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Proton Pump Inhibitor Induced Hypokalemia

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Abstract

Proton pump inhibitors (PPIs) act only in the stomach, although the proton pump, H^+, K^+-ATPase exists and contributes to H^+ and K^+ homeostasis in the kidney. We encountered two hypokalemic cases receiving omeprazole. These cases were in age's 65-year-old female and a 72-year-old male. Their serum potassium levels decreased with accelerated urinary potassium excretion with the use of omeprazole and recovered by potassium-supplement and the discontinuation of omeprazole. Because inhibitory effects of PPIs on H^+ K^+-ATPase are exerted only in acidic condition, hypokalemia is not generally introduced by PPIs alone. However, in extreme alkalosis or impaired K^+-recycling system, PPIs may cause hypokalemia unrelated to hypomagnesemia.

Keywords: H^+/K^+-ATPase; Hkα1; Hkα2; Omeprazole; Hypomagnesaemia; Hypoparathyroidism

Introduction

The gastric type of H^+K^+- ATPase (HKα1) is expressed in parietal cells of the stomach, but the same type of the enzyme is identified in the luminal side of the distal nephron segments of the kidney, where HKα1 works in K^+-reabsorption, H^+-excretion, and indirectly affects Na homeostasis, along with another subtype, the colonic type of H^+/K^+-ATPase (HKα2) [1]. Proton pump inhibitors (PPIs) covalently bind to HKα1, and inhibit its activity [2], meanwhile, the effect of PPIs on electrolytes handling is not apparent in the kidney, at least in healthy subjects [3]. In an extensive study of patients with relatively advanced age (65 years), PPI users showed rather higher serum potassium levels than PPI non-users [4]. The possible mechanisms of hyperkalemia included a decreased K^+- loss following the reduction of H^+ secretion in the gastro-intestinal tract through inactivated K-channels in the parietal cells [4,5], decreased aldosterone production by direct inhibitory effect of PPI on adrenocortical response to ACTH, and impaired renal function caused by latent interstitial nephritis [4]. Whereas, we recently encountered two cases of hypokalemia associated with administration of omeprazole in their clinical courses, not accompanied by hypomagnesemia. These cases showed hypokalemia and relatively higher levels of urinary pH (6.0) that were similar to the previous case report that showed trimethyltin chloride inhibited renal H^+,K^+- ATPase activity to induce hypokalemic renal tubular acidosis [6], as predicted by Kurtzman in his review [7]. The two cases reported here presented with some differences in their clinical parameters other than serum potassium, which may reflect heterogeneity in developing hypokalemia associated with the use of omeprazole.

Case Report

Case 1

The first case was a 70-year-old male with systemic hypertension and severe aortic regurgitation, accompanied by aortic valve replacement. The patient was admitted to the Gastroenterological Division of Norvic International Hospital with complaints of vomiting of blood and passing of black tarry stool. After admission, critical anemia caused by bleeding was revealed, although its cause and onset remained unclear. The supplementation of blood transfusion restored her general condition, but hypokalemia had gradually developed after the initiation of omeprazole (20 mg/day) for chronic gastritis because serum potassium level decreased to the critical level (2.54 mEq/L), and the blood pressure was raised, the patient was referred to the Cardiologist consultation. The patient showed high blood pressure, but no other abnormality was observed by the routine physical examination. As Table 1 shows, the laboratory examination demonstrated hypokalemia accompanied by an increased urinary potassium excretion and elevated serum bicarbonate concentration. The patient also received 40 mg of telmisartan, 10 mg of amlodipine, 1 gm of Ceftriaxone, Vit DV 60K once a week for 8 week, 25 mg of metoprolol, in addition to 20 mg of omeprazole, daily. As a possible cause of hypokalemia, both the activated rennin aldostrone system and suppression of 11β-hydroxysteroiddehydrogenase type 2 (11β-HSD2) were denied by the following examination (Table 1). As Table 2 shows, serum potassium levels apparently decreased after initiating omeprazole, Serum potassium levels were gradually elevated with potassium-supplement and subsequent discontinuation of omeprazole.

