Distal Renal Tubular Acidosis that Became Exacerbated by Proton Pump Inhibitor Use

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Abstract

Acid-base imbalances and electrolyte disorders induced by proton pump inhibitors (PPIs) are extremely rare. However, under certain conditions, PPIs may cause metabolic acidosis or hypokalemia, probably due to an inhibitory action on the proton pump that contributes to H⁺ and K⁺ homeostasis in the kidney. We herein present a case of marked hypokalemia accompanied by distal renal tubular acidosis in which a PPI appeared to contribute to the pathophysiology of metabolic acidosis.

Key words: proton pump inhibitor, distal renal tubular acidosis, metabolic acidosis, hypokalemia


Introduction

Proton pump inhibitors (PPIs) are extremely popular and prevalent medications that are widely used to treat acid-related diseases, including gastroesophageal reflux disease, peptic ulcer disease, and esophagitis/gastritis (1). While PPIs act only in the stomach, the kidney also has a proton pump, H⁺, K⁺ ATPase (HKα1), which contributes to H⁺ and K⁺ homeostasis (2). PPIs have been shown to have no effect on H⁺ and K⁺ handling in the kidney (3). Therefore, acid-base imbalances and electrolyte disorders induced by PPIs are extremely rare, with only one report published on a PPI causing hypokalemia, probably due to the inhibitory action of the PPI on the kidney’s proton pump (4). In this report, we present a case of marked hypokalemia accompanied by distal renal tubular acidosis (dRTA), which was associated with autoimmune hepatitis (AIH). The exacerbation of metabolic acidosis by the PPI was confirmed in a reproducible PPI challenge test, which indicated that the PPI appeared to contribute to the pathophysiology of metabolic acidosis by blocking HKα1 in the kidney.

Case Report

A 49-year-old woman with a two-year history of gastroesophageal reflux disease was admitted to our hospital in late May 2011 with complaints of muscular weakness and polydipsia following polyuria. She had noticed muscular weakness in her upper limbs two weeks earlier, which had then gradually progressed to the lower limbs. She had taken cimetidine and lansoprazole for two years, and glycyrrhizic acid and ursodeoxycholate for one year for mild liver dysfunction, as prescribed by her family doctor. Her serum potassium levels were normal (4.4 mEq/L) in January 2011, but decreased to 2.7 mEq/L in early May of that year; therefore, 1,800 mg of potassium chloride was prescribed. At the time of admission, her vital signs were normal except for mild hyperventilation with a respiratory rate of 24 breaths/min. On physical examination, she appeared extremely exhausted. Her lungs were clear on auscultation and the heart rhythm was regular, with no evidence of a murmur, rub, or gallop. An abdominal examination revealed no abnormalities, although she had mild pitting edema of the lower limbs. A neurological examination revealed muscle power...
The patient had been treated for mild liver dysfunction with glycerrhizic acid and ursoodeoxycholate for one year. At the time of admission, liver dysfunction was indicated by elevated glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and immunoglobulin G levels. In addition, she was positive for antinuclear antibodies at 1:320, thus suggesting the presence of autoimmune hepatitis. A liver biopsy performed on day 15 showed chronic active hepatitis [A1, F1 (A, activity; F, fibrosis)] (Fig. 3). As a result, a final diagnosis of hypokalemia due to dRTA associated with AIH was reached.

In cases of dRTA, bicarbonate replacement is essential for the treatment of hypokalemia (5). However, in the present case, potassium replacement alone restored the serum potassium levels to within the normal range (4.2 mEq/L) by day seven. The serum bicarbonate level also remained within the normal range after omeprazole was discontinued, although no bicarbonate supplement was administered (Fig. 1). Therefore, it was suspected that the PPI may have played a role in the development of metabolic acidosis. After informed consent was obtained, a challenge test with lansoprazole was performed from day 17. As expected, the metabolic acidosis recurred immediately following lansoprazole administration, and improved by day 24, when lansoprazole was discontinued. Potassium citrate/sodium citrate was finally administered, which resulted in stabilization of the serum potassium and bicarbonate levels to within the normal range, and she was subsequently discharged from our hospital on day 31.

