 2 Changes in serum bicarbonate during and after mannitol infusion. Within each group the control value is sampling point 1. There was no statistically significant difference between Group A and Group B.

TABLE II Maximum mean changes in electrolytes and osmolality

	Group	*Serum*	*Time†*	*Urine*	*Time†*
Na^+	A	−8.7	4	−64.9	5
($mmol \cdot L^{-1}$)	B	−20.7*	5	−76.6	4
K^+	A	−0.5	4	−34.3	6
($mmol \cdot L^{-1}$)	B	+1.5*	6	−34.6	5
Bic	A	−7	4		
($mmol \cdot L^{-1}$)	B	−8	4		
Osm	A	+11	4	−163	6
($mosm \cdot kg^{-1}$)	B	+32*	5	−104	6
Hgb	A	−25	4		
($gm \cdot L^{-1}$)	B	−22	4		

*$p \leq 0.05$ between Group A and B.
†Time = Time of measurement.
4 After $\frac{2}{3}$ mannitol infused.
5 Completion of mannitol infusion.
6 15 minutes postinfusion.

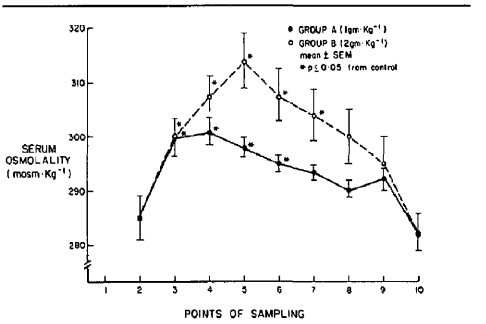

FIGURE 3 Changes in serum osmolality during and after mannitol infusion. Within each group the control value is sampling point 2. The increase was significantly greater in Group B compared to Group A ($p \leq 0.05$).

Again, by the time the patients had arrived in the Recovery Room serum potassium levels had returned to the preoperative level.

Intraoperative fluid administration during the time of the study was similar in both groups. Urine volume produced (up to one hour post-mannitol infusion) was twice as great in Group B as in Group A. Spot urine sampling showed a significant decrease in concentration of sodium, potassium, and osmolality in both groups. There was no significant difference between Group A and Group B.

Discussion

In our study we found a significant difference between the effect of low-dose (1 $gm \cdot kg^{-1}$) and high-dose (2 $gm \cdot kg^{-1}$) mannitol on serum electrolytes and osmolality. The changes in serum sodium, chloride, bicarbonate, osmolality, haemoglobin, and haematocrit in Group A of our study are similar to previous investigations of low dose mannitol.[6,7] the magnitude of the change with high-dose mannitol was significantly greater, although the duration of the changes was similar in both groups. Thus, though the acute changes were significant they were of short duration in these patients with normal cardiac and renal function.

The effect of mannitol on serum potassium has been investigated by a number of previous investigators, but the results are conflicting. This is summarized in Table III. These studies are not directly comparable as the dose of mannitol varied and was not always calculated on a per kilogram body weight basis, the duration of infusion of mannitol ranged from a bolus within four minutes to 100 minutes, and the time of measurement of serum potassium varied greatly. In another study, Coté *et al.* in cardiovascular patients on cardiopulmonary bypass reported a statistically significant decrease in potassium, but this decrease was clinically unimportant.[11] In our study, during low-dose mannitol, we found a maximum mean, but statistically not significant decrease of 0.5 $mmol \cdot L^{-1}$

TABLE III Effect of mannitol on serum potassium

Author	*Dose of mannitol*	*Duration of infusion*	*Time of measurement*	*Maximum change K^+ ($mmol \cdot L^{-1}$)†*
Wise[5]	1.1–3.6 $gm \cdot kg^{-1}$	45–90 min	Postoperative	0
Buckell[8]	100 gm	10–20 min	1 hour postinfusion	+0.4
Moreno[9]	100 gm	100 min	Postinfusion	+0.6*
Cottrell[6]	1 $gm \cdot kg^{-1}$	bolus	Onset of diuresis	−0.2*
Schettini[7]	1.4 $gm \cdot kg^{-1}$	20 min	Onset of diuresis	−0.3
Ravussin[10]	1 $gm \cdot kg^{-1}$	4 min	37 min postinfusion	+0.6
Manninen	1 $gm \cdot kg^{-1}$	18 ± 6 min	15 min postinfusion	−0.2
Manninen	2 $gm \cdot kg^{-1}$	36 ± 10 min	15 min postinfusion	+1.5*

*Statistically Significant
†Mean Value

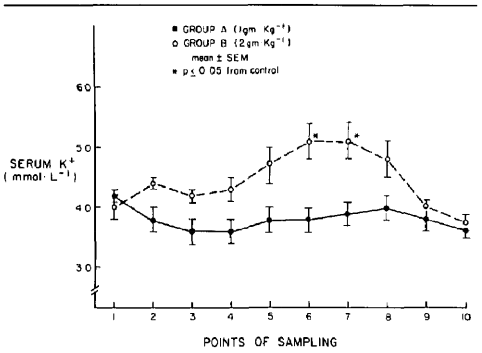

FIGURE 4 Changes in serum potassium during and after mannitol infusion. Within each group the control value is sampling point 1. The difference between Group A and Group B was statistically significant ($p \leq 0.05$).

