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Case Report

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Mannitol-induced acute renal failure

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Abstract. A 62-year-old man was admitted to the ophthalmologic department for operation of retinal detachment. Mannitol and acetazolamide were prescribed to reduce intraocular pressure. Seven days after operation, gradual onset of drowsy consciousness occurred. The laboratory findings of hypertonic hyponatremia (109 mEq/l), hyperosmolality (341 mosm/kg), metabolic acidosis (pH: 7.17) and acute renal failure (serum creatinine: 8.2 mg/dl) dictated a diagnosis of mannitol-induced acute kidney injury. First, 3% saline was given, but consciousness kept deteriorated with worsened dyspnea and metabolic acidosis. Hemodialysis was then performed subsequently and his consciousness and renal function completely recovered. A special emphasis on the treatment of hypertonic hyponatremia was given.

Introduction

Mannitol is widely used to reduce intraocular pressure and intracranial pressure. Mannitol-induced acute renal failure with hypertonic hyponatremia is rare in clinical practice. The risk factors are multiple and may include overdose of mannitol, preexisting renal function impairment and concomitant nephrotoxic medication. Although the diagnosis is easy and straightforward, delay of diagnosis is not uncommon because it usually presents in a non-oliguric form at the beginning. We present a case of mannitol-induced acute renal failure with special emphasis on the decision making of treatment.

Case report

A 62-year-old man was admitted to hospital for operation of retinal detachment. He had been well except for gout for 10 years. He took analgetics for gout attack intermittently.

Approximately 40 days before the current admission, the patient had ocular trauma by a high-speed iron particle into his left eye which resulted in blurred vision and some bleeding. Slip lamp examination revealed corneal and iris perforation at lower portion, with some exudate in the anterior chamber, OS (oculus sinister). At that time, the blood urea nitrogen (BUN) concentration was 29 mg/dl and serum creatinine (SCr) concentration was 1.5 mg/dl. Emergency operation for removal of foreign body was performed and he was discharged 1 week later. At follow-up 1 week after discharge, retinal detachment was found over lower portion, OS. So he was admitted again for operation of retinal detachment. Subsequently, increased intraocular pressure (IOP) of 50 mmHg of the left eye was found. Mannitol (20%) was prescribed for increased IOP. The dosage was 300 c.c. on Day 1, 400 c.c. on Day 2, and 300 c.c. twice a day from Day 3 – Day 8 (equal to 60 g on Day 1, 80 g on Day 2, and 120 g from Day 3 to Day 8). Despite the treatment with mannitol for 2 days, the IOP was still high hence acetazolamide (250 mg) 4 times a day was added.

Unfortunately, gradual onset of lethargy took place on post-op Day 5. Disorientation, decreased urine output and dyspnea developed in the following 3 days. Then, on the post-op Day 7, on examination, vital signs were stable as follows: mild hypertension (151/78 mmHg) with normal sinus rhythm (60/min), but tachypnea (25/min). Poor skin turgor and dry oral mucous membranes were detected at bedside. Consciousness was lethargic but still arousable. Neurological examination revealed no decreased muscle power and there was no Babinski sign. Laboratory data revealed normal hemogram, liver function, lipid profile and there was no hypoglycemia (156 mg/dl). However, there

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Table 1. Serial changes of biochemistry, blood gas and osmolality.

Post-op day	Na (meq/l)	K (meq/l)	BUN (mg/dl)	Cr (mg/dl)	VU (ml/day)	Glu (mg/dl)	pH	HCO_3^- (meq/l)	Osm_c* (mosm/kg)	Osm_m^+ (mosm/kg)	Osmolal gap (mosm/kg)	Tonicity#
–8	140	4.6	32	1.5	NA	NA	NA	NA	NA	NA	NA	NA
7	109	4.8	88	8.2	NA	156	7.17	14.1	258	341	83	309
7	107	5.6	92	9.1	350	118	7.214	9.7	253.4	348	94.6	315
Hemodialysis at 23:00												
8**	128	3.2	42	NA	3550	90	NA	NA	NA	306	NA	291
8	121	4.5	70	7.3		100	7.284	15.1	272	324	52	299
Hemodialysis												
9	139	3.2	43	3.0	2950	135	7.373	22.3	301	308	7	292
10	140	3.5	40	2.1	3250	109	NA	NA	300	300	0	285
11	137	3.4	33	1.7	2580	NA	NA	NA	NA	NA	NA	NA

