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Effect of a single dose of mannitol on hydration status and electrolyte concentrations in patients with tick-borne encephalitis

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Abstract

Objective: This study was performed to assess the effect of a single dose of 15% mannitol on the hydration status and electrolyte balance in patients with tick-borne encephalitis (TBE).

Methods: Forty-one patients with TBE were treated with 0.25 g/kg of 15% mannitol. The electrolyte concentrations (Na, K, and Cl), creatinine concentration, and hydration status were measured before and after mannitol infusion.

Results: After mannitol administration, 7 patients had hyponatremia, 3 had hypokalemia, 1 had hyperkalemia, and 17 had hypochloremia. The total body water volume (TBW) changed by 0.44% $\pm$ 0.55%, the external body water volume (EBW) changed by 0.12% $\pm$ 0.15%, and the internal body water volume (IBW) changed by 0.19% $\pm$ 0.40%. The mean ECW/ICW ratio was 0.7694 $\pm$ 0.07 before treatment and 0.7699 $\pm$ 0.07 after treatment. Age was correlated with the TBW change in men ($R = 0.42$, $p < 0.05$) and with the potassium change in women ($R = 0.66$, $p < 0.05$).

Conclusions: Patients with TBE should receive mannitol two to four times daily depending on the clinical manifestation. Administration of a single dose of mannitol (0.25 g/kg) requires at least 300 mL of fluid supplementation. Bioimpedance might be useful for individual evaluation of dehydration. Additionally, patients require monitoring for potential hyponatremia. Older men may be more prone to dehydration after receiving mannitol.

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Introduction

Mannitol is a nonreabsorbable sugar alcohol that acts as an osmotic diuretic, inhibiting sodium and water reabsorption in the proximal tubule and more importantly in the loop of Henle.[1] It is administered every 6 to 8 hours at a dosage of 0.25 to 1 g/kg/24 hour. The available solutions are 10%, 15%, and 20%. Effects of mannitol are visible a few minutes after administration, peaking after 1 hour and lasting for 4 to 24 hours.[2,3]

Mannitol is an essential medication in the treatment of increased intracranial pressure (ICP). The effectiveness of mannitol depends on the initial ICP, the dose administered in the previous 3 hours (lower doses are associated with higher effectiveness), and the speed of infusion. Rapid mannitol infusion reduces ICP more effectively; however the effect is of shorter duration. Slower mannitol administration results in less marked decrease in ICP, but the effect lasts longer.[4] Although mannitol is generally well tolerated, a variety of fluid, electrolyte, and renal complications can occur if the patient is not carefully monitored.

Mannitol is freely filtered by the glomerulus and does not undergo tubular reabsorption. Thus, it acts as an osmotic diuretic, increasing urinary loss of both sodium and electrolyte-free water. Lack of replacement of the fluid loss can lead to both volume depletion and severe hypernatremia.[5] Other complications of mannitol therapy are volume expansion, hyponatremia, hyperkalemia, hypokalemia, and metabolic acidosis.[6,7]

The effect of mannitol on the integrity of the blood–brain barrier is controversial. Many authors have reported that mannitol can disrupt the blood–brain barrier and increase its permeability,[8–15] while others have shown that it has no effect on the blood–brain barrier.[16,17]

Mannitol administration requires precise monitoring of patients to prevent water–electrolyte imbalance; however, lower mannitol concentrations provoke fewer adverse reactions. Serum osmolality should be maintained at 300 to 310 mOsm/L, and the patient should be properly hydrated.[4]

Mannitol should not be administered to patients allergic to the substance, severely dehydrated patients, or patients with anuria, advanced heart failure, pulmonary edema, active intracranial hemorrhage (except craniotomy), or a damaged blood–brain barrier.

Impaired kidney function and overdosing may lead to a longer mannitol half-life and therefore increase serum osmolality with transfer of water and potassium to the extracellular area. These changes may lead to hyponatremia, hyperkalemia, metabolic acidosis, and pulmonary edema. Excessive water loss by brain cells may also be life-threatening.[7,18]

Patients receiving 200 to 300 g of mannitol within 24 hour can reportedly develop reversible acute kidney failure.[19,20]

Tick-borne encephalitis (TBE) is a relatively frequent neuroinfection in Poland. Data from the National Health Institute showed that an average of 250 persons develop symptoms of TBE annually.[21] Most cases are registered in the northeastern part of the country, and Podlaskie Region is considered an endemic area for TBE. The Department of Infectious

Diseases and Neuroinfections in Białystok is a reference center and the main unit responsible for the treatment of patients with TBE in this region.