occurring after $\frac{3}{4}$ infusion of mannitol. Ravussin *et al.* showed a significant decrease in human volunteers after two minutes of rapid infusion of 1 gm·kg^{-1} mannitol.[10] After three minutes serum potassium returned to control levels and then showed a nonsignificant tendency to increase. The increase at 37 minutes after mannitol was 0.6 mmol·L^{-1}. In their study on volunteers, Moreno *et al.* found a significant increase in serum potassium and also observed changes on the electrocardiogram suggestive of hyperkalaemia.[9] In our study with 2 gm·kg^{-1} of mannitol (Group B) we also found a significant rise with a maximum mean increase of 1.5 mmol·L^{-1} occurring 15 minutes after infusion. We did not observe any electrocardiographic changes.

The occurrence of hyperkalaemia after the intravenous administration of hypertonic solutions has been investigated and some possible explanations offered include expansion acidosis, solvent drag, and haemolysis. The administration of a hypertonic solution with resultant expansion of extracellular space generally leads to acidaemia.[12] This acidaemia is attributed to dilution of the extracellular bicarbonate with a bicarbonate poor fluid from the intracellular space. Lilien studied the shifts of ions in *in vitro* experiments.[13] He concluded that there was a depression of plasma pH by dilution of bicarbonate by the movement of water from red blood cells. There was also a net loss of bicarbonate due to the movement of bicarbonate into red blood cells or the buffering of hydrogen ions which had moved into the plasma. Another explanation is that the rise in potassium may not be dependent on pH changes, but due to the shift of water out of cells to maintain isotonicity of extracellular fluid and the movement of potassium with it.[14] Makoff *et al.* in dogs found no correlation between the degree of acidosis and the magnitude of the increase in potassium concentration.[15] They also accounted for the increase in potassium by the movement of potassium along with the water out of cells.

The other possibility that has been considered is the direct effect of mannitol on the red blood cell. Red cell crenation does occur, but no haemolysis occurred as shown by Roberts.[16,17] An increased serum potassium ordinarily stimulates insulin release which then restores normal potassium levels.[18] The potential for very high levels of serum potassium is present when there is impaired function of glucoregulatory hormones or renal failure. Blood glucose levels in our study did not show any change in either group.

Expansion acidosis does not explain our study results. We found that potassium only increased with high-dose mannitol, but serum bicarbonate decreased in both groups and the decrease was not different between the high-dose and low-dose groups. We did not measure pH at every point of sampling though every patient did have blood gases analyzed at least twice during this study, and there was no indication of acidosis. The increase in serum osmolality was greater in the high-dose mannitol group. Perhaps this hyperosmolality resulted in greater flux of water as well as potassium from the cells.

The results from our study also did not suggest a renal mechanism to account for this increase in serum potassium. Our urine results, although showing significant decreases in the concentration of electrolytes and osmolality, reflecting excretion of water in excess of solute, revealed similar values between the low-dose and high-dose mannitol groups. However, the actual amount of potassium excreted was twice as great after high-dose mannitol.

Conclusion

The infusion of high-dose mannitol (2 gm·kg^{-1}) results in significant changes in serum eletrolytes and osmolality. These changes are most pronounced immediately after the infusion of mannitol. The most clinically important change is the dramatic increase in serum potassium that occurs with high-dose mannitol. This significant elevation may reach dangerous levels in some patients and potentially can result in serious complications. This is especially true in patients who have underlying medical disorders such as cardiac and renal disease or in patients who have pre-existing abnormal serum electrolytes. Although the mechanism of this rise in potassium has not been elucidated, it is prudent to administer high-dose mannitol cautiously. In patients with underlying medical disorders frequent measurements of serum electrolytes are advised.

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Résumé

On a examiné l'effet du mannitol sur les électrolytes et l'osmolalité sériques et urinaires en période intraopératoire chez les patients neurochirurgicaux. Les patients du groupe A (n = 7) ont reçu 1 $g \cdot kg^{-1}$ de 20 pour cent de mannitol ("faible" dose) et ceux du groupe B (n = 7), ont reçu 2 $g \cdot kg^{-1}$ (dose "élevée"). Une diminution significative du sodium et du bicarbonnate sérique, et une augmentation significative de l'osmolalité sérique s'est produite dans les deux groupes après l'administration du mannitol. La diminution du sodium sérique et l'augmentation de l'osmolalité sérique étaient beaucoup plus élevées chez les patients recevant une dose importante de mannitol. L'infusion d'une faible dose de mannitol a entraîné une légère diminution du potassium sérique. Par contre, après l'administration d'une dose élevée de mannitol, le potassium sérique a augmenté de façon significative atteignant une augmentation maximum moyenne de 1.5 $mmol \cdot L^{-1}$. La concentration électrolytique et l'osmolalité urinaire ont démontré une diminution semblable dans les deux groupes. Les changements significatifs qui se sont produits avec l'administration de mannitol étaient de courte durée chez les patients ayant une fonction cardiaque et une fonction rénale normales. Le changement clinique le plus important est l'augmentation du potassium sérique en présence d'une dose élevée de mannitol. On ne comprend pas encore clairement le mécanisme exact de cette augmentation.