Published in final edited form as:

Neurocrit Care. 2008 ; 9(2): 204–209. doi:10.1007/s12028-008-9118-3.

Variation in osmotic response to sustained mannitol administration

Salah G. Keyrouz, M.D.^{1,2}, Rajat Dhar, M.D.¹, and Michael N. Diringer, M.D.¹

¹ Neurology/Neurosurgery Intensive Care Unit, Department of Neurology and Neurological Surgery, Washington University, St. Louis, MO 63110

Abstract

Background—Osmotic agents such as mannitol remain a mainstay in the management of cerebral edema and raised intracranial pressure. Some patients do not respond to sustained mannitol administration with the expected rise in serum osmolality, and this may correlate with lack of therapeutic efficacy.

Objective—To examine the variation in osmotic response to mannitol therapy, and identify factors associated with a lack of an osmotic response to sustained mannitol administration.

Methods—Data on consecutive patients admitted to a Neurology/Neurosurgery Intensive Care Unit who received scheduled doses of mannitol for at least 48 hours were extracted from a prospectively collected database. All patients received intravenous isotonic saline solutions and had serial measurements of serum sodium and osmolality, at least twice daily. Non-responders were defined using two thresholds, a rise in serum sodium of ≤ 1 or ≤ 5 mEq/L over the 48-hour period.

Results—The cohort included 167 patients the majority with intracerebral and subarachnoid hemorrhage and brain tumors. 73 patients (44%) did not respond to mannitol with a rise in sodium of ≥ 5 mEq/L, and 37 (22%) did not see a rise of 1 mEq/L over 48 hours of treatment. There were minor differences between responders and non-responders (≥ 5 mEq/L) in terms of age (56 ± 15 vs. 48 ± 14), total mannitol dose (0.9 ± 0.2 vs. 0.7 ± 0.2 g/kg) and cumulative fluid balance at 72 hours (91 ± 1653 vs. -610 ± 1692 ml). Multivariate analysis found that younger age, lower weight-adjusted mannitol dose, and more negative fluid balance were associated with lack of osmotic response.

Discussion—A substantial proportion of patients receiving sustained mannitol do not manifest the expected osmotic response. This lack of response may correlate with the failure of clinical efficacy seen in a subgroup of patients, who then require alternate agents such as hypertonic saline. This association merits further exploration.

Keywords

mannitol; osmolality; brain edema; intracranial pressure

INTRODUCTION

Osmotic therapy is frequently used to treat intracranial hypertension, cerebral edema and tissue shifts due to intracranial mass lesions. Mannitol, a metabolically inert hexose, is the best-studied osmotic agent, and is typically used first-line for osmotherapy in the United States. It

Corresponding author: Michael N. Diringer, M.D., Washington University, Department of Neurology, Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110, Phone: 314-362-2999, Fax: 314-362-4397, e-mail: diringerm@neuro.wustl.edu.

²Current address: Department of Neurology, University of Arkansas for Medical Sciences, Little Rock, AR 72205

has been consistently shown to reduce intracranial pressure (ICP) (1,2). However, there is currently growing interest in hypertonic saline as an alternative to mannitol (3–5).

In most organs, mannitol is rapidly distributed throughout the extracellular compartment. In normal brain with an intact blood-brain-barrier (BBB), however, mannitol is confined to the intravascular compartment; this creates an osmotic gradient, which results in movement of water out of the intracellular and interstitial compartments of the brain into the vasculature. This osmotic effect reduces net intracranial volume and is the most widely accepted mechanism accounting for mannitol's ability to lower ICP (2,6–11). Even in the presence of a disrupted BBB, an osmotic gradient is still established and mannitol is still able to reduce total brain volume (12,13). Hypertonic mannitol solutions rapidly draw water into the extracellular compartment increasing plasma volume (2), which transiently dilutes extracellular sodium (14–16). In the kidney, mannitol acts as an osmotic diuretic resulting in the excretion of large volumes of free water (2,17). The overall effect on osmolality depends on the type of intravenous fluids administered. If hypotonic fluids are administered osmolality will remain stable, if isotonic saline solutions are given then repeated doses of mannitol should result in a net rise in osmolality and serum sodium concentration.