The treatment of TBE is symptomatic and includes administration of mannitol and nonsteroidal anti-inflammatory drugs. Patients with TBE are predisposed to hypovolemic hyponatremia due to dehydration caused by fever, vomiting, poor oral intake, and osmotherapy.[21] Therefore, one of the most important factors in patients' recovery is maintaining a proper electrolyte and fluid balance.

The present study was performed to precisely assess the effect of one dose of 15% mannitol on the hydration status and electrolyte balance of patients with TBE.

Materials and methods

Patients

Patients hospitalized for treatment of TBE in the Department of Infectious Diseases and Neuroinfections of the Medical University of Białystok were included in the study. The study started in 2016 and is planned to continue through 2018. The results of this preliminary study were obtained in 2016. All hospitalized patients with TBE were enrolled in the study. None of the patients had been vaccinated for TBE. The disease was diagnosed based on the clinical presentation, cerebrospinal fluid examination findings, and presence of specific antibodies in serum. The TBE antibody titer was measured with an enzyme-linked immunosorbent assay (Enzygnost Anti-TBE/FSME Virus IgG, IgM; Siemens, Munich, Germany).

TBE was considered mild when no neurological symptoms were present (meningitis form). Meningoencephalitis and meningoencephalomyelitis were considered severe forms of TBE.

Patients were treated with analgesics, anti-inflammatory drugs, and 0.25 g/kg of 15% mannitol per dose. None of the patients received dexamethasone.

Procedures

All patients underwent measurement of their serum electrolyte concentrations (Na, K, and Cl) and creatinine concentration. The first blood sample was taken immediately before the nurse administered the first intravenous dose of 15% mannitol (0.25 g/kg). The second blood sample was taken 1 hour after mannitol infusion.

The reference ranges for the measured parameters were as follows: Na, 136 to 145 mmol/L; K, 3.5 to 5.1 mmol/L; Cl, 98 to 107 mmol/L; and creatinine, 0.5 to 0.9 mg/dL for women and 0.7 to 1.2 mg/dL for men. The patients' hydration status was measured before and 1 hour after mannitol infusion by whole-body bioelectrical impedance with multiple-frequency equipment (QuadScan 4000; BodyStat, Douglas, Isle of Man, British Isles). The analyzed parameters were the total body water volume (TBW) in liters and percent of body mass, internal body water volume (IBW) in liters and percent of body mass, external body water volume (EBW) in liters and percent of body mass, and third-space body water.

All measurements were performed by qualified personnel according to the previously reported tetrapolar method.[22] The subject was fasting, had no metallic objects, had not exercised or entered a sauna for 8 hours before the study, and had consumed no alcohol within the previous 12 hours.

Throughout the examinations, all of the subjects had their arms and legs in abduction; a towel or pillow was placed between the legs of obese subjects to avoid contact between the thighs. The impedance values were obtained at frequencies of 5, 50, 100, and 200 kHz. Using a frequency of 50 kHz,

we obtained the resistance (R50), reactance (Xc50), and phase angle using BodyStat Phase Angle software (version 1.0, 2002). The frequency selected is a standard for bioelectrical impedance vector analysis. Additionally, we obtained the total impedance index, which is a body water distribution indicator, by dividing the 200-kHz frequency by the 5-kHz (Z200/Z5) frequency. The TBW and EBW were obtained using prediction equations.[23]

Ethics statements

Patients voluntarily agreed to participate in the study and gave their written informed consent upon admission to the hospital. The study was registered in ISRCTN Registry under the number ISRCTN48274252 (DOI 10.1186/ISRCTN48274252). The study was approved by the Ethics Committee of the Medical University of Bialystok.

Statistical analysis

The results were statistically analyzed using Statistica 10 (TIBCO Software, Palo Alto, CA, USA). The Wilcoxon signed rank test was used for the group analysis. Correlations were measured using Spearman's test.

