Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7325-21
Intern Med 61: 119-122, 2022
http://internmed.jp

【 CASE REPORT 】

Severe Hypomagnesemia Associated with the Long-term Use of the Potassium-competitive Acid Blocker Vonoprazan

Masaru Okamoto, Yu Wakunami and Kyoji Hashimoto

Abstract:
Hypomagnesemia caused by a proton pump inhibitor (PPI) was first reported in 2006. We herein report a case of hypomagnesemia due to the long-term use of vonoprazan, a potassium-competitive acid blocker (P-CAB). A 66-year-old man was admitted to our hospital complaining of disturbance of consciousness with evidence of hypomagnesemia noted on blood testing. The long-term use of vonoprazan was considered the cause of his hypomagnesemia, so it was discontinued, after which the hypomagnesemia improved. Hypomagnesemia can be induced not only by PPI treatment but also following the long-term use of P-CAB.

Key words: hypomagnesemia, potassium-competitive acid blocker, vonoprazan

(Intern Med 61: 119-122, 2022)
(DOI: 10.2169/internalmedicine.7325-21)

Introduction

Proton pump inhibitors (PPIs) are widely used as relatively safe drugs for gastric acid-related disease. However, various adverse events (AEs) of long-term PPI use have been reported, including absorption disorders, *Clostridium difficile* infection, chronic pneumonia, and microscopic enteritis (1). Hypomagnesemia due to PPI was first reported in 2006 (2); thereafter, similar studies have been performed.

Vonoprazan has a strong inhibitory effect on gastric acid secretion through a mechanism different from that of PPIs. It was introduced for use in Japan in 2015. To date, only a few reports have described AEs associated with vonoprazan, although AEs similar to those caused by PPIs can occur due to the suppression of gastric acid secretion. We herein report a case of hypomagnesemia caused by the long-term use of vonoprazan.

Case Report

A 66-year-old man with a history of myocardial infarction and cerebral infarction was admitted to our hospital because of disturbances in gait and consciousness. He had undergone endovascular aortic repair for abdominal aortic aneurysm at 64 years old; at that time, he had been taking a PPI until it was changed to vonoprazan. Approximately four months after that operation, he experienced sudden clonic convulsion. Although his electroencephalography findings were normal, he was diagnosed with symptomatic epilepsy associated with old cerebral infarction, and levetiracetam was started. The serum calcium (Ca) level at this time was slightly low at 7.2 mg/dL (albumin-corrected Ca 7.5 mg/dL), and the serum Mg level was not measured.

At two months before admission, he presented with diarrhea and appetite loss. Forty-three days before admission, he visited our emergency department with convulsions and disturbance of consciousness. Although blood tests revealed electrolyte abnormalities in serum magnesium (0.4 mg/dL), potassium (2.66 mEq/L), and albumin-corrected Ca (6.9 mg/dL), he left our hospital because his symptoms improved spontaneously. He gradually became unable to walk, and he was ultimately admitted to our hospital due to disturbance of consciousness. He had no history of alcohol consumption and was an ex-smoker with a 30-pack/year history before quitting at 64 years old. He was taking vonoprazan, levetiracetam, clopidogrel, diltiazem, telmisartan, amlodipine, nicorandil, bisoprolol, and isosorbide dinitrate.

On a physical examination at hospitalization, his heart rate was 109 beats per minute, blood pressure was 124/75

Department of General Internal Medicine, Tottori Prefectural Central Hospital, Japan
Received: February 12, 2021; Accepted: May 17, 2021; Advance Publication by J-STAGE: June 26, 2021
Correspondence to Dr. Masaru Okamoto, okamotoma@tp-ch.jp