There remain cases where mannitol is ineffective at controlling intracranial hypertension (4, 18). Such “mannitol resistant” patients may also manifest a failure of their serum sodium and osmolality to rise as expected. We have observed this phenomenon despite repeated doses of mannitol, normal renal function, and fluid administration consisting entirely of isotonic saline. This lack of osmotic response might, in part, explain cases of resistance to mannitol therapy, but the incidence and factors associated with it have not yet been adequately studied. To further our understanding of this phenomenon, we reviewed data on consecutive patients who received sustained mannitol therapy in order to define the frequency with which osmolality fails to rise with mannitol administration, and to identify factors associated with this lack of an osmotic response.

METHODS

Patient Population

The Neurology/Neurosurgery Intensive Care Unit (NNICU) is a 20-bed specialized unit located in a tertiary care academic center with over 1,600 admissions per year. Data on all patients admitted to the NNICU are prospectively collected and entered into a database (QuIC; Space Labs, Redmond, WA). Variables entered include patient demographics, diagnoses, therapeutic interventions, complications, physiologic measures, and hospital disposition. The Washington University Human Research Protection Office approved the retrospective extraction and analysis of these data.

Patient selection

A patient cohort was retrospectively identified from our database. We included consecutive patients admitted over a 29-month period (May 2004 through September 2006) who received scheduled mannitol boluses for at least 48 hours. We excluded those who concomitantly received hypertonic saline solutions so that we could determine the osmotic response to mannitol alone.

Mannitol administration and fluid management

Mannitol is routinely used in our practice to treat intracranial hypertension and in situations where cerebral edema or mass lesions causing tissue shifts are felt to be contributing to poor neurologic status. Indications included elevated ICP, mass effect from large ischemic stroke or intracerebral hemorrhage and post operative edema. In some cases it was initiated because

of a clinical decline but in many others mannitol was instituted based on imaging studies or empirically. A 20% solution is administered intravenously as intermittent boluses, infused at a rate of 1 liter/hour at intervals of 4 to 8 hours. Doses generally range between 0.5 and 1.25 gm/kg. Serum electrolytes, osmolality and renal function are measured at baseline if possible, and then 2–4 times a day. To minimize the impact of non-excreted mannitol on laboratory measurements, including the phenomenon of *pseudohyponatremia*, blood samples are collected immediately prior to mannitol administration. Urine output and total fluid balance are calculated every 2 hours. Intravenous fluids always consist of an isotonic (0.9%) saline solution while concentrated tube feeding formulas are administered without water flushes and enteral fluids are minimized. Fluid balance is reviewed at least twice daily and the rate of fluid administration adjusted as needed to achieve a neutral or slightly negative (–500 ml/24 hr) fluid balance, with close attention to avoid hypovolemia.

Data collection

The following data elements were extracted from our database: demographics (age, race, and sex), diagnoses classified as subarachnoid hemorrhage (SAH), head injury, intracerebral hemorrhage (ICH), central nervous system (CNS) tumor, ischemic stroke, CNS infection and others. Reason for mannitol administration was ascertained, by reviewing patients' history and imaging, and classified as: tissue shift, cerebral edema, or other. Total cumulative mannitol dose over 48 hours was calculated. Laboratory data were obtained from electronic medical records, including renal function, baseline serum sodium and osmolality (where available), and sodium and osmolality after 48 hours of mannitol. Fluid balance was abstracted daily.

Groups

We divided patients into responders and non-responders based on whether serum sodium concentration rose with sustained mannitol administration after 48 hours. As mannitol is often initiated under emergent conditions, baseline osmolality was not measured in a significant proportion of patients before administration of the first dose. Furthermore, we have shown that serum sodium, when measured immediately prior to a mannitol dose, correlates closely with serum osmolality (19), making the change in sodium an accurate surrogate of the osmotic response to mannitol.

There are no data to guide the choice of an appropriate threshold for determining the presence or absence of an osmotic response. Therefore we chose a range of thresholds: ≥ 1 and ≥ 5 mEq/L that although arbitrary, seemed rational and appropriate for this preliminary investigation. The 1 mEq/L threshold was selected to assess the lack of any rise in serum sodium despite sustained mannitol administration, and the 5 mEq/L cutoff to define a failure to achieve a rise that might be clinically meaningful. Those in whom sodium concentration rose above the threshold in this time frame were considered responders, and those in whom it did not, were considered non-responders. We did not use the equally arbitrary threshold of achieving an osmolality of 300 to 320 mOsm/L with mannitol therapy, as suggested in previous guidelines (20), as this target does not appear clinically useful (6), and is based on a fear of precipitating renal failure that has not been supported by recent evidence (21).

