MANNITOL INDUCED ACUTE KIDNEY INJURY DURING TREATMENT OF CEREBRAL EDEMA DUE TO DIABETIC KETOACIDOSIS IN AN ADOLESCENT

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ABSTRACT

Mannitol-induced acute renal injury is a rare condition. We have described an adolescent case of mannitol-induced acute kidney injury during treatment of cerebral edema associated with diabetic ketoacidosis. According to our knowledge, this is the first case in the pediatric age group. A 16-year-old girl with type one diabetes mellitus was admitted to the hospital with diabetic ketoacidosis. During the second hour of the 0.9% normal saline treatment, loss of consciousness occurred. After two hours of mannitol administration, acute renal injury was developed. Renal function improved over 6 days by hemodialysis. Although effective reversal of acute kidney injury with hemodialysis, the clinical awareness of mannitol nephrotoxicity is emphasized in patient with normal renal function.

Keywords: *Diabetic ketoacidosis, cerebral edema, mannitol, acute kidney injury, children* ***Nobel Med 2015; 11(2): 93-96***

ADÖLESAN BİR OLGUDA DİABETİK KETOASİDOZA BAĞLI SEREBRAL ÖDEM TEDAVİSİ SIRASINDA MANNİTOLE BAĞLI AKUT BÖBREK HASARI

ÖZET

Mannitole bağlı akut böbrek hasarı nadir bir durumdur. Diabetik ketoasidozla ilişkili serebral ödem tedavisi sırasında mannitole bağlı akut böbrek hasarı gelişen bir adölesan olgu anlattık. Bilgilerimize göre bu, pediatrik yaş grubundaki ilk olgudur. Tip 1 diabetes mellitus tanılı 16 yaşındaki kız hasta diabetik ketoasidoz tanısı ile hastanemize başvurmuştur. Serum fizyolojik tedavisinin ikinci saatinde bilinç kaybı gelişmiştir. Mannitol uygulamasından 2 saat sonra akut böbrek yetmezliği meydana gelmiştir. Hemodiyalizle renal fonksiyonlar 6 günde düzelmiştir.Hemodiyalizle akut böbrek hasarının etkin geri dönüşü sağlanabilirse de, normal renal fonksiyonlu bir hastada mannitol nefrotoksisitesinin klinik farkındalığı vurgulanmıştır.

Anahtar kelimeler: Diabetik ketoasidoz, serebral ödem, mannitol, akut böbrek hasarı, çocuk **Nobel Med 2015; 11(2): 93-96**

INTRODUCTION

The most feared complication of diabetic ketoacidosis (DKA) is cerebral edema, with symptomatic cerebral edema occurring in 0.55 to 1% of pediatric DKA episodes, associated with mortality in 21% to 24% of cases. In addition, 5% to 26 of survivors is left with permanent neurological damage. Treatment of increased intracranial pressure from cerebral edema has traditionally been hyperosmolar therapy with mannitol.[1]

We have described an adolescent case of standard dose mannitol-induced acute kidney injury (AKI) during treatment of cerebral edema associated with DKA with special emphasis on mannitol nephrotoxicity.

CASE

A 16-year-old girl was admitted to the hospital with vomiting, abdominal pain and restlessness. She had been treated with insulin therapy for diabetes mellitus for eight years. Approximately seven days before admission she hadn't administer the insulin doses regularly because of the non-compliance of the treatment. On physical examination the patient exhibited restlessness. Her Glasgow Coma Scale (GCS) score was 14. Vital signs were as follows: blood pressure, 130/80 mmHg; pulse 130 beats per minute; respiratory rate 38 breaths per minute with Kussmaul breathing pattern; temperature, 36.2°C; and oxyhemoglobin saturation 95% on room air. At that time serum sodium (133 mEq/L), (corrected sodium 142 mEq/L) potassium (5.3 mEq/L), urea (26 mg/dl) and creatinin (0.88 mg/dl) are in normal range. The laboratory findings of hyperglycemia (592 mg/dl), metabolic acidosis (pH: 7.1, HCO_3: 8.8 mEq/L, pCO_2: 17.1 mmHg) and ketonemia (7.9 mmol/l) supported a diagnosis of diabetic ketoacidosis.

