□ CASE REPORT □

Acetazolamide-induced Muscle Weakness in Hypokalemic Periodic Paralysis

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Abstract

A 46-year-old man with hypokalemic periodic paralysis (HypoPP) and diabetes mellitus (DM) had worsened muscle weakness after acetazolamide (ACZ) treatment. During the paralytic episode, serum potassium levels were reduced, and serum chloride and insulin levels were increased. The data suggested proximal renal tubular acidosis due to ACZ. We determined arterial-venous concentrations of potassium, insulin and glucose across the forearm. Venous potassium levels were markedly reduced. ACZ is thought to potentiate potassium uptake into muscles. Hyperinsulinemia and DM could contribute to ACZ-induced exacerbation in our patient. We should pay more attention to ACZ-treated HypoPP patients with hyperinsulinemia and DM.
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Key words: diabetes mellitus, hyperinsulinemia, arterial-venous differences of potassium and glucose, triamterene

Introduction

Hypokalemic periodic paralysis (HypoPP) is characterized by attacks of transient muscle weakness in the extremities. Acetazolamide (ACZ), a carbonic anhydrase inhibitor, is commonly used for the preventation of HypoPP attacks (1, 2). However, several reports suggest that this agent exacerbates attacks of muscle weakness in patients with HypoPP (3–5) or paramyotonia congenita (6). The mechanism of these harmful effects remains unknown. We report a unique patient with HypoPP and diabetes mellitus (DM) with ACZ-induced paralytic attacks and proximal renal tubular acidosis. In our patient, we analyzed arterial-venous concentrations of potassium, insulin and glucose across the forearm at paralytic and recovery periods. We discuss clinical hallmarks and possible mechanism of ACZ-induced HypoPP attacks.

Case Report

A 46-year-old man was diagnosed as HypoPP at the age of 28 years. When he received potassium (8 to 24 mEq/day) and spironolactone (25 mg/day) from 1996 to 1999, he had attacks of weakness a few times per month. Previous data showed that serum potassium levels were 3.8 to 4.2 mEq/*l* during non-attack periods. Treatment with ACZ (250 mg/day) and potassium (24 mEq/day) was started at a University hospital on January 6, 2000. On the day following the first administration of ACZ, he noticed mild muscle weakness. A moderate paralytic attack occurred on January 25. ACZ was gradually increased to 750 mg/day until February 25. The severity and the frequency of paralytic attacks were impaired. Mild or moderate weakness occurred twice per week. He had ACZ (750 mg/day) and habitual breakfast at 6 AM on March 6. A severe episode of muscle weakness presented at 8 AM. He was admitted to our department at 9 AM. There was no family history of HypoPP or DM.

His height was 171.0 cm and body weight was 79.8 kg. Body mass index was 27.3 kg/mm^2 (normal<24.9). Other physical examination findings were normal. Neurological examination revealed muscle weakness in the four extremities, predominantly in the proximal limbs. Using Medical Research Council scale, muscle strength was: 1/5 in the iliopsoas, quadriceps and hamstring muscles; 2/5 in the deltoid, pectoralis major, anterior tibialis and gastrocnemius muscles; and 3/5 in the biceps, triceps, wrist extensor and wrist flexor muscles. Respiratory muscles were intact. The grip strength was 5 kg (left) and 3 kg (right). Muscle tenderness and swelling presented in the extremities. Muscle tone was markedly reduced. Muscle stretch reflexes were decreased without Babinski's signs. Percussion-induced mounding phenomenon and myotonia were absent. Cranial nerves, sensory and cerebellar function were normal.

Before potassium administration, the first laboratory studies were performed at 3.5 hours following the final treatment

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with ACZ. Prominent hypokalemia and hyperinsulinemia were revealed. Serum concentrations of chloride, glucose and creatine kinase were elevated. Arterial blood gas analysis revealed metabolic acidosis. Urinary pH and potassium levels were markedly reduced. Urinary bicarbonate concentrations were increased (Table 1). Arterial and venous levels of potassium, insulin and glucose were measured across the forearm during the episode of weakness. Blood samples were simultaneously obtained from the right brachial artery and antecubital vein. Two arterial and venous samples were taken without the use of a tourniquet. Venous potassium concentrations were much lower than arterial potassium concentrations. Insulin concentrations did not differ between venous and arterial samples (Table 1).

Table 1. Laboratory Data during HypoPP Attack and Recovery Periods

	Normal values*	Attack**	Recovery*
Venous samples			
Potassium	3.3–4.8 mEq/*l*	1.8	4.1
Chloride	98–108 mEq/*l*	115	108
Creatine kinase	32–189 IU/*l*	381	123
Insulin	<17 μU/ml	91	15
Glucose	75–110 mg/dl	188	121
Arterial samples			
Potassium	3.3–4.8 mEq/*l*	2.5–2.8	3.9–4.1
Insulin	<17 μU/ml	90	14
Glucose	75–110 mg/dl	195	120
Arterial gas analysis			
pH	7.38–7.45	7.30	7.42
P_{CO2}	32–43 mmHg	36.3	38.3
P_{O2}	74–102 mmHg	102.7	95.0
Bicarbonate	20–28 mM	17.6	25.1
Urinary samples			
pH	5.5–7.0	5.0	7.0
Potassium	50–100 mEq/*l*	6.3	78.9
Bicarbonate	12<mM	12.6	<5.0

*Data of normal subjects and recovery time are measured at fasting state. **Data of attack period are determined at 3.5 hours after ACZ administration and breakfast.