Results

Forty-one patients (17 women, 24 men; age, 19–73 years; mean, 41.28±15.76 years) were included in this study. The changes in the patients' hydration status and electrolyte balance after mannitol administration are presented in Table 1. The initial examination on admission revealed dehydration in 19 patients, mild hyponatremia in 2, hypochloremia in 12, and hypokalemia in 3. After mannitol administration, 7 patients had hyponatremia [1 had moderate hyponatremia (125 mmol/L), 3 had hypokalemia, 1 had hyperkalemia, and 17 had hypochloremia]. The mean changes in the sodium, potassium, and chloride concentrations

Table 1. Water and electrolyte balance before and after mannitol administration

	All patients (n=41)			Women (n=17)			Men (n=24)		
	Before mannitol	After mannitol	p	Before mannitol	After mannitol	p	Before mannitol	After mannitol	p
Na (mmol/L)	139.37 ± 3.00	136.68 ± 3.90	0.0002	140.29 ± 3.29	137.77 ± 3.72	0.01	138.83 ± 2.75	135.89 ± 3.94	0.004
K (mmol/L)	4.34 ± 0.43	4.33 ± 0.56	ns	4.07 ± 0.40	4.13 ± 0.67	ns	4.48 ± 0.37	4.48 ± 0.44	ns
Cl (mmol/L)	101.89 ± 6.39	98.26 ± 4.10	0.0001	103.18 ± 5.02	100.00 ± 4.02	0.02	101.32 ± 6.93	97.00 ± 3.77	0.004
Creatinine (mg/dL)	0.89 ± 0.24	0.86 ± 0.24	ns	0.68 ± 0.09	0.66 ± 0.06	ns	0.99 ± 0.23	0.99 ± 0.22	ns
TBW (L)	41.32 ± 6.84	40.97 ± 6.66	0.0001	33.72 ± 3.94	33.50 ± 3.95	0.007	45.12 ± 4.31	44.70 ± 4.06	0.0002
TBW%	52.57 ± 5.33	52.14 ± 5.28	0.0001	47.50 ± 4.26	47.18 ± 4.10	0.007	55.11 ± 3.81	54.62 ± 3.89	0.0002
ECW (L)	18.90 ± 2.80	18.78 ± 2.76	0.0001	17.95 ± 3.56	17.85 ± 3.52	0.02	19.38 ± 2.26	19.24 ± 2.23	0.001
ECW%	21.87 ± 2.91	21.72 ± 2.88	0.0001	20.28 ± 3.75	20.15 ± 3.71	0.02	22.67 ± 2.03	22.50 ± 2.08	0.001
ICW (L)	24.82 ± 4.53	24.63 ± 4.43	0.0001	20.95 ± 4.25	20.82 ± 4.16	0.01	26.75 ± 3.29	26.54 ± 3.19	0.003
ICW%	28.61 ± 4.86	28.40 ± 4.81	0.0001	23.63 ± 4.19	23.51 ± 4.23	0.01	31.20 ± 2.69	30.95 ± 2.64	0.003

Data are presented as mean ± standard deviation.
TBW, total body water; ECW, extracellular water; ICW, intracellular water; ns, not significant.

were -2.50 ± 3.62, 0.02 ± 0.40, and -1.86 ± 2.42 mmol/L, respectively.

One hour after mannitol administration, the TBW changed by $0.44\% \pm 0.55\%$ (353 ± 488 mL) (range, 0–2500 mL), the EBW changed by $0.12\% \pm 0.15\%$ (151 ± 168 mL) (range, 0–500 mL), and the IBW changed by $0.19\% \pm 0.40\%$ (205 ± 447 mL) (range, 0–2300 mL).

The mean ECW/ICW ratio was 0.7694 ± 0.07 before mannitol treatment and 0.7699 ± 0.07 at 1 hour after mannitol treatment. The change was not statistically significant.

With respect to disease severity, no significant differences were observed in the patients' electrolyte or water balance after mannitol administration.

In men, age was correlated with the change in TBW ($R = 0.42$, $p < 0.05$), while in women, age was correlated with the change in potassium ($R = 0.66$, $p < 0.05$). To confirm these correlations, we divided the patients into two age groups: 18 to 50 and >50 years old. Comparison of these groups confirmed a significant difference in men (mean change in TBW in younger vs. older patients was $0.07\% \pm 0.12\%$ vs. $0.84\% \pm 0.76\%$, respectively; $p < 0.05$), while in women, the difference in the change in potassium between the age groups was not statistically significant.