*calculated osmolality = 2Na + glucose/18 + BUN/2.8 (unit = glucose = mg/dl, BUN = mg/dl).**immediate following hemodialysis. NA = not available; VU = daily urine volume; +measured osmolality; #effective osmolality (Osmm-osmolality of urea).

were poor renal function (BUN/Cr = 88/8.2 mg/dl), hyponatremia (109 mEq/l), hypochloremia (80 mEq/l), and high anion gap metabolic acidosis (pH = 7.170, HCO_3^- = 14.1, anion gap = 14.9 mEq/l). Abdominal sonography revealed no hydronephrosis or distention of urinary bladder. Blood osmolality was 341 mosm/kg with an osmolal gap of 83 mosm/kg. Potential nephrotoxic drugs such as NSAID or aminoglycoside were not used. The clinical manifestation and laboratory findings of hypertonic hyponatremia, metabolic acidosis, hyperosmolality, elevated osmolal gap and acute renal failure dictated a diagnosis of mannitol-induced acute kidney injury. Mannitol and acetazolamide were discontinued and 3% saline was given at a rate of 12 ml/h for 5 hours. But the consciousness kept deteriorated with worsened dyspnea and metabolic acidosis (HCO_3^- = 7.214) while hyponatremia (107 mEq/l) and hyperosmolarity (348 mosm/kg) persisted. Hemodialysis was performed subsequently. The sodium concentration was set at 135 mEq/l and no ultrafiltration of water was performed in order to avoid possible change of hemodynamics. After 2 hours of hemodialysis, laboratory data showed less hyponatremia (128 mEq/l) and less hyperosmolality (306 mosm/l). The daily urine output increased from 350 c.c. to 3,550 c.c. on the next day without using diuretics. His consciousness completely recovered after the 2nd hemodialysis. Laboratory data on the 10th hospital day revealed a significantly improved renal function (BUN = 40 mg/dl, Cr = 1.7 mg/dl) and the osmolal gap was 0. There was no neurological deficit at last follow-up (4 days after discharge). The serial laboratory data is summarized on Table 1.

Discussion

Mannitol is metabolically inert and mostly excreted by the kidney [1] with only about 7% reabsorption over the renal tubule [2]. Being an extracellular solute with an osmotic effect, mannitol is widely used to reduce intracranial pressure and intraocular pressure (IOP). Half life is 1.2 hours in individuals with normal renal function, but may extend to 36 hours in uremia, although it is dialyzable by hemodialysis [3]. Routine use of mannitol in ophthalmology rarely causes complications. However, anecdotal cases with mannitol-induced acute renal injury are still being reported in the literature. For the reported case, at least three risk factors can be identified. Firstly, the accumulative dose of mannitol was 1,220 gm which is well above the recommended dose (below 750 – 1,000 gm) [4]. Secondly, the concomitant use of acetazolamide which pos-

sesses a diuretic effect may have exaggerated dehydration. The pathogenetic mechanisms of mannitol-associated acute kidney injury involve dehydration, tubuloglomerular feedback, osmotic injury and vasoconstriction [5]. At a serum concentration of higher than 1,000 mg/dl, mannitol has a vasoconstrictive effect [5]. Although we did not measure serum mannitol concentration, we still can predict the concentration by using the following formula proposed by Dorman et al. [6]:

Concentration of mannitol = osmolal gap × 182/10

where the osmolal gap is the difference between calculated and measured osmolality and 182 is the molecular weight of mannitol.

