Myoclonus and Metabolic Alkalosis from Licorice in Antacid

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Abstract

A 90-year-old woman with hypertension developed metabolic alkalosis and myoclonus. Her medications included diltiazem hydrochloride, benidipine hydrochloride, kallidinogenase, procaterol hydrochloride, sennoside, dihydrocodeine phosphate, and KM powder[®] antacid that contained 354 mg of licorice and 900 mg of sodium bicarbonate per 3.9 g of powder. Endocrinological studies showed slightly reduced plasma renin activity and normal plasma aldosterone concentration. A provisional diagnosis of licorice-induced metabolic alkalosis was established and the patient was successfully treated after correction of serum pH and cessation of the medications. Licorice-induced metabolic alkalosis must be considered in the differential diagnosis of myoclonus. (Internal Medicine 43: 59–62, 2004)

Key words: metabolic alkalosis, myoclonus, hypokalemia, licorice, glycyrrhizin, antacid

Introduction

Metabolic alkalosis is defined as an abnormal physiologic process characterized by a primary gain of strong base or loss of strong acid in the extracellular fluid (1). Although alkalosis is generally less dangerous than acidosis, severe hydrogen-ion deficit may be life threatening. Severe acute metabolic alkalosis with pH values above 7.55 often reduces cerebral blood flow and causes seizure and coma (2). Photo-myoclonus and myoclonic-like involuntary movements were reported in states of alkalosis (3, 4). We describe the presentation of a 90-year-old woman who developed myoclonus

and metabolic alkalosis after long-term ingestion of licorice contained in an antacid.

Case Report

A 90-year-old Japanese woman had been treated for hypertension at a local clinic for 20 years. Her daily oral medications on admission included diltiazem hydrochloride (Herbesser[®]) 90 mg, benidipine hydrochloride (Coniel[®]) 2 mg, kallidinogenase (Kallikrein[®]) 90 IU, procaterol hydrochloride (Meptin[®]) 50 µg, sennoside (Pursennid[®]) 12 mg, dihydrocodeine phosphate (Codeine Phosphate[®]) 30 mg, and KM powder[®] antacid that contained 354 mg of licorice and 900 mg of sodium bicarbonate per 3.9 g of powder. At 7:30 PM, on August 7, 2001, she was suddenly went into an attack of systemic tremor, which occurred intermittently. She visited her local clinic and temporally recovered from the attack after receiving an intravenous infusion of 500 ml saline. On the next morning, she developed the tremor again and was referred to our hospital. She had undergone a surgical operation for hydatidiform mole 62 years ago. She had no history of diarrhea, vomiting, gastrointestinal surgery, or diuretic use. The family history was negative.

Physical examination on admission revealed body weight and height were 45 kg and 148 cm, respectively and body temperature of 37.5°C. The blood pressure was 142/70 mmHg and pulse rate was regular at 90 beats/min. Her palpebral conjunctiva was slightly anemic, but bulbar conjunctiva did not appear jaundiced. Heart and respiratory sounds were normal. There were no significant findings on abdominal examination and there was no peripheral edema. Neurological physical examination found systemic myoclonus. A chest X-ray examination showed the presence of cardiac dilatation (cardiothoracic ratio: 54.2%). Echocardiography showed mild mitral regurgitation and left atrial dilatation.

Laboratory findings on admission indicated the presence

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Table 1. Laboratory Data (August 8, 2001)

Urinalysis		Serology			
Protein	(-)	ESR	83 mm/h	Na	138 mmol/l
Sugar	(-)	CRP	6.0 mg/dl	K	2.5 mmol/l
Occult blood	(-)			Cl	77 mmol/l
		Serum Biochemistry		Ca	6.2 mg/dl
Hematology		AST	63 IU/l	IP	3.5 mg/dl
RBC	306×10 ⁴ /μl	ALT	20 IU/l	Mg	0.8 mg/dl
Hb	9.2 g/dl	LDH	974 IU/l	TP	6.5 g/dl
Ht	27%	ALP	20 IU/l	Alb	3.0 g/dl
WBC	15,590/μl	CPK	3,260 IU/l	FBS	91 mg/dl
Stab 0, Seg 83, Eos 0,		γ-GTP	8 IU/l		
Baso 0, Mon 5, Lym 12%		BUN	17.1 mg/dl		
Platelet	51.8×10 ⁴ /μl	Cr	1.5 mg/dl		

of an acute inflammatory reaction (leukocyte count: 15,590/mm³, C-reactive protein (CRP): 6.0 mg/dl, erythrocyte sedimentation rate (ESR): 83 and 125 mm on the first and second hour, respectively). Biochemical analysis showed an elevated creatine phosphokinase (CPK) level, hypokalemia, hypochloremia, hypocalcemia, hypomagnesemia (Table 1). A spinal tap examination and culture of spinal fluid showed normal findings. There were no other findings suggestive of a focus of bacterial infection elsewhere. Arterial blood gas analysis revealed severe metabolic alkalosis (pH 7.579, PCO₂ 50.5 Torr, Po₂ 53.6 Torr, HCO₃⁻ 47.4 mEq/l, base excess 21.8 mEq/l, saturation of oxygen 93.7%). Endocrinological studies showed a slightly reduced plasma renin activity (PRA) and normal plasma aldosterone concentration (PAC) (Table 2). There were no other remarkable endocrine findings. An abdominal computed tomography (CT) did not show swelling of the adrenal gland or tumorous lesions. Twenty-four-hour urinary collections showed renal potassium wasting (Fig. 1). Urine calcium, phosphate, and magnesium levels on August 13, 2001 were 78 mg/day (100–300), 37 mg/day (500–2,000), and 20 mg/day (20–130), respectively (normal limits).