Statistical analysis

Statistical analysis of the data was performed using commercially available software (SPSS Release 11.5.0, SPSS, Chicago, IL). For the purpose of the analysis, patients were divided into 2 groups: those in whom osmolality rose with mannitol and those in whom osmolality did not rise, as described above. For normally distributed continuous variables, groups were compared using two-tailed unpaired *t* tests. For non-normally distributed continuous and categorical variables, Chi-squares, Mann-Whitney U and Fisher exact tests were used as appropriate. The

relationship between serum sodium concentration and osmolality was analyzed with a 2-tailed Pearson correlation coefficient.

Logistic regression analysis was performed in order to determine factors associated with lack of osmotic response. All variables were screened and only those with $p < 0.20$ on univariate analysis were entered into a forward stepwise conditional model. Covariates were considered to have a significant effect at the 5% level ($p < 0.05$), whereas covariates with p -values between 0.05 and 0.10 were considered not to have a significant effect on the outcome, but being of sufficient importance for the model fit to be kept in the final model.

Results

During the 29-month period studied, 435 out of 3,825 patients admitted to the NNICU received mannitol. Of those, 263 patients were excluded for the following reasons: mannitol use < 48 hours (238), concomitant administration of hypertonic saline (27) and missing sodium values (5), leaving 167 patients in the final analysis. The most common diagnoses were ICH (45), SAH (39), and brain tumors (22).

Serum sodium levels and osmolality were tightly correlated with an R^2 of 0.834, (Figure 1). In 37 (22%) of the 167 patients, sodium did not rise by even 1 mEq/L after 48 hours of mannitol therapy, while in 73 patients (44%) it did not rise by at least 5 mEq/L. The differences between responders and non-responders were similar whether a threshold of 1 or 5 mEq/L was analyzed (Table 1). In univariate analysis, the responders were significantly older, were more likely to have ICH, received more mannitol (total dose corrected for body weight) and had a more positive fluid balance (Table 1).

Multivariate analysis using the 5 mEq/L threshold identified younger age, lower mannitol dose per body weight, and more negative fluid balance on day 3 as being predictive of no change in sodium following mannitol administration (Table 2). The model correctly predicted responders 81% of the time and non-responders 67% of the time for a total correct prediction rate of 75%.

DISCUSSION

This retrospective review was performed to systematically study the osmotic response to mannitol, and determine how often repeated doses fail to increase serum sodium concentration and osmolality. We found that sodium concentration failed to rise by at least 1 mEq/L in 22%, and by at least 5 mEq/L in 44% of patients who received scheduled mannitol doses for ≥ 48 hours. Therefore, the expected hyperosmolar response to mannitol fails to occur in a significant proportion of patients.

Time course of osmotic effects of mannitol

The effects of mannitol on serum osmolality occur over two time frames. One is the response to a single bolus, and the second reflects the osmotic changes that occur with repeated doses. Following a single bolus, mannitol is distributed throughout the extracellular fluid (except in normal brain) within 2–3 minutes (22). There is an acute rise in extracellular osmolality due to presence of the drug itself, which causes an influx of water from the intracellular compartment; this restores osmotic equilibrium between the intra- and extracellular compartments, at a higher level than prior to mannitol administration. This water shift also dilutes serum sodium, transiently lowering serum sodium concentration. This is followed by clearance of mannitol from the circulation through the kidneys, producing an osmotic diuresis and elimination of a large volume of free water, further raising total body osmolality and serum sodium (17). Thus, the net effect of a single dose of mannitol is a no change or small net rise

in total body osmolality. With sustained use, it will result in a hyperosmolar hypovolemic state unless replacement fluids are administered. The response is different depending on the choice of fluids. With free water (D₅W), osmolality will remain relatively stable. On the other hand, if isotonic saline is administered there should be a consistent rise in serum osmolality and sodium concentration.

In order to better understand the osmotic response to repeated doses of mannitol, we studied a group of patients managed in a consistent fashion. The analysis was restricted to patients who received 1) scheduled doses of mannitol for at least 48 hours, 2) intravenous fluid replacement with only isotonic (0.9%) saline, 3) fluid management targeted at a net 24 hour fluid balance of even to -500 ml, and 4) did not receive hypertonic saline solutions. In this setting, all aspects of fluid and electrolyte management were directed towards driving sodium concentration and osmolality higher. The novel observation that almost half our population, despite this intent, did not manifest even a small 5 mEq/L rise in serum sodium over 48 hours, highlights the presence of a group of “mannitol non-responders.” As mannitol’s beneficial action likely depends on its osmotic effect, this absence of response may be a harbinger of clinical failure. In these cases, hypertonic saline may prove an effective alternative. Early identification of patients likely not to respond to mannitol therapy is therefore clinically important. A recent study found that failure of sodium to rise by ≥ 5 mEq/L after hypertonic saline administration correlated with failure to reverse the clinical manifestation of transtentorial herniation, supporting the importance of the osmotic response with such agents to their clinical efficacy (23).