## Discussion

We encountered a case of marked hypokalemia accompa-
hypokalemia, as well as acidemia, by inhibiting HKα1 in the kidney. However, in the present case, the serum potassium levels increased unexpectedly during the PPI challenge test, although acidemia recurred. To explain this discrepancy in effects, we speculated that excess supplementation with potassium chloride may have masked the hypokalemic effect of the PPI on HKα1. In a previously reported case, normalization of the serum potassium levels occurred with oral potassium supplementation, despite simultaneous PPI administration (4). In the present case, the dose of oral potassium was much higher (36-54 mEq daily) than that in the above mentioned case (5.4-8 mEq daily). Furthermore, high urinary potassium excretion levels (about 2-4 g daily during the course of treatment) and continuously elevated TTKG levels (17.4 to 10.8 before and after the PPI challenge test) suggested potassium overdose (7). Therefore, we speculated that potassium supplementation may have masked the hypokalemic effect of the PPI on HKα1 in the kidney, despite simultaneous PPI administration.

PPIs rarely cause hypokalemia due to hypomagnesemic-induced kaliuresis (8). In the present case, the serum magnesium levels were normal. In addition, PPIs rarely cause acute interstitial nephritis (AIN) (9). In the present case, the possibility of AIN was initially considered because N-acetyl-β-D-glucosaminidase (NAG) and β2MG, markers of interstitial nephritis, were both elevated. However, in our study, potassium supplementation stabilized the NAG and β2MG levels to within the normal range without the need for glucocorticoid administration or hemodialysis, which is often required in the treatment of AIN induced by PPI (10). Furthermore, the NAG and β2MG levels were not elevated during the PPI challenge test. These results suggest that the PPI did not cause AIN in the present case, and
that NAG and β2MG increased solely due to rhabdomyolysis secondary to hypokalemia.

RTA is an uncommon clinical state of systemic hyperchloremic acidosis resulting from impaired urinary acidification. RTA has been recognized to have three possible forms: proximal (pRTA), distal (dRTA), and hyperkalemic. Proximal RTA is caused by an impairment of bicarbonate reabsorption in the renal proximal tubules and is characterized by a decreased renal bicarbonate threshold. Distal RTA is caused by defective H⁺ secretion in the distal tubules and is characterized by the inability to acidify the urine below pH 5.5 during systemic acidemia (5). In order to obtain a clear demonstration of impaired renal net acid excretion, a urinary acidification test must be performed, either by acute administration of an acid load, such as with oral ammonium chloride (0.1 g/kg), or by oral administration of fludrocortisones (0.1 mg) and furosemide (40 mg) (11).

The causes of dRTA are idiopathic and include tubulointerstitial nephropathies and autoimmune disorders such as Sjögren’s syndrome, Hashimoto’s thyroiditis, systemic lupus erythematosus, primary biliary cirrhosis, and AIH (12-14). In addition, dRTA also develops more frequently in cases with chronic liver disease, and is seen in 30% of patients with AIH, although the precise mechanism underlying its development is unclear (15). To examine the relationship between AIH and dRTA, we focused on two molecules, the anion exchanger (AE) and H⁺-ATPase. The AE is an isoform of band 3 protein expressed in the cell membranes of the kidney endothelium (16). H⁺-ATPase has been reported to be localized in the collecting ducts of the kidney (17). In the renal tubule, AE and H⁺-ATPase are involved in the regulation of intracellular pH (bicarbonate efflux), which leads to acidification (17, 18). A disturbance of AE or H⁺-ATPase causes dRTA (5). In fact, evidence of the downregulation of AE immunoreactivity has been found in the kidney tubular tissue of patients with RTA (19). In addition, mutations in the AE gene have been shown to cause primary genetic dRTA (20). In a dRTA patient with Sjögren’s syndrome, a lack of absence of H⁺-ATPase or AE in the collecting duct has been reported (21). In addition, AE and H⁺-ATPase are both expressed in hepatocytes and collecting ducts in the
kidney (22, 23). Therefore, we speculated that either AE or H^+\text{-ATPase} were impaired together in the liver and kidney in the present case, and may have played a role in the underlying mechanism responsible for the association observed between AIH and dRTA (Fig. 4). To clarify this hypothesis, further studies measuring AE and H^+\text{-ATPase} activity in the liver and kidney obtained from patients with dRTA associated with AIH should be conducted in the future.

In conclusion, we encountered a case of severe hypokalemia accompanied by dRTA associated with PPI use. The effect of PPI on metabolic acidosis was incidentally observed during treatment for dRTA, and was considered to be the result of HKα1 blockage in the kidney, thus leading to an exacerbation of hypokalemia. This case demonstrates the necessity to consider the possibility that PPIs may cause metabolic acidosis and hypokalemia in patients with a number of underlying diseases.

The authors state that they have no Conflict of Interest (COI).

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References