Case Report

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Proton-Pump Inhibitor-Induced Hypocalcemia and Hypomagnesemia

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A 7-day-old female neonate who visited emergency department due to generalized tonic seizure. Laboratory test results showed hypocalcemia (5.7 mg/dL), hypomagnesemia (0.55 mmol/L), low parathyroid hormone (7.5 pg/mL), and normal 25(OH) vitamin D_3. Symptom and metabolic abnormalities were normalized with intravenous calcium gluconate and magnesium sulfate. Discharged with supplement of oral calcium, vitamin D, phenobarbital, and lansoprazol, she was re-admitted with hypocalcemia (4.8 mg/dL) with normal level of parathyroid hormone (12.3 pg/mL). Hypocalcemia was resolved with discontinuation of proton pump inhibitor. We report a case of recurrent hypocalcemia and hypomagnesemia due to proton-pump inhibitor.

Key Words: Hypoparathyroidism; Proton-pump inhibitors; Hypocalcemia

Introduction

Hypocalcemia is defined as serum total calcium level less than 8.5 mg/dL, or ionized calcium less than 4.7 mg/dL. Neonatal hypocalcemia usually clinically asymptomatic, but it may cause neuromuscular irritability such as tetany and seizure, apnea, cyanosis, and/or cardiac rhythm abnormalities. Early neonatal hypocalcemia occurs within the first 72 hours after birth, secondary to suppression of parathyroid hormone (PTH) secretion, prolonged secretion of calcitonin, and/or hypomagnesemia. Late neonatal hypocalcemia occurs after 72 hours of postnatal age and is more common in coexistence with vitamin D deficiency and hypomanesemia[1]. Magnesium is necessary for both PTH secretion and peripheral responsive to PTH. Therefore, hypomagnesemia indirectly associate with the level of calcium along with homeostasis of calcium, PTH, and vitamin D[2].

Recently, proton-pump inhibitors (PPIs) (e.g. omeprazole, esomeprazole, lansoprazole, and pantoprazole) are reported as one of the cause of hypomagnesemia. In this report, we describe a patient with primary hypoparathyroidism treated with calcium and vitamin D, while developing hypomagnesemia and hypocalcemia induced by PPI.

Case Report

A female neonate was born at gestational age of 40^{+5} weeks with birth weight of 3.12 kg through spontaneous vaginal delivery. On 7th day after birth, she visited emergency department with chief complaint of generalized tonic seizure. At presentation, the laboratory tests showed hypocalcemia (5.7 mg/dL), hypomagnesemia (0.55 mmol/L range, 0.65-1.0 mmol/L), and a low PTH (7.5 pg/mL range, 10-65 pg/mL). Serum 25(OH) vitamin D_3 level was normal (32.7 pg/mL range, 5-42 ng/mL), while 1,25(OH) vitamin D_3 was elevated (106.2 pg/mL range, 8-72 pg/mL). The serum level of total protein was 6.0 g/dL (range, 4.4-7.6 g/dL) and albumin was 4.0 g/dL (3.2-4.8 g/dL) which maintained within normal range. Transient

