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Iatrogenic Severe Hypernatremia: A Case Report

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Abstract. Lactulose is a common first-line therapy for acute and chronic hepatic encephalopathy, which is generally considered a safe medication and used liberally. This report aims to highlight an uncommon but serious side effect of using lactulose. A case study is presented of a severe and acute hypernatremia caused by lactulose therapy for acute hepatic encephalopathy precipitated by a transjugular intrahepatic portosystemic shunt procedure.

Keywords: Hypernatremia, Lactulose, Hepatic encephalopathy

Introduction

Hepatic encephalopathy is a serious condition of complicated acute and chronic liver disease. It is a clinical syndrome characterized by altered mental status that occurs in patients with severe hepatic insufficiency[1]. Lactulose remains first line therapy for this condition, despite conflicting evidence[2]. Side effects of lactulose therapy are few, with volume contraction due to diarrhea being the main effect. Hypernatremia has been previously reported in this situation, but not to the level observed in this case[3].

Conventionally, hypernatremia is treated by gradual correction of the sodium level, usually by replacing free water deficit[4]. Rapid lowering of chronically elevated sodium levels is known to be a precipitating cause of cerebral edema, a serious and potentially fatal condition[5]. Acute

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hypernatremia can be treated more rapidly as the brain is unable to adapt to the elevated sodium promptly[5].

Case Report

A 58-year-old woman was referred to the Nephrology Service with severe hypernatremia. She was a known case of liver failure secondary to cryptogenic cirrhosis, and possible Hepatitis C with a previous failed liver transplant 1½ years ago and a history of diabetes. The patient was discharged 3 days prior to this presentation following an uncomplicated transjugular intrahepatic portosystemic shunt (TIPS) procedure. She was subsequently brought to the Emergency Department with a one-day history of worsening level of consciousness and confusion. She was afebrile and her vitals were stable.

Physical examination was negative apart from the manifestations of hepatic encephalopathy. She was admitted for management of hepatic encephalopathy.

Initial blood work revealed the following electrolytes; Na 132 mmol/L, K 3.1 mmol/L, Cl 96, HCO_3 26, Creatinine 93 µmol/L, BUN 10.4 and Albumin was 22 grams/L. She was started on lactulose 30 mls orally Q hourly until awake, and albumin infusion was added on the following day. The patient responded to the lactulose with watery bowel movements every hour, and an initial slight improvement in her level of consciousness (LOC). However, on the second day her LOC worsened and she became obtunded. Blood work done on the third day of admission revealed a sodium level of 180, repeated for confirmation and found to be 183 mmol/L. Potassium was 2.0 mmol/L, Cl 150, HCO_3 22, Creatinine 99 µmol/L, BUN 8.5 mmol/L, random glucose 8.6 mmol/L. She was switched to lactulose enema and cultures were drawn. The neurology and ICU teams were consulted. Computed tomography scan of the brain showed no evidence of cerebral edema.

Both oral and rectal forms of lactulose were held, and the IV fluid was changed to D_5Water at the rate of 175 cc/ hr and, most importantly, free water replacement was initiated *via* nasogastric (NG) tube at a rate of 125 cc/hr. Free water deficit was calculated using the following equation:

$$\text{Water deficit} = \text{TBW} \times (\text{plasma sodium concentration} - 140)/140,$$

i.e. water deficit = $(55 \times 0.40) \times (183-140)/140 = 6.75$L[4]

Because of the rapidity of the change in sodium and mental status, the author selected to correct her sodium faster than the usual recommendation of less than 0.5mEq/L/hr. Repeat measurement of sodium was 170 mmol/L after 4 hrs, 165 mmol/L after 8 hrs, 157 mmol/L after 12 hrs, 152 mmol/L after 16 hrs and 143 mmol/L after 22 hrs. Mental status returned quickly to normal, and subsequent magnetic resonance imaging of the brain was normal with no evidence of demyelination.

Discussion

The underlying pathophysiology of hypernatremia is mainly a deficit in free water. The cause of this deficit may vary. The differential diagnosis is presented in Table 1[5].

Table 1. Differential diagnosis of hypernatremia[5].