Table. **Laboratory Data on Admission.**

Hematology		Normal range	**Blood chemistry**		Normal range
WBC(/μL)	112×10^2	40-80	TP(g/dL)	6.2	6.5-8.1
RBC(/μL)	342×10^4	427-570	Alb(g/dL)	3.2	4.0-5.0
Hb(g/dL)	10.8	13.5-17.6	AST(U/L)	16	13-33
Ht(%)	32.0	39.8-51.8	ALT(U/L)	10	8-42
Plt(/μL)	42.9×104	15.0-35.0	ALP(U/L)	173	115-359
			γ-GT(U/L)	22	11-58
Serum hormones			LD(U/L)	412	119-229
Intact PTH(pg/mL)	28	10-65	CK(U/L)	676	62-287
Calcitonin(pg/mL)	<0.50	<5.15	BUN(mg/dL)	17.0	8.0-20.0
			Cr(mg/dL)	2.0	0.50-1.10
Urinalysis			Na(mEq/L)	145.3	135-150
pH	6.5	4.5-7.5	K(mEq/L)	3.0	3.6-5.3
Protein	(+)	(-)-(±)	Cl(mEq/L)	105.9	98-110
Sugar	(-)	(-)	Ca(mg/dL)	4.9	8.7-11.0
Occult bood	(++)	(-)	P(mg/dL)	3.2	2.3-4.3
Na(mEq/L)	133.1		Mg(mg/dL)	0.2	1.8-2.4
K(mEq/L)	15.3		Glucose(mg/dL)	119	70-110
Ca(mg/dL)	0.4		CRP(mg/dL)	2.34	<0.30
P(mg/dL)	8.8		Vitamin B1(ng/mL)	34.8	21.3-81.9
Mg(mg/dL)	0.0		Vitamin B12(pg/mL)	963	233-914
Cr(mg/dL)	62.3		Folic acid(ng/mL)	2.4	3.6-12.9
			1.25(OH)Vitamin D(pg/mL)	33	20.0-60.0
Arterial blood gas analysis					
(Room air)					
pH	7.39				
pCO_2(mmHg)	26.6				
pO_2(mmHg)	73.2				
HCO_3(mmol/L)	18.1				
B.E.(mmol/L)	-8.3				
sO_2(%)	90.3				
Lactate(mmol/L)	6.0				
Anion gap	21.3				

Intact PTH: intact parathyroid hormone, B.E.: base excess

mmHg, and body temperature was 36.6℃. Although his consciousness was disturbed, as he was in a semi-comatose state, he gradually recovered after arriving at the hospital. He did not have typical symptoms of tetany. Computed tomography of the head did not reveal novel findings other than an old cerebral infarction, and no abnormalities were found on electroencephalography. The electrocardiogram results were also almost normal.

Laboratory examinations showed a serum magnesium level of 0.2 mg/dL, potassium of 3.0 mEq/L and albumin-corrected Ca of 5.7 mg/dL (Table). Serum intact-parathyroid hormone, 1,25-dihydroxyvitamin D, and calcitonin levels were all within normal ranges. The blood ammonia level was not measured. We considered his elevated serum CK level and lactic acidosis to indicate that the patient was having convulsions. These electrolyte disorders might have induced convulsions and conscious disturbance through symptomatic epilepsy.

We initiated treatment to correct his magnesium levels intravenously and his Ca levels orally because his urinary magnesium excretion had decreased to 0.0 mg/dL, which indicated a poor oral intake. His serum magnesium levels increased to 2.0 mg/dL on the second admission day, and his consciousness improved (Figure). His serum Ca levels improved steadily, but his magnesium levels rapidly declined once intravenous administration was discontinued, even though he had a sufficient intake after hospitalization. In addition to a poor oral intake, we suspected that he had experienced magnesium malabsorption induced by long-term treatment with an antacid drug and vonoprazan, which had been used for over two years; vonoprazan was therefore ceased from the fifth admission day.

Although temporary intravenous administration of magnesium was needed again as serum magnesium decreased to 1.1 mg/dL on the 10th admission day, his serum magnesium level increased naturally to 1.6 mg/dL on day 20 after discontinuation of vonoprazan. An H2 antagonist was started instead of vonoprazan on the same day, and serum magnesium has not decreased again.