We found that patients who were mannitol non-responders were younger and had a more negative fluid balance on day 3. This difference in fluid balance between groups was small however, with a difference of just 700 mL over two days, and we feel therefore unlikely to account for the variation in osmotic response. Weight-adjusted cumulative mannitol dose was also lower in non-responders (7.72 ± 2.48 vs. 5.9 ± 2.51 g/kg/48 hr), but was still on the high-end of the recommended dosing range.

Possible explanations for the findings

There are a number of possible explanations for our findings. Some patients may have impaired renal function that limited the diuretic effect of mannitol, thus potentiating a rise in osmolality; however, indicators of renal function, such as blood urea nitrogen (BUN) and creatinine were no different between responders and non-responders. Some patients may have had elevated levels of circulating antidiuretic hormone (ADH), limiting water excretion. An elevation of ADH has been shown in healthy volunteers following the administration of a single dose of mannitol (24,25). While this might be true in health, it is unclear how possible elevation of ADH and mannitol-induced osmotic and electrolyte changes interact in disease states. Alternatively, in some patients mannitol may produce not only an osmotic diuresis but also increases sodium excretion (natriuresis). Within two hours after a dose of mannitol (1 g/Kg), urinary sodium excretion increases significantly and then drops to pre-mannitol levels (14). This might represent a physiologic response to the acute, but transient increase in plasma volume that accompany mannitol administration (26), as evidenced by the concomitant drop in serum rennin activity and aldosterone level (24). Moreover, mannitol is believed to directly stimulate atrial natriuretic peptide (ANP) release, through a non-mechanical stimulus (27). The interplay of these phenomena, which can be altered in critically ill patients, may result in an abnormally pronounced natriuretic response to mannitol administration. While such enhanced natriuresis might partially explain the more negative fluid balance in those whose sodium failed to rise after mannitol, without collecting neurohormonal markers and urine studies we cannot test this hypothesis. However, this possible explanation for our findings could be examined in future studies.

Limitations of the study

This study has two important limitations. First, a number of our patients did not have a baseline osmolality measurement before the initiation of mannitol therapy. Thus we had to use serum sodium concentration as a surrogate. We were able to minimize any impact of mannitol on serum sodium determination by always measuring serum sodium concentration just prior to a mannitol dose, a time when all the mannitol from a previous dose should have been excreted, and any change in serum sodium concentration will directly reflect change in osmolality. We therefore feel that those without an increment in serum sodium would similarly fail to manifest such a rise in serum osmolality with mannitol. The use of sodium as a surrogate for osmolality in assessing response to therapy is supported by a report on use of hypertonic saline, which found that failure of sodium to rise by ≥ 5 mEq/L correlated with clinical failure to reverse transtentorial herniation (23).

The second limitation is that we did not correlate the osmotic response to the effect on ICP, edema, mass effect, or clinical outcome. There are a number of reasons for this. The patients in our study were complex and often received multiple therapies, some simultaneously, that may have influenced ICP, edema, and mass effect. Second, in order to study the impact of mannitol alone, we had to study patients over a relatively brief time frame, 48 hours. Some of these patients had a considerably longer course in the NNICU. Thus the clinical and radiographic responses may not have been evident in the timeframe studied. Third, many of the patients were receiving mannitol to treat edema or mass effect, factors that are very difficult to measure with a high degree of sensitivity (12). Finally, the retrospective nature of the study limited the data available to assess these parameters. An important validation to our findings would be a study correlating lack of osmotic response to lack of clinical efficacy, such as ICP and overall outcome.

Conclusions

This is the first study to investigate disparities in the osmotic effects of mannitol in critically ill neurologic and neurosurgical patients. We found that, depending on the threshold used 20–40% of patients do not have a significant rise in osmolality over 48 hours of repeated mannitol administration. We hypothesize that this may account for the lack of therapeutic effect of mannitol observed in some patients. Further prospective studies are needed to assess the relationship between change in osmolality and clinical and radiographic response and to determine the mechanisms responsible for this phenomenon.

