Acute Renal Failure Following Hypokalemic Rhabdomyolysis due to Chronic Glycyrrhizic Acid Administration

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A 72-year-old man developed acute renal failure (ARF) following severe hypokalemic rhabdomyolysis. The hypokalemia was due to chronic glycyrrhizin (glycyrrhizic acid) administration. Although glycyrrhizin-induced hypokalemic rhabdomyolysis has been occasionally reported, the association of this type of rhabdomyolysis with ARF has not been described. In the present case, there was a sensitivity to glycyrrhizin the preceding renal insufficiency, and dehydration which was thought to have contributed to ARF. It should be recognized that elderly patients with such predisposing factors may be susceptible to a rapid deterioration of renal function after glycyrrhizin-induced hypokalemic rhabdomyolysis.
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Key words: glycyrrhizin, hypokalemia, myoglobinuric renal failure

Introduction

Hypokalemia is a known complication of chronic administration of glycyrrhizin (glycyrrhizic acid), which has mineralocorticoid-like effects and causes hypertension, hypernatremia and decreased plasma concentrations of renin and aldosterone (1, 2). Although glycyrrhizin-induced hypokalemia may cause occasionally severe rhabdomyolysis, the complication of acute renal failure (ARF) derived from the rhabdomyolysis is extremely rare. This is consistent with the possibility that the mineralocorticoid-like actions of glycyrrhizin cause sodium retention and volume expansion, and thereby prevent the decrease in the glomerular filtration rate and the development of ARF (3). Nevertheless, we report an elderly patient who developed ARF following hypokalemic rhabdomyolysis due to chronic glycyrrhizin administration.

Case Report

A 72-year-old male was admitted in December 26, 1989 with the complaint of convulsion and delirium. The patient had been treated with glycyrrhizin-containing antacid (glycyrrhizin 90mg daily) from 1988, with an added daily dose of glycyrrhizin (150mg daily) since

February 1989. There was a three-year history of chronic renal insufficiency, and the creatinine clearance was 46 ml/min in December 1988.

In mid-December 1989, the patient complained of anorexia and general malaise. Five days prior to entry, he consulted his physician, who found hypertension and edema, and prescribed furosemide. At that time, his serum potassium was 1.4 mEq/l, serum creatinine 1.8 mg/dl, glutamic-oxaloacetic transaminase (GOT) 450 U/l, glutamic-pyruvic transaminase (GPT) 235 U/l. Three days before admission, the patient noticed muscle weakness which made him unable to stand up, and on the same day this was followed by a decrease of urine volume and an appearance of dark brown urine. On December 26, the patient experienced generalized seizures and on the same day, he was transferred to our hospital.

The temperature was 38.5°C, blood pressure was 102/70 mmHg, and respirations were 24. On physical examination the patient's skin was dry and markedly dehydrated, and his consciousness was delirious. He suffered from frequent tonic-clonic seizures. Blood urea nitrogen (BUN) was 95.3 mg/dl, serum creatinine was 9.5 mg/dl, and uric acid was 19.0 mg/dl. Serum concentration of potassium (K) was 1.9 mEq/l, sodium (Na) 128 mEq/l, chloride (Cl) 64 mEq/l, and calcium (Ca)

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Rhabdomyolysis and ARF from Glycyrrhizin

Fig. 1. Clinical Course. CPK: creatine phosphokinase, Cr: serum creatinine, HD: hemodialysis, K: serum potassium, LDH: lactate dehydrogenase, PEX: plasma exchange.

Fig. 2. Changes in serum and urinary potassium, plasma levels of renin activity and aldosterone before, during and after the re-administration of glycyrrhizin. Cl: chloride, K: potassium, Na: sodium, PAC: plasma aldosterone concentration, PRA: plasma renin activity, SNMC: Stronger Neo-Minophagen C® (glycyrrhizic acid preparation available in Japan).

6.8 mg/dl. Serum creatine phosphokinase (CPK) was 112,700 U/l, lactate dehydrogenase (LDH) 8,270 U/l, GOT 860 U/l, GPT 335 U/l, serum myoglobin 111,300 ng/ml. The urine was dark brown with a Na concentration of 57 mEq/l, and K concentration of 14 mEq/l. An arterial blood gas showed pH of 7.52, PaO₂ 55.5 mmHg, PaCO₂ 49.5 mmHg, and base excess 15.0 mEq/l. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were 1.6 ng/ml/h and 91 pg/ml, respectively. An electrocardiogram showed a high P wave in limb leads and prominent U wave.

The patient was immediately treated with plasma exchange and hemodialysis (Fig. 1). He received 350 mEq of potassium via a central venous line during the first three days. On the 8th hospital day, serum potassium returned to normal (3.6 mEq/l), and serum LDH and CPK fell to 1,329 U/l and 694 U/l, respectively. The patient suddenly passed massive bloody stool, and subsequently developed hypovolemic shock on the 14th hospital day. Although hemodialysis was discontinued on that day because of intermittent melena and hypotension, serum creatinine gradually returned to the baseline level, and it was 1.5 mg/dl on the 38th hospital day. With respect to massive melena, mesenteric angiographic examinations and a computed tomographic scan of the abdomen gave negative results.