Insufficient water intake	Water unavailable Impaired thirst (*i.e.*, hypodipsia-adipsia, age-related) Neurologic deficit (*i.e.*, impaired mental status, hypothalamic lesion)
Hypotonic fluid depletion	Diabetes insipidus • Central (*i.e.*, impaired AVP secretion) • Nephrogenic (*i.e.*, impaired renal effect AVP) Renal losses • Osmotic diuresis (*i.e.*, glucose, mannitol, urea, IVIg) • Diuretics (*i.e.*, furosemide, thiazides) • Post-obstructive diuresis Non-renal losses • Insensible losses (*i.e.*, dermal, respiratory) • Gastrointestinal losses (*i.e.*, diarrhea, vomiting, nasogastric suction) • Peritoneal dialysis
Transient water shift into cells	Severe exercise Seizures
Sodium overload (in excess of body water)	Hypertonic sodium solutions • Excess sodium administration (*i.e.*, 3% NaCl, 0.9% NaCl, NaHCO3) • Ingestion of seawater Other hypertonic solutions • Hyperalimentation (intravenous, parenteral) Primary hyperaldosteronism Cushing's syndrome

Hypernatremia is an infrequent complication of hepatic encephalopathy compared to hyponatremia. One study showed the

incidence of hypernatremia to be 3% in 75 admissions for hepatic encephalopathy before lactulose treatment[3].

Lactulose is a non-absorbable disaccharide commonly used in treating patients with hepatic encephalopathy[2]. The exact mechanism is unclear; the main theory is that prevention of the production and absorption of ammonia is a key element in treating this condition. Use of lactulose causes an osmotic diarrhea as a direct effect of this drug and there are previous suggestions that lactulose-induced diarrhea can cause hypernatremia[3,6,7].

The studied patient was treated with high dose lactulose and experienced frequent diarrhea. The progressive rise in sodium level from 132 mmol/L to 183 mmol/L within two days of starting the treatment, which indicates that the lactulose treatment was the cause in the 6 L water deficit; there was no other source of fluid loss.

Hypernatremia, defined as serum sodium above 145 mmol/L is associated with various symptoms. These symptoms range in severity, with more severe symptoms accompanying faster and larger elevations in serum sodium. Initial symptoms may be subtle and non-specific, and include anorexia, restlessness, irritability, lethargy, muscle weakness, and nausea. If the hypernatremia is not corrected, these can progress to more serious manifestations, such as hyperreflexia, seizures, coma and even death[5].

Lactulose acts as a cathartic that is hydrolyzed in the colon into lactic acid and other organic acids primarily by anaerobic bacteria. These break-down products exert an osmotic effect. In diarrhea caused by osmotic cathartics the stool contains a high concentration of poorly absorbed solutes and relatively low concentration of sodium. Free water is therefore lost in excess of sodium[3].

By reviewing the literature, there is one case report of hypernatremia in a patient with hepatic encephalopathy treated with lactulose[1]. The sodium in that case was 164mmol/l while in our patient it reached 183mmol/l. To avoid such complications, the dose of lactulose should be adjusted to produce no more than 2-3 soft stools daily. This goal can be often be achieved with a dose of 90 ml/day or less.

In one report, the mortality was 41% in patients in whom hypernatremia developed, as compared with 14% in those remained

normonatremic[3]. The interesting observation in that study[3] is that patients who died had persistent hypernatremia. However, in patients who eventually recovered, the serum sodium level returned to normal. Therefore, this concludes that rapid correction of lactulose-induced hypernatremia in patients with hepatic encephalopathy is an important issue to consider as it affects mortality.

Rapid correction of hypernatremia has classically been associated with the development of central pontine myelinolysis (CPM). However, this was not seen in this patient as her sodium level was corrected rapidly in a short period of time, with no evidence of CPM in both her clinical status and brain magnetic resonance imaging. This indicates that lactulose-induced hypernatremia in patients with hepatic encephalopathy can be safely treated more rapidly than other causes of hypernatremia.

Conclusion

From this case report, it concludes that severe hypernatremia is rare, and if untreated, potentially fatal, complication of lactulose therapy in patients with hepatic encephalopathy. Therefore, sodium levels should be monitored closely during aggressive lactulose therapy in these patients. Rapid lowering of hypernatremia in this situation is safe and not associated with central pontine myelinolysis.

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ارتفاع شديد في مستوى الصوديوم علاجي المنشأ حالة تقرير عن

هلا هشام موصلي

قسم الباطنة، كليةالطب، جامعة الملك عبدالعزيز

جدة – المملكة العربية السعودية

المستخلص. لاكتيولوز هو الخيار الأول لعلاج اعتلال الدماغ الكبدي الحاد والمزمن. ويعتبر عموما دواءً آمناً ويستخدم بحرية. حالتنا تهدف إلى تسليط الضوء على تأثير جانبي شائع، لكن خطير، من استخدام لاكتيولوز. نقدم حالة من ارتفاع صوديوم الدم الحاد الناجم عن علاج اعتلال الدماغ الكبدي الحاد باللاكتيولوز.