Acknowledgements

Support: NIH (NS535966)

References

1. Bereczki D, Liu M, Prado GF, Fekete I. Cochrane report: A systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. *Stroke* 2000;31:2719–2722. [PubMed: 11062300]
2. Wise BL, Chater N. The value of hypertonic mannitol solution in decreasing brain mass and lowering cerebro-spinal-fluid pressure. *J Neurosurg* 1962;19:1038–1043. [PubMed: 14001309]
3. Ogden AT, Mayer SA, Connolly ES Jr. Hyperosmolar agents in neurosurgical practice: the evolving role of hypertonic saline. *Neurosurgery* 2005;57:207–215. 207–215. [PubMed: 16094147]
4. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke* 2002;33:136–140. [PubMed: 11779902]
5. Violet R, Albanese J, Thomachot L, et al. Isovolumetric hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003;31:1683–1687. [PubMed: 12794404]

6. Diringner MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care* 2004;1:219–233. [PubMed: 16174920]
7. Donato T, Shapira Y, Artru A, Powers K. Effect of mannitol on cerebrospinal fluid dynamics and brain tissue edema. *Anesth Analg* 1994;78:58–66. [PubMed: 8267182]
8. Elkinton JR. The Volume of Distribution of Mannitol as a Measure of the Volume of Extracellular Fluid, with a Study of the Mannitol Method. *J Clin Invest* 1947;26:1088–1097. [PubMed: 16695510]
9. Kaufmann AM, Cardoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. *J Neurosurg* 1992;77:584–589. [PubMed: 1527619]
10. Videen TO, Zazulia AR, Manno EM, et al. Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. *Neurology* 2001;57:2120–2122. [PubMed: 11739839]
11. Wise BL, Chater N. Use Of Hypertonic Mannitol Solutions To Lower Cerebrospinal Fluid Pressure And Decrease Brain Bulk In Man. *Surgical Forum* 1961;12:398–399. [PubMed: 14007661]
12. Manno EM, Adams RE, Derdeyn CP, Powers WJ, Diringner MN. The effects of mannitol on cerebral edema after large hemispheric cerebral infarct. *Neurology* 1999;52:583–587. [PubMed: 10025792]
13. Paczynski RP, He YY, Diringner MN, Hsu CY. Multiple-dose mannitol reduces brain water content in a rat model of cortical infarction. *Stroke* 1997;28:1437–1443. 1444. [PubMed: 9227697]
14. Bracali AM, Zanghi F, Sabato AF, De Francisci G, Bondoli A. Biochemical changes in neurosurgical patients under critical care treated with mannitol. *Resuscitation* 1980;8:95–100. [PubMed: 6779362]
15. Manninen PH, Lam AM, Gelb AW, Brown SC. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. *Can J Anaesth* 1987;34:442–446. [PubMed: 3117392]
16. Schettini A, Stahurski B, Young HF. Osmotic and osmotic-loop diuresis in brain surgery. Effects on plasma and CSF electrolytes and ion excretion. *J Neurosurg* 1982;56:679–684. [PubMed: 6802937]
17. Wise BL. Effects of Infusion of Hypertonic Mannitol on Electrolyte Balance and on Osmolarity of Serum and Cerebrospinal Fluid. *J Neurosurg* 1963;20:961–967. [PubMed: 14186098]
18. Suarez JJ, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med* 1998;26:1118–1122. [PubMed: 9635664]
19. Garcia-Morales EJ, Cariappa R, Parvin CA, Scott MG, Diringner MN. Osmole gap in neurologic-neurosurgical intensive care unit: Its normal value, calculation, and relationship with mannitol serum concentrations. *Crit Care Med* 2004;32:986–991. [PubMed: 15071390]
20. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Use of mannitol. *J Neurotrauma* 2000;17:521–525. [PubMed: 10937895]
21. Gondim Fde A, Aiyagari V, Shackelford A, Diringner MN. Osmolality not predictive of mannitol-induced acute renal insufficiency. *J Neurosurg* 2005;103:444–447. [PubMed: 16235675]
22. Cloyd JC, Snyder BD, Cleeremans B, Bundlie SR, Blomquist CH, Lakatua DJ. Mannitol pharmacokinetics and serum osmolality in dogs and humans. *J Pharmacol Exp Ther* 1986;236:301–306. [PubMed: 3080582]
23. Koenig MA, Bryan M, Lewin JL 3rd, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. *Neurology* 2008;70:1023–1029. [PubMed: 18272864]
24. Ambuhl PM, Ballmer PE, Krahenbuhl S, Krapf R. Quantification and predictors of plasma volume expansion from mannitol treatment. *Intensive Care Med* 1997;23:1159–1164. [PubMed: 9434922]
25. Phillips EM, Butler T, Baylis PH. Osmoregulation of vasopressin and thirst: comparison of 20% mannitol with 5% saline as osmotic stimulants in healthy man. *Clin Endocrinol (Oxf)* 1994;41:207–212. [PubMed: 7923825]
26. Barry KG, Berman AR. Mannitol infusion. III The acute effect of the intravenous infusion of mannitol on blood and plasma volumes. *N Engl J Med* 1961;264:1085–1088. [PubMed: 13687351]
27. Kurnik BR, Weisberg LS, Askenase AD, Kurnik PB. Mannitol stimulates atrial natriuretic peptide release in humans. *Am J Kidney Dis* 1991;17:62–68. [PubMed: 1824736]

