

[ CASE REPORT ]

## Convulsive Seizure Due to Hypomagnesemia Caused by Short-term Vonoprazan Intake

Masayuki Aiba, Yutaka Tsutsumi, Jun Nagai, Takahiro Tateno and Shinichi Ito

### Abstract:

A 71-year-old woman was admitted for the treatment of diffuse large B-cell lymphoma of the ileum. She had been taking lansoprazole but was switched to vonoprazan due to epigastric discomfort. Three weeks after starting vonoprazan intake, she had a convulsive seizure, and a blood test showed hypomagnesemia. The cause of hypomagnesemia was considered to be malabsorption of magnesium from the intestinal tract associated with vonoprazan. After discontinuation of vonoprazan, the magnesium level quickly recovered, and the seizures did not relapse. It is important to consider the risk of hypomagnesemia in patients taking vonoprazan, even for a short period of time.

**Key words:** vonoprazan, proton-pump inhibitor, hypomagnesemia, seizure

(Intern Med 61: 237-240, 2022)

(DOI: 10.2169/internalmedicine.7758-21)

### Introduction

Vonoprazan fumarate (Vonoprazan), a potassium-competitive acid blocker (P-CAB), is a gastric acid secretion inhibitor with a faster onset and longer duration of effect than conventional proton-pump inhibitors (PPIs), and it is widely used in the treatment of reflux esophagitis and eradication of *Helicobacter pylori* (1, 2). Hypomagnesemia is a side effect associated with PPIs, and more than 40 cases have been reported since 2006 (3). At present, there have been no case reports of hypomagnesemia caused by vonoprazan. In addition, most of the case reports of PPI-induced hypomagnesemia involved patients who had been taking PPIs for more than one year (4), and there are few case reports of hypomagnesemia caused by PPIs taken for a short period of time.

We herein report a case of convulsive seizures due to hypomagnesemia that occurred just three weeks after the start of vonoprazan administration.

### Case Report

A 71-year-old woman visited her previous physician for a detailed examination of anemia, and computed tomography

(CT) showed wall thickening of the terminal ileum and multiple lymphadenopathy in the abdominal cavity. The patient underwent laparoscopic ileocecal resection, and the pathological diagnosis was diffuse large B-cell lymphoma. Subsequently, she was admitted to our hospital for a further investigation and treatment, and THP-COP-R therapy (pirarubicin 30 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, vincristine 1 mg/m<sup>2</sup>, predonisone 40 mg/body, rituximab 375 mg/m<sup>2</sup>) was started.

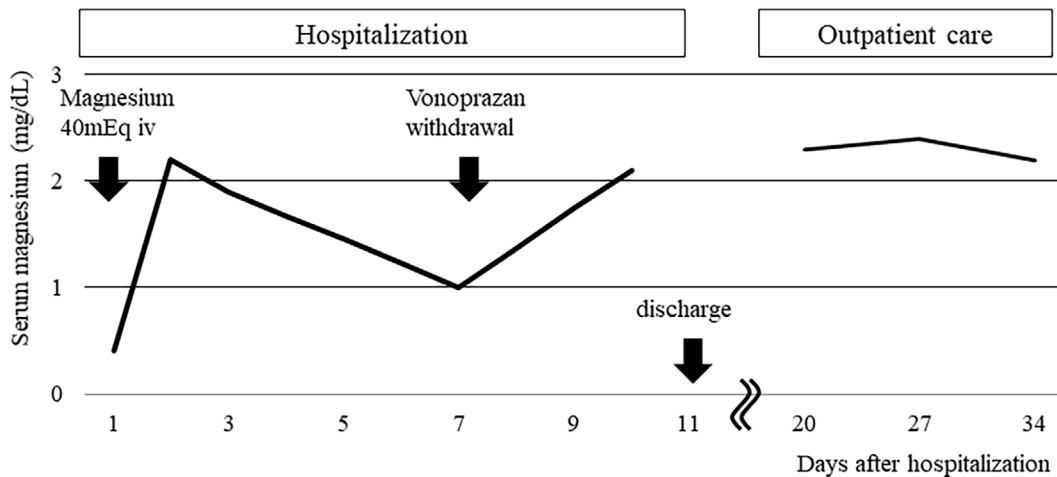
The patient was taking lansoprazole to prevent gastric mucosal injury but was switched to vonoprazan because of epigastric discomfort and heartburn. Afterwards she experienced no further particular symptoms, but when she visited the outpatient clinic due to a poor physical condition three weeks after starting vonoprazan, she had a convulsive seizure with loss of consciousness and left co-movement. The seizure resolved spontaneously within about three minutes, and her level of consciousness gradually recovered. The patient was admitted to the hospital for follow-up and to investigate the cause of her first convulsive seizure.