First, 0.9% normal saline was given intravenously at 10 cc/kg/dose in an hour after then deficit and maintenance therapy was applied according to the ISPAD Clinical Consensus Guidelines of DKA management.[2] According to this guideline clinical estimates of the volume deficit should be based on the severity of the diabetic ketoacidosis. Therefore the patient had moderate volume deficit. The total amount of 3000 cc/m^2 fluid was planned to give over 24 hours. At the same time insulin infusion has been started at 0.1 U/kg/dose. For first four hour, 0.9% normal saline was planned to give. During the second hour of the treatment, enuresis and loss of consciousness occurred. At that time the GCS score was three points. Bilateral pupils were reactive. Cerebral edema was diagnosed clinically.[2] Then the rate of fluid administration was reduced by one-third and mannitol was given at 1 g/kg dose (70 gr). After two hours of mannitol administration, serum creatinine begun to increase and her mental status did not improve. Therefore she received 3% saline boluses for a total of 6 ml/kg. But the consciousness kept deteriorated with worsened metabolic acidosis (pH=6.87). After 18 hours from unconsciousness her urine output decreased and generalized edema developed. Meanwhile, serum creatinine was 3.3 mg/dl and blood pressure, serum albumin and hemoglobin were in normal levels. Hemodialysis was performed subsequently for hypervolemia due to oliguric acute kidney injury. Laboratory data revealed normal hemogram and liver function. However there were hyperglycemia (756 mg/dl), poor renal function (urea/creatinin:29/1.35 mg/dl), high anion gap metabolic acidosis (pH: 6.87 HCO_3-: 3.3 mEq/L, pCO_2: 11.9 mmHg, anion gap 15 mEq/L) despite of reduced blood beta-hydroxybutyrate (2.2 mmol/L). Abdominal sonography revealed no hydronephrosis or distention urinary bladder. Mannitol was not repeated. At 2 days of dialysis, her consciousness started to recover and she had less hyperosmolality. After three hemodialysis sessions, her consciousness was recovered completely and she has started to diuresis (Table 1). On the fourth hospital day renal failure begun to resolve as indicated by the changes in urine output and serum creatinine. The daily urine output increased from 240 cc to 2000 cc on the next day without using diuretics. At discharge, the serum creatinine concentration had declined to 0.99 mg/dl and there was no neurological deficit at last follows up three months.

DISCUSSION

We describe here the successful management of the mannitol induced AKI during treatment of cerebral edema due to DKA in an adolescent. This is the first reported case of adolescent.

In diabetic ketoacidosis, cerebral edema is probably resulting of number factors, which are dehydration, acidosis, hyperglycemia and low carbon dioxide levels. Together with these factors lead to decreased blood flow to parts of the brain, which then swells up once fluid replacement has been commenced.[3] It was shown that DKA is associated with systemic inflammation affecting the functional status of cerebrovascular endothelial cells that line the luminal surface of the blood brain barrier. Cerebrovascular endothelial cells dysfunction might translate to blood brain barrier disruption at the level of intercellular junctions, thereby allowing fluid to freely pass into the brain parenchyma.[4] The swelling of brain tissue leads to raise intracranial pressure ultimately

leading to death. However there are relatively few therapeutic measures that are recommended for the treatment of these children. Hyperventilation should be avoided as it worsens ischemia and is associated with worsened outcome.[5] Mannitol and hypertonic saline have favorable neurologic effects that improve cerebral blood flow as well as osmotic effects that reduce cerebral edema.[2]

First we have reduced the fluid rate, after then we have given mannitol over 20 minutes. Because there was no initial response in 2 hours, we have used hypertonic saline for a second line of therapy. However consciousness has not improved. Furthermore oliguric AKI developed and hemodialysis was performed subsequently. Potential nephrotoxic drugs such as non-steroid anti-inflammatory drugs or aminoglycosides were not used. The all-clinical findings of hypertonicity, high anion gap metabolic acidosis and oliguric acute kidney failure showed a diagnosis of mannitol-induced AKI. We think that brain edema in our patient was treated with hypertonic saline. However metabolic acidosis due to acute renal failure could delay the recovery of unconsciousness.