Discussion

Dehydration and electrolyte imbalance are disorders commonly observed in the course of viral encephalitis and may exacerbate the already serious condition of the patient. They are usually caused by fever, poor oral fluid intake, or syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, these disorders might also be drug-induced.[21]

Mannitol is frequently used to decrease ICP and is administered as a standard symptomatic treatment for neuroinfections.[2] The adverse effects of mannitol are well known; however, little data are available concerning the actual impact of a single dose of mannitol on patients' hydration status and electrolyte balance.[1,5–7] The present study has shown that a single dose of 15% mannitol (0.25 g/kg) decreases the sodium and chloride concentrations in serum by 2.4 and 1.5 mmol/dL, respectively. Moreover, it decreases the TBW by approximately 300 mL.

Seo and Oh[24] observed hypernatremia in 10% of their study subjects on the first day of mannitol administration and in 10% to 21% of subjects throughout the 7-day mannitol administration period.

In the present study, hyponatremia was observed in 12.2% of our subjects on the first day of mannitol administration and in 9% to 24% of subjects throughout the 7-day period. In addition, no significant differences were found between changes in the rates of hypernatremia and hyponatremia throughout the 7-day administration period. The most notable finding was the high rate of hypokalemia observed during mannitol administration. Hypokalemia was observed in 22.0% of subjects on the first day and continuously increased to 52.3%, and this increase was significant.[24]

Although the adverse effects of mannitol are usually mild, proper monitoring and fluid/electrolyte supplementation may be of high importance in already dehydrated patients because dehydration and dyselectrolytemia may deteriorate the patients' clinical state.[21]

The hydration status is difficult to measure in clinical practice. Several symptom-based methods are used in everyday practice, such as measurement of the mucosal dryness, capillary return delay, urine output, central venous pressure, It is also possible to precisely measure patients' hydration status with bioimpedance using modern equipment, which may be useful in routine clinical practice.[25]

From the results of our study, we conclude that patients treated with standard doses of mannitol (0.25 g/kg two to four times a day) need supplementation of at least 300 mL of fluids per dose of mannitol and should be carefully monitored for hyponatremia and hypokalemia. This is a very important issue in patients with meningitis or encephalitis who are additionally dehydrated due to their disease.

In the present study, the influence of mannitol did not depend on the severity of the disease. However, patients with the severe form of TBE are more prone to develop hyponatremia due to SIADH; therefore, mannitol should be administered with particular care in this group.[21] For the purpose of this study, we chose a homogenous group of patients with TBE; nevertheless, the results might be able to be extrapolated to other patients with viral meningitis treated with mannitol. In the future, we plan to compare patients with TBE with different groups of patients to assess whether the response to mannitol differs depending on the etiological factor.

The main limitation of our study was the small group of examined patients; therefore, further studies are planned. The strongest and most innovative point of our study is the use of modern bioimpedance technology for adequate measurement of the effect of mannitol on patients' hydration status, including the intracellular and extracellular water volume. Such technology enables precise monitoring and maintenance of the patient's water balance. The results of our study were repeatable, which allows us to predict that hydration evaluation based on bioimpedance may be of use in routine clinical practice.

Conclusions

Patients with TBE should receive mannitol two to four times a day depending on their clinical presentation. Administration of a single dose of mannitol (0.25 g/kg) requires at least 300 mL of fluid supplementation. Bioimpedance might be useful for evaluation of dehydration in individual patients. Patients also require monitoring for potential hyponatremia. Finally, men of advanced age may be more prone to dehydration after mannitol treatment.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Seely JF and Dirks JH. Micropuncture study of hypertonic mannitol diuresis in the proximal and distal tubule of the dog kidney. *J Clin Invest* 1969; 48: 2330–2340.
2. Dennis LJ and Mayer SA. Diagnosis and management of increased intracranial pressure. *Neurol India* 2001; 49(Suppl 1): S37–S50.
3. Jafar JJ, Johns LM and Mullan SF. The effect of mannitol on cerebral blood flow. *J Neurosurg* 1986; 64: 754–759.
4. Tiroumourougane SV, Raghava P and Srinivasan S. Japanese viral encephalitis. *Postgrad Med J* 2002; 78: 205–215.
5. Gipstein RM and Boyle JD. Hypernatremia complicating prolonged mannitol diuresis. *N Engl J Med* 1965; 272: 1116–1117.
6. Fanous AA, Tick RC, Gu EY, et al. Life-threatening mannitol-induced hyperkalemia in neurosurgical patients. *World Neurosurg* 2016; 91: 672.e5–672.e9.
7. Manninen PH, Lam AM, Gelb AW, et al. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. *Can J Anaesth* 1987; 34: 442–446.
8. Louboutin JP, Chekmasova AA, Marusich E, et al. Efficient CNS gene delivery by