As the hepatic enzymes had elevated gradually, a glycyrrhizin preparation, 40 mg daily, was administered intravenously with extreme care, from the 44th to the 69th day in hospital (Fig. 2). During this period, his serum potassium decreased gradually to 2.3 mEq/l, although the daily urinary excretion of potassium did not exceed 50 mEq/day. At the same time, rhabdomyolysis was not observed. Serum potassium level increased to normal two weeks after the cessation of glycyrrhizin preparation. Although PRA and PAC were within the normal range before the administration of glycyrrhizin, they were 1.0 ng/ml/h and below 10 pg/ml, respectively, two weeks later. Thereafter, serum potassium and sodium have remained within normal range, although the potassium has not been supplemented.

Discussion

We report a patient with hypokalemic rhabdomyolysis complicated by ARF. There seems to be little doubt that in the present case, glycyrrhizin was mainly responsible for the severe hypokalemia in spite of the low dose of glycyrrhizin (240 mg/day). Although hypokalemia and hypertension usually result from chronic ingestion of 1 mg or more daily of glycyrrhizin in Western countries (1–5), there have been several Japanese reports that smaller doses of glycyrrhizin (20–250 mg per day) could have produced severe hypokalemic rhabdomyolysis (6–10). Kuriyama et al (6) described a patient who developed marked hypokalemia due to chronic adminis-

tration of glycyrrhizin (150 mg daily) and speculated that an extreme sensitivity to glycyrrhizin might be related to the occurrence of hypokalemia in their patient. In the present case, we also prescribed a very small dose of glycyrrhizin, 40 mg per day, after the patient's serum potassium and creatinine had recovered to his baseline levels. One month later, the patient developed moderate hypokalemia and a definite depression of the renin-aldosterone axis, although rhabdomyolysis did not develop. These values returned to normal in a short period after discontinuation of glycyrrhizin. Recently, several reports have claimed that glycyrrhizin induces hypermineralocorticoidism by inhibiting 11 β -hydroxysteroid dehydrogenase and then producing a high level of cortisol, which binds to and activates mineralocorticoid receptors in the kidney (11, 12). Furthermore, there is now evidence that 11 β -hydroxysteroid dehydrogenase deficiency may occur in a number of common clinical situations including chronic renal failure. Accordingly, 11 β -hydroxysteroid dehydrogenase deficiency can partly explain the sensitivity to glycyrrhizin in the present patient.

The most striking feature in the present case is the development of ARF following hypokalemic rhabdomyolysis. Although ARF is not rare in patients with rhabdomyolysis [its incidence ranges from 16.5% to 67% in a reported series (13, 14), and glycyrrhizin-induced hypokalemia sometimes evokes rhabdomyolysis, the complication of ARF in glycyrrhizin-induced hypokalemic rhabdomyolysis has not been reported previously (1–10). With regard to the mechanism of protection against ARF, Heidemann and Kreuzfelder (3) described that sodium retention and volume expansion via the mineralocorticoid-like action of glycyrrhizin might be protective against the development of ARF in hypokalemic rhabdomyolysis.

In the present case, several factors seem to participate in the occurrence of ARF. First, the serum creatinine had been mildly elevated for three years, although the urinalysis was negative. The long-standing hypokalemia might have evoked tubulointerstitial nephritis (15), and might have consequently caused the chronic renal insufficiency in this patient. Ward (13) reported that a previous renal disease is not predictive of the development of ARF in patients with rhabdomyolysis. However, he defined a previous renal disease by clinical history alone, and it is still possible that a decreased renal function prior to rhabdomyolysis may be responsible for the development of ARF in the setting of rhabdomyolysis. Secondly the present patient had been severely dehydrated prior to admission. Multiple factors including long-standing anorexia, fever, and diuretics may have additively contributed to this patient's dehydration. In fact, Ward (13) described the dehydration at presentation as one of the most predictive factors of ARF in rhabdomyolysis. Kageyama (14) indicated that plasma volume

contraction might be responsible for the development of ARF in patients with rhabdomyolysis. Furthermore, experimental studies on animal models of rhabdomyolysis have emphasized the importance of dehydration in predisposing ARF (16, 17). Thirdly, the present patient experienced recurrent generalized seizures on the day of admission, and these seizures may have further precipitated the pre-existing rhabdomyolysis due to hypokalemia (18).

In conclusion, the present case demonstrates the possibility that ARF could develop even in patients with hypokalemic rhabdomyolysis due to chronic glycyrrhizin administration. Although Heidemann and Kreuzfelder (3) emphasized that the mineralocorticoid-like action of glycyrrhizin might be protective against the development of ARF in hypokalemic rhabdomyolysis, we suppose that this mechanism could not be fully effective in severely dehydrated patients. It is important to recognize that glycyrrhizin-induced hypokalemic rhabdomyolysis could result in ARF, especially in elderly patients who have a decreased renal function and are susceptible to dehydrating conditions.

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