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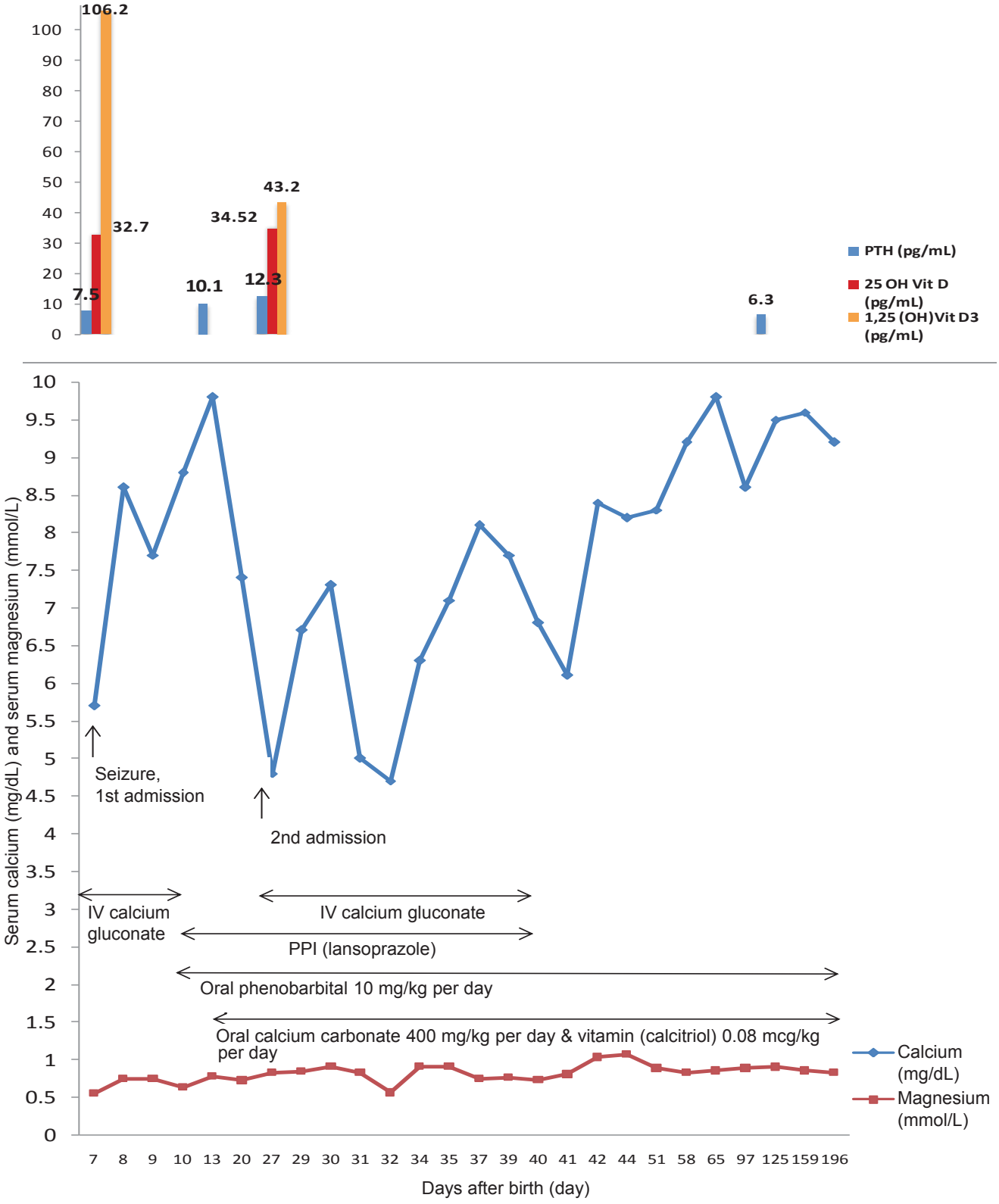

Fig. 1. Flow sheet of hormone levels, serum level of calcium and magnesium with progress of treatment. Abbreviation: PTH;parathyroid hormone, PPI; proton-pump inhibitor.

hypoparathyroidism due to hypomagnesemia or immature parathyroid gland was a consideration for explanation of hypocalcemia. We observed the changes in serum calcium and magnesium level with continuous supplement of intravenous or oral calcium and magnesium, and calcitriol.