Table 2. Arterial-venous Differences of Glucose and Potassium Concentrations, and Venous Insulin Levels after ACZ Administration

	Normal ranges*	Attack**
Arterial-venous differences		
Glucose (mg/dl)	–0.75–2.00	7.0
Potassium (mEq/*l*)	–0.02–0.03	0.7–1.0
Venous insulin (μU/ml)	8.63–10.50	91

*Mean data of eight normal subjects who received 12 doses of ACZ (3 to 4 mg/kg, p.o.) every 6 hours at fasting state before oral glucose tolerance test (11). **Data of attack period are measured at 3.5 hours after ACZ administration and breakfast.

Arterial-venous differences of glucose and potassium concentrations were markedly increased (Table 2). Oral administration of potassium chloride (5.0 g) ameliorated quadriparesis rapidly. Laboratory studies were performed at fasting condition on March 7 (24 hours after the last administration of ACZ: 6 AM). Arterial blood gas analysis and serum concentrations of potassium, chloride and insulin returned to normal ranges. Urinary pH, potassium and bicarbonate levels were also normal (Table 1). Arterial-venous differences of glucose and potassium levels were reduced to normal ranges during the recovery time. Under normal condition, fasting serum glucose and blood hemoglobin A1c levels were mildly increased to 120–130 mg/dl and 6.2% (normal<5.8), respectively. Glucose tolerance test was not performed. Other endocrine and renal function were normal. Immunological analyses, including anti-insulin antibodies, were negative. Electrocardiogram and its monitoring were not changed between the episode and recovery of muscle weakness. Bone X-rays disclosed no osteomalacia. Muscle biopsy was undertaken from the left quadriceps muscle during attack-free intervals 4 years ago. The histopathological study exhibited a few ragged red fibers, ringed fibers and small angular fibers. There were no abnormal sizes or distribution of type I and II muscle fibers. Our results suggested mild DM, hyperinsulinemia and proximal renal tubular acidosis. The repeated laboratory data showed no proximal or distal renal tubular acidosis following ACZ cessation. Triamterene (150 mg/day) was administered orally on March 12, 2000. Afterwards, the frequency and the severity of paralysis were improved dramatically. He had no severe or moderate episodes of muscle weakness for 2 years.

Discussion

ACZ is often utilized as a prophylactic drug for HypoPP attacks. Dichlorphenamide, a more potent carbonic anhydrase inhibitor, has been given to patients with HypoPP and primary PP in an attempt to prevent attacks of weakness. The clinical trial excludes patients who have a history of worsening symptoms after medication of other carbonic anhydrase inhibitors (7). While ACZ treatment is effective in many patients, this drug precipitated HypoPP attacks and caused hypokalemia, hyperinsulinemia and proximal renal tubular acidosis in our patient.

Carbonic anhydrase is localized in the endothelium of muscle capillaries and the muscle membrane (8). ACZ may act directly on muscle membrane of the skeletal muscle via this enzyme (9). The prophylactic effect of ACZ on HypoPP could be related to metabolic acidosis (10), the decline of serum glucose and insulin concentrations during paralytic attacks (1) and the non-acidosis-dependent alternation of the muscle membrane (11). The degree of ACZ-induced metabolic acidosis is similar between patients that improved and worsened with the drug (2, 4). Previous reports describe that ACZ-induced weakness is associated with potassium loss, DM, a variant form of HypoPP or therapeutic effects of triamterene (3–5). The clinical and laboratory features of the present patient showed mild

DM, hyperinsulinemia, proximal renal tubular acidosis and benefits of triamterene. The first common hallmark points out that ACZ produces mild to severe HypoPP attacks within three days after the initial administration of this drug in all patients (3–5), including our patient. After HypoPP patients receive the first treatment with ACZ, we should evaluate the degree and the frequency of their attacks cautiously. It is of interest that triamterene administration dramatically inhibited paralytic attacks in most of the previous cases (3–5) and in our patient. Triamterene, an aldosterone antagonist, is sometimes used for the prevention of HypoPP attacks. In a family with ACZ-induced exacerbation of HypoPP, this drug increases serum potassium levels. Triamterene administration attenuates hyperglycemia and hypokalemia in the intravenous glucose-insulin loading test (4). The metabolic mechanism of potassium, glucose and insulin differs obviously between triamterene and ACZ treatment in patients with ACZ-induced HypoPP. Triamterene is probably the best prophylactic drug in those patients. Another common aspect was proposed that ACZ-induced HypoPP attacks could contribute to latent or mild DM and hyperinsulinemia, like our patient (4). In previous studies of oral glucose tolerance and ACZ stress tests, ACZ enhances glucose uptake and suppresses potassium uptake across forearm muscles in normal subjects. Venous insulin levels are reduced slightly in ACZ-treated normal subjects (11). In contrast, our arterial-venous analyses indicated that ACZ triggered conspicuous hyperinsulinemia and prompted potassium transport from blood to skeletal muscles in the present patient. Marked reduction of urinary potassium was detected during the paralysis in our patient. The remarkable decrease of venous potassium levels may be implicated in both direct effects of ACZ on muscle membranes and proximal renal tubular acidosis due to ACZ. Our data support the possibility that this agent generates paroxysmal augmentation of insulin secretion and can potentiate potassium uptake into skeletal muscles in ACZ-induced HypoPP patients. Electrophysiological studies suggest that insulin diminishes inward rectifier potassium ion current and amplifies depolarization of HypoPP muscle fibers (12). DM and hyperinsulinemia might play an important role in the pathogenesis of HypoPP exacerbation due to ACZ administration. Thus, ACZ therapy should be carefully interpreted in HypoPP patients who have hyperinsulinemia and DM. Further studies of genetic and environmental factors are needed to elucidate the precise mechanism of ACZ-induced paralysis in HypoPP patients. We are currently analyzing HypoPP gene in our patient.

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