Initially, the osmolal gap was 83 mosm/kg, correspondent to a concentration of mannitol of 1,510 mg/dl. Hence, a prominent vasoconstrictive effect can be anticipated. This might have compromised renal perfusion which was further exaggerated by the concomitant use of mannitol and acetazolamide; both agents might have caused dehydration through their diuretic effect. Finally, our patient had a baseline serum creatinine of 1.5 mg/dl, implying a preexisting chronic kidney disease, probably Stage 3. Patients with renal impairment, old age and concomitant use of nephrotoxic agents have been proposed as risk factors for mannitol-induced acute renal failure. So patients should be screened for renal function before mannitol being considered. The prompt diuretic response to hemodialysis implies rapid reversal of the vasoconstrictive effect when mannitol was removed from the serum. Thus, mannitol-related acute renal injury is most likely induced through renal hemodynamic alteration instead of mechanical problems as suggested by Dorman et al. [6]. As for hyponatremia (109 mEq/l) in our patient, the most likely cause is "pseudohyponatremia" similar to what is seen in patients with marked hyperglycemia. Based on a similar molecular weight of these two components (182 for mannitol and 180 for glucose), it has been suggested that for each rise of 100 mg/dl of mannitol concentration, serum sodium will fall by 1.6 mmol/l [5]. With a mannitol concentration of 1,510 mg/dl calculated before, we can obtain a theoretical serum sodium concentration of 111 mEq/l by the following equation:

135 – (1,510/100) × 1.6

which is very close to the measured concentration of sodium (109 mEq/l on post-op Day 7).

The initial prescription of 3% saline intravenous infusion was a wrong decision because it made hyperosmolality even more severe. Clinically, this was associated with deteriorated consciousness, worsened dyspnea and metabolic acidosis. The lesson one may learn from this case is that hypertonic saline should not be used in a case with severe hyponatremia and drowsy consciousness without obtaining a serum osmolality first.

Rapid correction of hyponatremia after one session of hemodialysis (107 mEq/l raised to 128 mEq/l) (Table 1) in our case may elicit the concern of central pontine myelinolysis (CPM). The pathogenesis of CPM is unknown but one of the hypotheses is the osmotic hypothesis by which cells conditioned to a hypoosmotic hyponatremia may have a reduced adaptive capacity to osmotic stress [7] which involves a persistent shrinkage of cells induced by hypertonic stress [8]. In our case, it is hyperosmolal state which may have rendered brain cells "shrinked". With correction of hyperosmolality following hemodialysis, free water may shift into brain cells, a direction that is opposite to what happens in CPM, but similar to what takes place in patients with dialysis-disequilibrium syndrome (DDS). Thus, CPM probably did not occur in our case, but DDS should be a real concern. Fortunately, the patient regained consciousness rapidly without any neurological sequelae. The prominent diuresis following hemodialysis might have partially eliminated the detrimental effect of DDS in our patient. Because of complexity of osmotic and electrolyte change, rapid correction should be avoided and frequent monitoring must be done. Initial duration of dialysis should not exceed 2 hours and the next hemodialysis probably should be done on the next day or a minimum of 12 hours later.

In conclusion, we have described a case of mannitol-induced acute renal failure, with special emphasis on the decision-making for the treatment of hypertonic hyponatremia. Although effective in removing mannitol and reversal of acute renal failure with hemodialysis, DDS is still a matter of concern and warrants further study to prove its safety.

References

[1] *Smith WW, Finkelstein N, Smith HW.* Renal excretion of hexitols and their derivatives and of endogenous creatinine-like chromogen in dog and man. J Biol Chem. 1940; *135:* 231-250.

[2] *Rabetoy GM, Fredricks MR, Hostettler CF.* Where the kidney is concerned, how much mannitol is too much. Ann Pharmacother. 1993; *27:* 25-28.

[3] *Borges HF, Hocks J, Kjellstrand CM.* Mannitol intoxication in patients with renal failure. Arch Intern Med. 1982; *142:* 63-66.

[4] *Better OS, Rubinstein I, Winaver JM, Knochel JP.* Mannitol therapy revisited (1940 – 1997). Kidney Int. 1997; *52:* 886.

[5] *Gadallah MF, Lynn M, Work J.* Case report: Mannitol nephrotoxicity syndrome: Role of hemodialyis and postulate of mechanisms. Am J Med Sci. 1995; *309:* 219-222.

[6] *Dorman HR, Sodheimer JH, Cadnapaphornchai P.* Mannitol induced acute renal failure. Medicine (Baltimore). 1990; *69:* 153-159.

[7] *Laureno R, Karp BI.* Myelinolysis after correction of hyponatremia. Ann Intern Med. 1997; *126:* 57-62.

[8] *Martin RJ.* Central pontine and extra-pontine myelinolysis: the osmotic demyelination syndromes. Neurol Neurosurg Psychiatry. 2004; *75:* 22-28.