Case 2

The second case was an 65-year-old woman diagnosis with exacerbation of COPD with respiratory failure, type – DM and hypertension. The patient had two episodes of acute kidney injury caused by non-steroidal anti-inflammatory drugs (NSAIDs) and dehydration, two years before the present visit. The patient daily receiving various medicines among all 20 mg of omeprazole for a few years from the department of Pulmonary Medicine of Norvic International hospital.

Discussion

As one of the well-known adverse reactions, PPIs occasionally cause interstitial nephritis [8,9], which may have occurred in the cases reported here. However, hypokalemia in both cases was not accompanied by progressive azotemia, elevated CRP (C-Reactive protein) levels, pyuria or other clinical manifestations suggesting tubular damage, except for increased urinary NAG (N-acetyl-beta-D-glucosaminidase) and β2MG (beta2-microglobulin) excretion even in their recovery phase. Moreover,

Table 1: Lab data investigation for both case

Case 1	Case 2
TLC-5700 CELL/CUMM	tlc-19500cum/mm
DLC- N-72,L-26,M-2%	DLC-N-92,L-8,
HB-5.4 %	HB-10.7 mg%
PLATELET COUNT-108000	PLATELET COUNT-11600CELL/CUM
PCV-16.5%	PCV-34%
RBC-1.88	RBC-3.82 MILLION/CUMM
MCV-87.8	MCV-89.3 FL
MCH-28.7	MCH-28.0-Pg
MCHC-32.7	MCHC-31.4%
PT TIME-16.8 SEC	BLOOD SUGER-120
INR-1.56	UREA-27mg%
BIOCHEMISTRY- UREA-149MG%	S.CR.-0.4 mg%
S.CR.2MG%	S.Na-146meq/L
S.Na-148Meq/l	S.K-4.5 meq/L
S.K-4meq/l	

List of abbreviations should be provided
TLC-Total leucocyte count
DLC-Diffrential Leucocyte count
HB-Hemoglobin
PCV-Packed cell volume
RBC-red blood cell
MCV-Mean corpuscular volume
MCHC-mean corpuscular hemoglobin concentration

Table 2: Potassium Value daily reduced along with omeprazole but again came to normal range after discontinuation of it with other H2 receptor blocker.

CASE-1-NIR MAYA SHRESTHA	CASE-2-GOBIND BK
18SEP-4.5meq/L	14JUNE-4meq/l
19-3.5	15-4.3
20-3.2	16-4
21-2.7	18-3.8
22-2.6	19-3.4
23-2.5	22-3.2
24-3	

in both cases hypokalemia was improved by potassium-supplement and cessation of omeprazole. Since the patients were of relatively advanced aged with restricted activities of daily living (ADL), renal biopsy had not been planned. Therefore, interstitial nephritis could not be ruled out, although their clinical findings were not typical to PPI induced interstitial nephritis according to the several points described above [8,9]. Moreover, concurrent diabetic nephropathy may have modified the symptoms in case 1 Case 2 also had preceding renal damage by repeated NSAIDs nephropathy and dehydration. But serum potassium levels of the patient were soon recovered by potassium supplement and discontinuation of omeprazole. These facts suggested that hypokalemia evolved from transient disturbance in tubular function, rather than additional tissue damage, such as interstitial nephritis. Omeprazole can bind to HKα1 only in acidic conditions [2]. HKα1 is expressed in the luminal side of the tubule, and PPI binds to the extracellular domain of HKα1.

PPI is permeable to the cell membrane, but protonated PPI cannot pass through the cell membrane. Therefore, PPI can bind to HKα1 only in the luminal side of the tubule. Consequently, pH of luminal fluid mostly affects the binding capacity of PPI to HKα1, which is increased in pH below 6. That is why substantial binding of isotope-labeled omeprazole was observed in the stomach, and much less in the kidney [10]. Moreover, HKα1 exerts its effect only in potassium-repleted condition, and not in K-deprivation. Instead, HKα2 is unregulated in K-restricted condition [11-13]. These features of omeprazole and H^+,K^+-ATPase subtypes may explain why isolated hypokalemia caused by PPIs have never been reported. Meanwhile, these facts also suggest that PPIs may cause hypokalemia in certain conditions, such as acid-loading (burden of more acidic luminal fluid in the distal nephron), disrupted K-recycling systems [14], or induction disturbance of HKα2. While direct evidences suggesting these possibilities could not be specified in the cases reported here, several factors were considered to be involved in developing hypokalemia.