On admission, her body temperature was 37.1 °C, heart rate was 100 beats per minute, blood pressure was 164/107 mmHg, and level of consciousness was E4V4M6, based on the Glasgow Coma Scale. There were no obvious trauma marks on the body surface and no tongue bite. No abnor-

**Table. Laboratory Data on Admission.**

Complete blood count and coagulation		Biochemistry		Cerebrospinal fluid	
WBC	6,100 / $\mu$ L	T-Bil	1.3 mg/dL	Glucose	50 mg/dL
RBC	$4.10 \times 10^6$ / $\mu$ L	Alb	3.3 g/dL	Chloride	121 mEq/L
Hb	11.4 g/dL	AST	51 U/L	Protein	48 mg/dL
Hct	35.8 %	ALT	70 U/L	Cell count	1 / $\mu$ L
Plt	$28.9 \times 10^4$ / $\mu$ L	LDH	189 U/L	IgG	4.2 mg/dL
MCV	87.3 fL	Na	143 mEq/L		
		K	2.8 mEq/L		
APTT	12.0 sec	Ca	7.7 mg/dL		
PT-INR	1.03	Mg	0.4 mg/dL		
Fib	293 mg/dL	BUN	7.8 mg/dL		
D-dimer	1.3 $\mu$ g/mL	Cre	0.40 mg/dL		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, APTT: activated partial thromboplastin time, PT-INR: prothrombin time international normalized ratio, Fib: fibrinogen, T-Bil: total bilirubin, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic acid dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, IgG: immunoglobulin G



**Figure.** Clinical course and course of serum magnesium. Serum magnesium was elevated by magnesium infusion on the first day, but it soon decreased. After withdrawal of vonoprazan, it increased to the normal range, and hypomagnesemia did not relapse. iv: intravenous injection

mality was observed on routine physical or neurological examinations. Initial blood test results showed a decreased serum magnesium level (0.4 mg/dL), hypokalemia, elevated bilirubin, elevated AST and ALT levels (Table). No special abnormality was found in a cerebrospinal fluid (CSF) test, and the CSF cytology was class I. Magnetic resonance imaging (MRI) of the head showed no obvious intracranial abnormalities.

Based on the above results, hypomagnesemia was considered the cause of the seizure, and magnesium was administered at 40 mEq intravenously on the 1st day. On the 2nd day, the magnesium level had improved to 2.2 mg/dL, and the intravenous infusion was terminated, but the magnesium level decreased gradually (Figure). The cause of hypomagnesemia was considered to be insufficient absorption from the intestinal tract, since she had had no episodes of renal loss of magnesium, such as that caused by a high alcohol

intake or diuretic medication.

We also considered the involvement of drugs, as there was no history of picky eating, diarrhea, or fatty stool. Since hypomagnesemia is known to be a side effect of PPI medication, lansoprazole was considered a suspect drug. However, because three weeks had passed since the discontinuation of PPI medication, we considered it not relevant. We had newly started vonoprazan, which is a gastric acid secretion inhibitor, so we suspected that hypomagnesemia had been caused by malabsorption from the intestinal tract due to vonoprazan and discontinued vonoprazan on the 7th day. By the 10th day, the magnesium level had rapidly improved to 2.1 mg/dL, and she had shown no further recurrence of hypomagnesemia, so she was discharged after receiving anti-cancer therapy for lymphoma. The antacid was switched to famotidine, and she continues to receive outpatient treatment for lymphoma without recurrence of hypomagnesemia or

epigastric discomfort.