Since the patient had been given a licorice-containing agent for a long period and other endocrinological studies found no abnormality, she was diagnosed as licorice-induced metabolic alkalosis. To correct the pH value, an NH₄Cl solution and saline were administered. Intravenous calcium gluconate and potassium chloride were given to normalize serum electrolyte levels (Fig. 1). Metabolic alkalosis and serum electrolyte abnormalities were corrected within two

weeks and intravenous solutions were tapered (Fig. 1). Myoclonus completely disappeared after correction of the acid-base balance.

Discussion

Metabolic alkalosis is a primary pathophysiologic event characterized by the gain of bicarbonate or the loss of non-volatile acid from extracellular fluid (5). Many disorders seen in clinical practice may lead to the development of metabolic alkalosis. Only a few of these, such as loss of gastric fluid, aggressive diuretic therapy, and hyperadrenocorticism associated with neoplasm result in extreme alkalosis (plasma bicarbonate greater than 50 mEq/l) (6). Although alkalosis is generally less dangerous than acidosis, severe hydrogen-ion deficit may be life threatening. Metabolic alkalosis is generally considered severe if [HCO₃⁻] exceeds 40–42 mmol/l and treatment is mandatory (7). Severe acute metabolic alkalosis with pH values above 7.55 often reduces cerebral blood flow and causes seizures and coma (2).

In this case urine chloride levels were more than 20 mEq/l and plasma renin and aldosterone levels were low. According to an algorithmic approach, combined clinical problem solving for hypokalemia accompanied by an acid-base disturbance, the differential diagnosis was narrowed to licorice ingestion, Cushing's syndrome, the hydroxylase deficiencies, or Liddle's syndrome (8). Although blood pressure of the present case during admission was normal, she apparently had been on licorice-containing medicine for a long time. Endocrinological studies excluded the possibility

Table 2. Endocrinological Data

Plasma renin activity	0.2 ng/ml/h	(0.3–2.9)	9. Aug. 01
Plasma aldosterone concentration	43 pg/ml	(29.9–159)	9. Aug. 01
Plasma cortisol	19.1 mg/dl	(4.0–18.3)	9. Aug. 01
Urine 17-KS	2.3 mg/day	(2.4–11.0)	13. Aug. 01
Urine 17-OHCS	4.4 mg/day	(2.2–7.3)	13. Aug. 01

17-KS: 17-ketosteroids, 17-OHCS: 17-hydroxycorticoids, (normal limits).

Figure 1. Clinical course. Myoclonus disappeared after acid-base balance correction.

of Cushing's syndrome and the hydroxylase deficiencies. Liddle's syndrome was also excluded because plasma renin and aldosterone levels were not suppressed and her acid-base balance was maintained normal without any medication after cessation of licorice-ingestion.

Biochemical analysis of the present case showed hypokalemia, hypochloremia, hypocalcemia, and hypomagnesemia. Twenty-four-hour urinary collections revealed renal potassium wasting. Spot urine chloride was more than 20 mEq/l and plasma renin and aldosterone levels were low and normal, respectively. It is known that licorice ingestion results in hypokalemic metabolic alkalosis. The compound impairs the action of the enzyme 11-beta-hydroxysteroid dehydrogenase that converts cortisol to cortisone in aldosterone-responsive tissues such as the collecting tubules in the kidney (5). Therefore cortisol is allowed to occupy type I renal mineralocorticoid receptors, mimicking aldosterone (9). We speculate the cause of hypomagnesemia may be attributed to pseudoaldosterism induced by licorice. In this case, it is unclear why the patient had suddenly developed metabolic alkalosis after medication of licorice for 20 years. It is conceivable that dehydration enhanced reabsorption of

bicarbonate at the proximal tubules, resulting in developing metabolic alkalosis.

Myoclonus is defined as sudden, brief, shock-like, involuntary movements caused by muscular contractions or inhibitors (10). It is a symptom that occurs in a wide variety of metabolic and neurologic disorders. However, to our knowledge only one case was reported as myoclonus with metabolic alkalosis (11). Okada et al suggested that metabolic alkalosis is the etiology of myoclonus. Although the mechanism of myoclonus induced by metabolic alkalosis is still unclear, it is known that severe metabolic alkalosis can lower the seizure threshold (11). It is apparent that severe metabolic alkalosis in this case played an important role in the development of myoclonus. On the other hand, laboratory data of the patient showed hypomagnesemia during myoclonus and after normalization of serum magnesium levels myoclonus disappeared. Therefore, it is also possible that hypomagnesemia induced myoclonus. Although the pathophysiology of hypomagnesemic seizures remains unclear, hypomagnesemia has been reported as an uncommon cause of seizures especially in infants and neonates (12). In this case the laboratory data on admission showed increased

leukocyte counts and elevated serum CPK and CRP levels. Temporal elevation of serum CPK level is demonstrated in epileptic and nonepileptic seizure patients. It is reported that convulsions produce changes in muscle tissue membranes that persist for three to eight days and result in CPK leakage into plasma and extracellular fluid (13). On the other hand, it is known that activation of inflammation may occur after epileptic seizures without any evidence of systemic or central nervous system infection (14). According to Peltola et al, production of interleukin-6 (IL-6) in the central nervous system can stimulate increased production of IL-6 in peripheral blood, which subsequently activates the acute phase reaction (14). The acute phase reaction in this case may be explained by this mechanism.

In conclusion, we described a 90-year-old woman with severe metabolic alkalosis and myoclonus. The physician must consider the possible ingestion of licorice contained antacid, like KM powder® in the different diagnosis of metabolic alkalosis.

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