In case 1, supplementation of vitamin D analogue to hypoparathyroidism with omeprazole might have increased these rum bicarbonate levels through elevation of serum calcium [15,16] and subsequently might have enhanced hypokalemia. In case 2, urinary pH stayed around 7 even in reduced serum bicarbonate levels due to the pre exsting impairment of renal function, which may suggest a disturbance in H^+-secretion by suppressed HKα1 activity, as reported previously [6]. Metabolic acidosis also enhances the expression of HKα1 [1] and PPI-affinity to HKα1 [2]. In contrast to this possibility, the serum bicarbonate level returned to the normal range (24.5 mEq/L) five months after discontinuation.

Case 1

Administration of vitamin D analogue against hypoparathyroidism

↓

Calcium-alkali syndrome

↓

K+-shift to the intracellular space through Na^+-K^+ ATPase

↓

Increased fluid-burden to the distal nephron through the ROMK impeded by

2^+-senseing receptor in the thick ascending loop of Henle [15]

Electrical driving of K^+-excretion by increased HCO3- in collecting tubules

Inhibition of HKα1 activity by PPI (albeit less binding activity in alkaline tubular fluid)

↓

Increased urinary K+-loss

Case 2

Metabolic acidosis

↓

Increased expression of HKα1 and enhanced binding activity of PPI to HKα1

↓

Increased urinary K^+-loss

Possible mechanism of hypokalemia. In addition to the above description, the impairment of HKα2 and other K^+-handling systems may also have been involved in inducing hypokalemia in both cases. Severe hypomagnesaemia which is one of the adverse reactions of PPI and potentially a cause of hypokalemia had not been observed in these two cases, although serum Mg was examined only after stopping omeprazole in case 2 outer medullary K^+-channel which may deny the possibility described above and render it impossible to identify any specific cause of hypokalemia in case 2. Recently, several cases of PPI-induced hypomagnesemia has been reported [17-20], which was caused by the inhibitory effect of active magnesium transport in the intestine

[19], and recognized as a class effect of PPI s [20]. Hypomagnesaemia may cause hypokalemia by increasing K secretion in the kidney [21]. Actually, hypokalemia coincided with hypomagnesemia in some case reports [17,18]. Case 1 in this report showed mild hypomagnesemia (1.7-2.0 mg/dL), but serum magnesium had stayed in lower ranges (1.6-1.9 mg/dL) even before administrating omeprazol (Case 1). Thus, this hypomagnesaemia was probably caused by hypoparathyroidism or diabetes mellitus [22], even though hypomagnesemia may accelerate hypokalemia [21]. The present case 2 did not show hypomagnesaemia, and her serum magnesium levels stayed between 2.1-2.2 mg/dL, although serum magnesium had not been examined during administration of omeprazole. In conclusion, this is the first report of isolated hypokalemia associated with use of a proton pump inhibitor, omeprazole. The possible mechanisms of hypokalemia are summarized in Case 1 and 2. To clarify the actual mechanism and the association of hypokalemia and omeprazole, serial observation of electrolyte profiles in PPI-users will be needed. Since omeprazole is similar to other PPIs in its inhibitory effect on HKα1 and pH-dependence [2], hypokalemia may occur in other PPI users. Thus serum potassium levels should be carefully monitored in patients receiving PPIs especially with omeprazole.

The authors state that they have no Conflict of Interest (COI) but drug induced or adverse drug reaction should must be monitor. (In my personal view with all scientifically reason for hypokalemia that particular drug may or may not cause hypokalemia or the pharmaceutical company may not harm by this report but as the matter is concern for regulatory body regarding detection of expected Adr to be monitor for all this drug product which we are using.)

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