## Discussion

Magnesium is the fourth-most abundant cation in the human body and is widely involved in the maintenance of human physiological and physical functions (5). The balance of magnesium in the body is mainly regulated by absorption from the intestinal tract and excretion from the kidneys, and hypomagnesemia occurs when this balance is disrupted. Conditions that may lead to hypomagnesemia include alcoholism, Crohn's disease, chronic renal failure, and side effects of drugs, such as aminoglycoside antibiotics, cisplatin, and PPIs (3).

PPI-induced hypomagnesemia was first reported by Epstein et al. in 2006 (6), and more than 40 cases have been reported since then (3). In 2011, the United States Food and Drug Administration issued a safety announcement regarding the association between long-term PPI use and hypomagnesemia, and hypomagnesemia has since become known as a rare but serious side effect of PPIs. However, to our knowledge, hypomagnesemia associated with vonoprazan, the same antacid, has not been reported.

Magnesium is absorbed in the small intestine through passive and active mechanisms. Magnesium is passively absorbed into the blood through the concentration gradient between the lumen and the interstitium and is then actively absorbed into the intestinal cells via transient receptor potential melastin (TRPM) 6 and TRPM7, which are magnesium transporters in the intestinal mucosa (3). TRPM has a high affinity for magnesium and plays an important role in the maintenance of magnesium concentrations in the body, and its activity increases as the surrounding environment becomes more acidic (7). Therefore, one possible mechanism of PPI-induced hypomagnesemia is that PPIs inhibit gastric acid secretion, which raises the pH in the intestine, thereby decreasing the activity of TRPM6/7 and impairing the active absorption of magnesium (3, 7). Mackay et al. reported that oral or intravenous magnesium supplementation had a limited effect on the treatment of PPI-induced hypomagnesemia and that discontinuation of PPIs improved serum magnesium levels within about one week (8). In the present patient, hypomagnesemia was considered a result of vonoprazan intake, considering that she developed hypomagnesemia three weeks after starting vonoprazan and the magnesium level improved within one week after the discontinuation of vonoprazan.

The risk of PPI-induced hypomagnesemia reportedly increases with prolonged medication use (9-11), and in previous case reports, the majority of patients had been taking PPIs for more than one year (4). Kieboom et al. also reported a correlation between histamine 2 receptor inhibitor medication for more than 111 days and the development of hypomagnesemia (10), suggesting that hypomagnesemia may be a side effect of long-term antacid medication, regardless of the type. Since this patient had been taking lan-

soprazole for a long time and had slight hypomagnesemia (1.8 mg/dL) before switching to vonoprazan, it cannot be said that lansoprazole had no effect on her hypomagnesemia at all. However, this patient developed rapid hypomagnesemia within a relatively short period of just three weeks after taking vonoprazan. The mechanism underlying the development of hypomagnesemia induced by short-term antacid administration is unclear, but we considered the possibility that the strong inhibitory effect of vonoprazan on gastric acid secretion might have been involved, resulting in convulsive seizures.

Regarding the relationship between the strength of an antacid and the development of hypomagnesemia, Srinutta et al. reported that the risk of hypomagnesemia increased with increasing PPI dose (11). High-dose PPIs reportedly cause an increase in intragastric pH (12), and the activity of TRPM7 decreases as the pH of the surrounding environment increases (13), suggesting that the risk of hypomagnesemia increases as gastric acid secretion is suppressed. Vonoprazan has a different mechanism of action from conventional PPIs, inhibiting H<sup>+</sup>/K<sup>+</sup> ATPase in the gastric wall, and is a drug that produces a stronger inhibitory effect on acid secretion in a shorter period of time (1, 2, 14). Therefore, it is possible that vonoprazan caused a rapid pH increase in the intestinal tract in this patient, resulting in a rapid decrease in TRPM7 activity in the intestinal mucosa. In Japan, vonoprazan treatment for reflux esophagitis is covered by health insurance for up to four weeks, and the present case suggests that hypomagnesemia may occur even when vonoprazan is administered in accordance with insurance coverage. The mechanism by which vonoprazan causes hypomagnesemia and the duration until the onset of hypomagnesemia are unclear, so further analyses should be conducted.