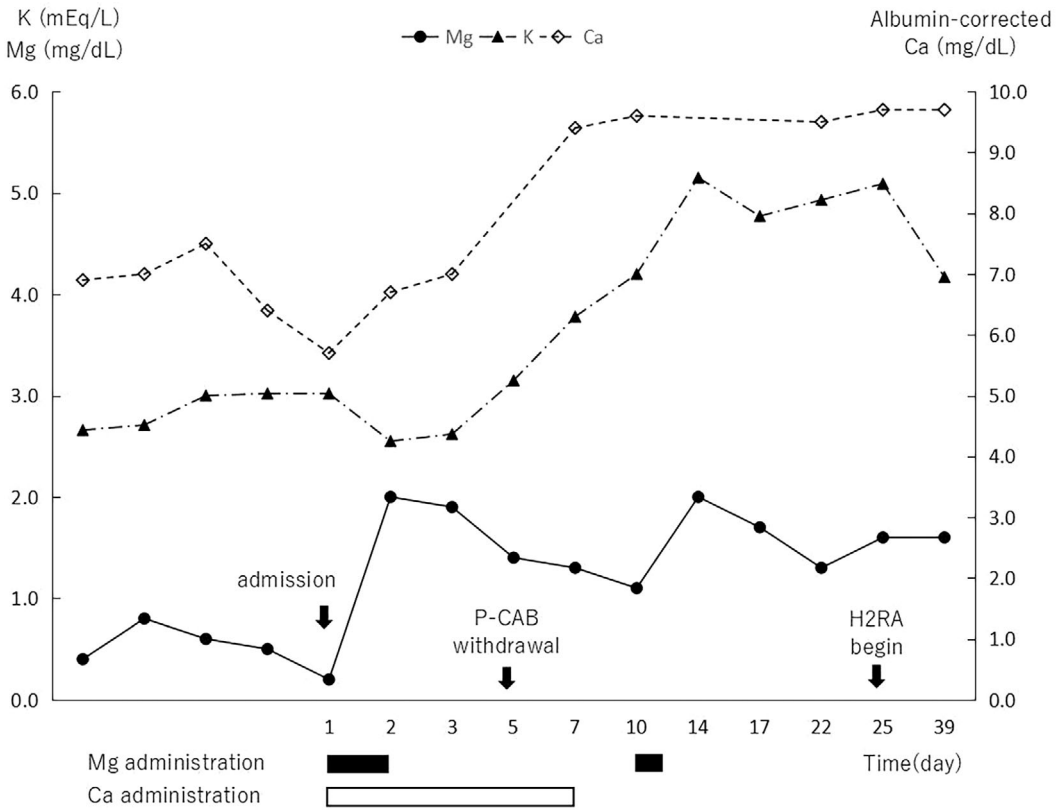

Figure. **Clinical course. Although temporary intravenous administration of magnesium was needed again after the serum level of magnesium decreased to 1.1 mg/dL on the 10th admission day, the serum magnesium level increased naturally to 1.6 mg/dL on day 20 after the discontinuation of vonoprazan.**

Discussion

Magnesium is involved in various activities in the body, including energy metabolism, regulation of ion channels, and ATP metabolism in particular. Approximately 99% of magnesium exists in cells. Extracellular magnesium constitutes approximately 1% of the total amount, and serum magnesium is maintained in the range of 1.8-2.6 mg/dL. Magnesium in the body is dynamically regulated by its absorption from the intestine, exchange with bone, and excretion through the kidney. Magnesium deficiency causes serious symptoms, such as consciousness disorders, convulsions, and arrhythmia, and is often associated with hypokalemia and hypocalcemia due to hypoparathyroidism (3, 4).

Magnesium deficiency results from dietary deprivation, gastrointestinal malabsorption, and increased renal excretion induced by diuretics or nephrotoxic drugs or by hyperthyroidism or hypercalcemia. Recently, hypomagnesemia caused by the long-term use of PPIs has also been reported (2).

The divalent cation channels transient receptor potential melastatin ion channel (TRPM) 6 and TRPM7 are strongly involved in magnesium homeostasis. Intracellular magnesium is maintained at a constant concentration compared with the fluctuating extracellular magnesium level because TRPM7, which is widely distributed in the body, regulates the influx of magnesium into the cells (5). The presence of TRPM6 in the apical membrane of enterocytes is critical for the active absorption of magnesium. TRPM6 requires the cooperation of TRPM7 and forms the TRPM6/7 complex (6). Under normal dietary conditions in healthy individuals, 30-50% of magnesium is absorbed mainly from the distal jejunum and the ileum. Approximately 90% of magnesium passively passes through the paracellular pathway between the enterocytes via a concentration gradient, and the remainder is actively absorbed through the intracellular pathway (3). When the luminal magnesium concentration is low, active transport by TRPM6/7 is important for magnesium absorption.

There have been numerous reports of hypomagnesemia due to PPI treatment since 2006 (2). A PPI acts not only on the H^+/K^+-adenosinetriphosphatase (ATPase) of gastric parietal cells to suppress H^+ secretion into the gastric lumen but also on the gastric-type H^+/K^+-ATPase present in pancreatic duct epithelial cells to suppress H^+ secretion into the pancreatic duct. Because this reduces the intracellular pH, HCO_3 secretion from cells is also suppressed to maintain intracellular acid-base equilibrium. Thus, the secretion HCO_3-rich pancreatic juice into the pancreatic duct is suppressed. Generally, the use of antacid drugs is followed by an increase in intestinal pH. However, with long-term use of PPIs, the in-

testinal pH is decreased because H^+ influx from the stomach is not neutralized by adequate secretion of pancreatic juice. H^+ ions promote the influx of monovalent cations, such as sodium, and generate an inward current by competing with divalent cations, such as magnesium and calcium, through TRPM7. For this reason, increased H^+ in the intestine due to continuous use of PPIs is thought to disturb the influx of magnesium ions into the cell, causing magnesium deficiency (7-9).

Vonoprazan, a potassium-competitive acid blocker (P-CAB), was introduced for use in Japan in 2015. The H^+/K^+-ATPase pump secretes H^+ into the stomach, exchanging K^+ through the lumen-facing conduit, and generates an ion flux, and P-CAB binds to its cation-binding site and competes with potassium ion to suppress gastric acid secretion (10). Although, there have been no reports of hypomagnesemia associated with P-CAB use, P-CAB is known to also act on the gastric H^+/K^+-ATPase in the pancreatic epithelium (8); therefore, it may inhibit magnesium absorption by a mechanism similar to that of a PPI, although further exploration will be needed.