Mannitol has been used for the prevention of AKI because of its potentially renal protective effects: removal of obstructing tubular casts, dilution of nephrotoxic substances in the tubular fluid, and reduction in the swelling of tubular elements via osmotic extraction of water.[6] On the other hand, potential nephrotoxicity of mannitol raised clinician's concerns. Mannitol seems to have both nephrotoxic and nephron-protective effects. Considering this, it has been proposed that a low dose of mannitol acts as renal vasodilator while high-dose as renal vasoconstrictor.[7,8] However, in children, there is no data on exact dose for nephrotoxicity.

The reported risk factors are larger cumulative doses, factors that increase serum creatinine levels such as old age and chronic renal insufficiency, the concomitant use of acetazolamide and furosemide.[9-11] The accumulated reported total dose of mannitol that precipitated acute kidney failure in patient with normal baseline renal function was 1220 gr.[12] Mannitol may induce extensive isometric renal proximal tubular vacuolization, intense afferent arteriolar constriction and acute renal failure in higher doses.[13] In our patient the prompt diuretic response to hemodialysis implies rapid reversal of the vasoconstrictive effect when mannitol was removed from serum.

The most widely accepted explanation for lesions in mannitol induced nephropathy is the "pinocytosis theory".[14] Mannitol and similar solutes can enter tubular cells via pinocytosis, form vacuoles that subsequently fuse with lysosomes containing hydrolytic enzymes. It is at this level where lysosomal degradation and digestion can get impaired in diseases like diabetes mellitus and chronic kidney diseases that predisposes to mannitol induced nephropathy. While earlier and mild vacuolar changes are reversible, more overt damage can result in permanent injury to the renal tubules.[14,15] Therefore, diabetes mellitus which was the major pathology in our patient might be caused mannitol-induced nephrotoxicity.

Table 1. Laboratory parameters

Time (hour)	Na (mEq/l)	K (mEq/l)	Urea (mg/dl)	Cr (mg/dl)	pH	HCO_3 (mEq/l)	pCO_2 (mmHg)	Glu (mg/dl)	UO ml/hour
Application	133	5.3	26	0.88	7.1	8.8	17.1	592	
2nd *	-	-	-	-	7.0	3.3	12.9	718	400
4th **	134	5.5	29	1.35	6.87	3.3	11.9	756	175
10th	161	5.5	34	2.05	7.23	5.8	14.2	184	80
20th ***	155	5.3	52	3.3	7.12	7.9	24.6	377	26
24th	146	3.5	43	2.66	7.36	9.1	16.2	328	10
48th	135	3.5	-	1.95	7.51	19.1	19.2	152	20
96th	136	5.3	21	1.55	7.46	20	22	167	85

Na: Sodium, **K:** potassium, **Cr:** creatinine, **Glu:** glucose, **UO:** urine output,
*: loss of consciousness, after then mannitol infusion, **: mental status did not improve and 3% saline boluses, ***: Hemodialysis (HD) was started

In a systematic review and meta-analysis in high-risk patients whom undergo cardiovascular surgery, renal transplant and use nephrotoxic agent, it was demonstrated that intravascular administration of mannitol for AKI prevention does not convey additional beneficial effects.[6] So patients should be screened for renal function before mannitol being consideration. However our patient had a normal baseline serum creatinine, after second hour of mannitol infusion it was increased.

In conclusion, cerebral edema is a rare condition with high mortality during DKA. The first option in the treatment of brain edema is still mannitol. However patients with unresponsive or side effect of mannitol seems to have benefit from hypertonic saline. It should be keep in mind mannitol induced AKI which may require hemodialysis especially in patient prone to kidney failure. Although effective reversal of AKI with hemodialysis, the clinical awareness of the mannitol nephrotoxicity is emphasized also in patient with normal renal function.

* The authors declare that there are no conflicts of interest.

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