The present patient had undergone ileocecal resection for lymphoma of the terminal ileum. Since 56% of magnesium absorbed in the gastrointestinal tract is absorbed in the ileum (15) and hypomagnesemia has been reported in patients with short bowel syndrome (16), it is possible that ileocecal resection was one of the factors that caused hypomagnesemia in this patient. However, since the patient did not show recurrence of hypomagnesemia after the discontinuation of vonoprazan, it is unlikely that her ileocecal resection procedure was directly involved in hypomagnesemia in this case.

In summary, we experienced a case of convulsive seizure due to hypomagnesemia caused by oral vonoprazan after a relatively short period of three weeks. Although hypomagnesemia is often asymptomatic, it is a serious complication that can lead to impaired consciousness and convulsive seizures. It is important to monitor the serum magnesium level in patients taking vonoprazan, even when taking it for a short period of time, and to consider hypomagnesemia due to vonoprazan as a cause of disturbance of consciousness or seizures, especially in patients who have been taking PPIs in the past.

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

#### Acknowledgement

The authors are grateful for the assistance provided by the staff at the Hematology Unit, Hakodate Municipal Hospital.

#### References

- Graham DY, Dore MP. Update on the use of vonoprazan: a competitive acid blocker. *Gastroenterology* **154**: 462-466, 2018.
- Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects--a randomised open-label cross-over study. *Aliment Pharmacol Ther* **42**: 719-730, 2015.
- Gröber U. Magnesium and drugs. *Int J Mol Sci* **20**: 2094, 2019.
- Reed LG, Mok JY. Proton pump inhibitor-associated hypomagnesemia: a retrospective case-control study. *Fed Pract* **33**: 18-21, 2016.
- Schuchardt JP, Hahn A. Intestinal absorption and factors influencing bioavailability of magnesium - an update. *Curr Nutr Food Sci* **13**: 260-278, 2017.
- Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med* **355**: 1834-1836, 2006.
- William JH, Danziger J. Proton-pump inhibitor-induced hypomagnesemia: current research and proposed mechanisms. *World J Nephrol* **5**: 152-157, 2016.
- Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. *QJM* **103**: 387-395, 2010.
- Cundy T, Mackay J. Proton pump inhibitors and severe hypomagnesaemia. *Curr Opin Gastroenterol* **27**: 180-185, 2011.
- Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, et al. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. *Am J Kidney Dis* **66**: 775-782, 2015.
- Srinutta T, Chewcharat A, Takkavatakarn K, et al. Proton pump inhibitors and hypomagnesemia: a meta-analysis of observational studies. *Medicine (Baltimore)* **98**: e17788, 2019.
- Udd M, Töyry J, Miettinen P, Vanninen E, Mustonen H, Julkunen R. The effect of regular and high doses of omeprazole on the intragastric acidity in patients with bleeding peptic ulcer treated endoscopically: a clinical trial with continuous intragastric pH monitoring. *Eur J Gastroenterol Hepatol* **17**: 1351-1356, 2005.
- Jiang J, Li M, Yue L. Potentiation of TRPM7 inward currents by protons. *J Gen Physiol* **126**: 137-150, 2005.
- Shin JM, Inatomi N, Munson K, et al. Characterization of a novel potassium-competitive acid blocker of the gastric H, K-ATPase, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438). *J Pharmacol Exp Ther* **339**: 412-420, 2011.
- Workinger JL, Doyle RP, Bortz J. Challenges in the diagnosis of magnesium status. *Nutrients* **10**: 1202, 2018.
- Braga CB, Ferreira IM, Marchini JS, Cunha SF. Copper and magnesium deficiencies in patients with short bowel syndrome receiving parenteral nutrition or oral feeding. *Arq Gastroenterol* **52**: 94-99, 2015.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).