intravenous injection. *Nat Methods* 2010; 7: 905–907.
9. Weidman EK, Foley CP, Kallas O, et al. Evaluating permeability surface-area product as a measure of blood-brain barrier permeability in a murine model. *Am J Neuroradiol* 2016; 37: 1267–1274.
10. Okuma Y, Wang F, Toyoshima A, et al. Mannitol enhances therapeutic effects of intra-arterial transplantation of mesenchymal stem cells into the brain after traumatic brain injury. *Neurosci Lett* 2013; 554: 156–161.
11. Gonzales-Portillo GS, Sanberg PR, Franzblau M, et al. Mannitol-enhanced delivery of stem cells and their growth factors across the blood-brain barrier. *Cell Transplant* 2014; 23: 531–539.
12. Youn SW, Jung KH, Chu K, Lee JY, et al. Feasibility and safety of intra-arterial pericyte progenitor cell delivery following mannitol-induced transient blood-brain barrier opening in a canine model. *Cell Transplant* 2015; 24: 1469–1479.
13. Foley CP, Rubin DG, Santillan A, et al. Intra-arterial delivery of AAV vectors to the mouse brain after Mannitol mediated blood brain barrier disruption. *J Control Release* 2014; 196: 71–78.
14. Doolittle ND, Muldoon LL, Culp AY, et al. Delivery of chemotherapeutics across the blood-brain barrier: challenges and advances. *Adv Pharmacol* 2014; 71: 203–243.
15. Tajiri N, Lee JY, Acosta S, et al. Breaking the blood-brain barrier with mannitol to aid stem cell therapeutics in the chronic stroke brain. *Cell Transplant* 2016; 25: 1453–1460.
16. Chen KB, Wei VC, Yen LF, et al. Intravenous mannitol does not increase blood-brain barrier permeability to inert dyes in the adult rat forebrain. *Neuroreport* 2013; 24: 303–307.
17. Brown RC, Egleton RD and Davis TP. Mannitol opening of the blood-brain barrier: regional variation in the permeability of sucrose, but not 86Rb+ or albumin. *Brain Res* 2004; 1014: 221–227.
18. Oster JR and Singer I. Hyponatremia, hyposmolality, and hypotonicity: tables and fables. *Arch Intern Med* 1999; 159: 333–336.
19. Better OS, Rubinstein I, Winaver JM, et al. Mannitol therapy revisited (1940–1997). *Kidney Int* 1997; 52: 886–894.
20. Dickenmann M, Oettl T and Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. *Am J Kidney Dis* 2008; 51: 491–503.
21. Czupryna P, Moniuszko A, Garkowski A, et al. Comparison of hyponatremia and SIADH frequency in patients with tick borne encephalitis and meningitis of other origin. *Scand J Clin Lab Invest* 2016; 76: 159–164.
22. Lukaski HC, Bolonchuk WW, Hall CB, et al. Validation of tetrapolar bioelectrical impedance method to assess human body composition. *J Appl Physiol (1985)* 1986; 60: 1327–1332.
23. Castillo-Martínez L, Santillan-Díaz C, Orea-Tejeda A, et al. Body composition changes assessed by bioelectrical impedance and their associations with functional class deterioration in stable heart failure patients. *Nutr Hosp* 2016; 33: 623–628.
24. Seo W and Oh H. Alterations in serum osmolality, sodium, and potassium levels after repeated Mannitol administration. *J Neurosci Nurs* 2010; 42: 201–207.
25. Bak A, Tsiami A and Greene C. Methods of assessment of hydration status and their usefulness in detecting dehydration in the elderly. *Curr Res Nutr Food Sci* 2017; 5: 43–54.