Hess et al. reported that the time from PPI administration to the onset of hypomagnesemia ranges from 14 days to 13 years, with a median time of 5.5 years, and most cases recover from hypomagnesemia by approximately 14 days after PPI discontinuation. Histamine-2-receptor antagonists (H2 RAs) are commonly used as an alternative drug, and a study reported that H2RAs prevent recurrence of hypomagnesemia (11).

In our patient, the active administration of electrolytes improved symptoms, but serum magnesium levels immediately decreased upon its discontinuation. We suspected that vonoprazan may have affected the magnesium absorption in addition to the poor oral intake, so the treatment was suspended. Consequently, the serum magnesium levels recovered nearly to the normal range by 10 days after cessation of vonoprazan. Hypomagnesemia did not recur with the administration of an H2RA for more than a year, so we concluded that vonoprazan was the cause of hypomagnesemia.

Generally, because magnesium abundantly stored as hydroxyapatite in the bone is the first to be released when the plasma magnesium concentration is reduced, serum magnesium levels do not immediately decrease. In other words, the serum magnesium levels decrease only when the total stored magnesium has decreased considerably. A reduction in magnesium stores can easily lead to hypomagnesemia, especially in elderly patients with low magnesium stores due to aging (3). As mentioned above, the mechanism of active magnesium absorption by TRPM is affected by low luminal magnesium levels. Therefore, we suspected that symptomatic hypomagnesemia rapidly developed due to a combination of a poor oral intake in a patient with decreased magnesium stores secondary to gradual mechanisms, such as aging and long-term P-CAB use.

Various AEs have been reported with long-term PPI use, including absorption disorders, *C. difficile* infection, and microscopic enteritis (1). Although similar AEs may occur with P-CAB treatment, to our knowledge, there have been no reports describing cases of hypomagnesemia, other than a case of collagenous colitis associated with vonoprazan use (12, 13). We predict that reports of hypomagnesemia will increase in the future as interest in AEs associated with the long-term use of P-CAB grows and the population ages.

The serum magnesium and calcium levels in the present patient were hardly ever measured despite the long-term use of vonoprazan for two years. Although PPIs and P-CAB are often continued in patients such as those with reflux esophagitis, their side effects should be thoroughly monitored, and their aimless long-term administration should be avoided.

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

References

1. Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. Therap Adv Gastroenterol **11**: 11.1177/1756283X17745776, 2018.
2. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med **355**: 1834-1836, 2006.
3. Vormann J. Magnesium: nutrition and homoeostasis. AIMS Public Health **3**: 329-340, 2016.
4. Agus ZS. Mechanisms and causes of hypomagnesemia. Curr Opin Nephrol Hypertens **25**: 301-307, 2015.
5. Schmitz C, Perraud AL, Johnson CO, et al. Regulation of vertebrate cellular Mg^{2+} homeostasis by TRPM7. Cell **114**: 191-200, 2003.
6. Li M, Jiang J, Yue L. Functional characterization of homo- and heteromeric channel kinases TRPM6 and TRPM7. J Gen Physiol **127**: 525-537, 2006.
7. Bai JP, Hausman E, Lionberger R, Zang X. Modeling and simulation of the effect of proton pump inhibitors on magnesium homeostasis. 1. Oral absorption of magnesium. Mol Pharm **9**: 3495-3505, 2012.
8. Novak I, Wang J, Henriksen KL, et al. Pancreatic bicarbonate secretion involves two proton pumps. J Biol Chem **286**: 280-289, 2011.
9. Jiang J, Li M, Yue L. Potentiation of TRPM7 inward currents by protons. J Gen Physiol **126**: 137-150, 2005.
10. Abe K, Irie K, Nakanishi H, Suzuki H, Fujiyoshi Y. Crystal structures of the gastric proton pump. Nature **556**: 214-218, 2018.
11. Hess MW, Hoenderop JG, Bindels RJ, Drenth JP. Systematic review: hypomagnesaemia induced by proton pump inhibition. Aliment Pharmacol Ther **36**: 405-413, 2012.
12. Konuma H, Konuma I. A case of vonoprazan-induced collagenous colitis. Prog Dig Endosc **94**: 104-106, 2019 (in Japanese).
13. Takecab® Tablets 10 mg & 20 mg. Interview form, 13th version. 2020 (in Japanese) [Internet]. [cited 2021 May 10]. Available from: https://www.takedamed.com/mcm/medicine/download.jsp?id=162&type=INTERVIEW_FORM