Figure 1.
Relationship between serum sodium levels and osmolality

Table 1Patients with and without rise in serum sodium concentration of ≥ 1 or ≥ 5 mEq/L

Characteristics	Responders (48 hours Δ Na ≥ 1 mEq/L)	Non-responders (48 hours Δ Na < 1 mEq/L)	Responders (48 hours Δ Na ≥ 5 mEq/L)	Non-responders (48 hours Δ Na < 5mEq/L)
Patients	130 (78)	37 (22)	94 (56)	73 (44)
Age (years)	53 $\pm$ 15	51 $\pm$ 14	56 $\pm$ 15	48 $\pm$ 14
Male sex (%)	41	46	39	45
Race (%)				
Caucasian	68	78	66	77
African-American	32	22	36	23
Other	>1	0	1	0
Diagnosis - n (%)				
SAH	30 (23)	9 (24)	22 (23)	17 (23)
Brain tumor	13 (10)	9 (24)	7 (7)	15 (21)
ICH	39 (30)	6 (16)	36 (38)	9 (12)
Ischemia	10 (8)	2 (5)	10 (11)	2 (3)
Infection	5 (4)	2 (5)	2 (2)	5 (7)
Head injury	17 (13)	1 (3)	9 (10)	9 (12)
Other	16 (12)	8 (22)	8 (9)	16 (22)
Admission weight (Kg)	80 $\pm$ 20	81 $\pm$ 22	80 $\pm$ 21	81 $\pm$ 20
Renal function				
BUN (mg/dL)	12 $\pm$ 5	11 $\pm$ 4	12 $\pm$ 6	11 $\pm$ 4
Creatinine (mg/dL)	0.7 $\pm$ 0.2	0.7 $\pm$ 0.2	0.7 $\pm$ 0.2	0.7 $\pm$ 0.2
Baseline sodium (mEq/L)	140 $\pm$ 5	142 $\pm$ 3	140 $\pm$ 5	141 $\pm$ 4
Baseline osmolality (mOsm/Kg)	299 $\pm$ 14	304 $\pm$ 11	302 $\pm$ 14	298 $\pm$ 13
Treatment period with mannitol (days)	5 $\pm$ 3	5 $\pm$ 3	5 $\pm$ 3	5 $\pm$ 3
Total mannitol dose (g/kg)over 48 hrs	7.31 $\pm$ 2.63	5.65 $\pm$ 2.26	7.72 $\pm$ 2.48	5.9 $\pm$ 2.51
Cumulative fluid balance (ml)				
48 hours	-134 $\pm$ 1761	-499 $\pm$ 1458	91 $\pm$ 1653	-610 $\pm$ 1692
72 hours	-111 $\pm$ 2188	-889 $\pm$ 1815	229 $\pm$ 2052	-924 $\pm$ 2061
Sodium Change at 48 hours (mEq/L)	9 $\pm$ 7	-3 $\pm$ 2	12 $\pm$ 6	0 $\pm$ 3
Osmolality change at 48hours (mOsm/Kg)	19 $\pm$ 15	-6 $\pm$ 11	24 $\pm$ 15	2 $\pm$ 11

Data expressed as mean $\pm$ standard deviation or count (%) as appropriate

Table 2

Final multiple regression analysis model to predict lack of osmotic response

	Exp(B)	95% CI for Exp(B)		p value
		Lower	Upper	
Age (years)	1.034	1.008	1.062	.012
Total 48 hr dose/kg	53.357	10.757	264.664	.000
72 hr fluid balance (L)	1.356	1.127	1.632	.001
Constant	.011			.000

Exp (B) = exponent (B); CI = confidence interval