We confirmed the presence of thymus on chest ultrasonograhy and normal findings of echocardiography and as a result, we were able to rule out DiGeorge syndrome. Brain magnetic resonance imaging (MRI) showed subtle edema of white matter in bilateral frontal area and electroencephalography (EEG) showed right posterior quadrant slow and occasional sharp wave in right occipital area. With frequent vomiting after feeding, esophagography showed velopharyngeal incoordination which may lead to gastroesophageal reflux (GERD). We started 1 mg/kg/day of lansoprazole for GERD and 10 mg/kg per day of oral phenobarbital for prophylaxis of seizure. Observation of serum calcium level with oral calcium supplementation and calcitriol showed maintenance of calcium level within normal range above 8.5 mg/dL. The patient was discharged at 15th hospital day with supplement of medication with calcitriol 0.25 mcg/day (0.08 mcg/kg), calcium carbonate 400 mg/kg/day (elemental calcium 150 mg/kg/day), oral pheno-barbital 10 mg/kg/day, and lansoprazole 1 mg/kg/day. At 1 week follow up after discharge, she was re-admitted due to recurrent hypocalcemia (4.8 mg/dL) and serum magnesium level of 0.72 mmol/L without any clinical symptoms. 1,25(OH) vitamin D_3 was 43.2 pg/mL, PTH of 12.3 pg/mL, total protein of 5.3 g/dL, and albumin of 4.0 g/dL at the time of re-admission. Intravenous calcium gluconate and magnesium were again infused. After confirming the normal level of calcium, intravenous supplement was discontinued and switched to oral calcium. However, cessation of intravenous calcium supplement followed by hypocalcemia and hypomagnesemia repeated during the hospital days. We decided to discontinue the use of PPI with refer to several case reports on hypomagnesemia and hypocalcemia during the use of PPI. First day after withdrawal of PPI, the level of serum calcium (from 6.1 mg/dL to 8.4 mg/dL) and magnesium (from 0.55 mmol/L to 0.74 mmol/L) was normalized. For the next 5 days, average serum calcium level was 8.2 mg/dL with oral supplement of calcium and calcitriol and we discharged the patient. Fig. 1 shows the summary of 1st and 2nd admission with indication of the progress of serum level of calcium, magnesium, PTH, 25(OH) vitamin D_3, 1, 25(OH) vitamin D_3 and the progression of treatment. After discharge, the level of serum calcium (8.5 mg/dL) and magnesium (0.88 mmol/L) were in normal range while steadily tapering oral calcium and vitamin D supplement. The level of PTH checked at 3 months after discharge was 6.3 pg/mL while the serum calcium level maintained in the range between 8.5 and 9.2 mg/dL.

Discussion

In this report, we describe a patient with primary hypoparathyroidism treated with calcium and vitamin D, while developing recurrent aggravated hypomagnesemia and hypocalcemia induced by PPI and treated successfully by cessation of the PPI.

PPI potently inhibit the secretion of gastric acid, by blocking the hydrogen-potassium adenosine triphosphatase enzyme system of the gastric parietal cell and induce achlorhydria[3].

PPI can cause severe and symptomatic hypomagnesemia. Two transport systems in the small intestine are involved in intestinal magnesium absorption. Firstly, the most part of magnesium is absorbed by passive diffusion through paracellular pathways between the enterocytes. Secondly, the transcellular active transport mechanism operating by transient receptor potential melastatin (TRPM), TRPM6 and TRPM7, is involved in absorbing the magnesium at low luminal magnesium concentration in a condition of low magnesium intake. The mechanism for the magnesium absorption reducing action of PPI drugs has yet to be elucidated. It is speculated that PPI may affect channel function in the paracellular pathway either directly or by changing the intestinal pH; or alternatively affect TRPM6 channel function[2, 3, 8, 9].

PPI also causes hypocalcemia. Acidic environemnt necessary for the absorption of calcium is inhibited in the case of PPI intake by blocking H-K ATPase of parietal cell in the stomach in which cause achlorydiria. Maintenance of achlorhydria reduces lypolysis necessary for the absorption of calcium in the gut, therefore reducing the calcium absorption by 80% in gastrointestinal tract causes hypocalcemia. In addition, low-dose supplement of protein may reduce the solubility and absorption of calcium independent of acidity[5, 6].

PPI treatment induces serum hypocalcemia and hypomagenesemia with symptoms usually minimal or absent but clinically severe. In 2006, Epstien et al.[7] reported two cases of patients with PPI treatment presented with tetany caused by hypomagnesemic hypoparathyroidism. In 2008, Agarwal et al.[3] reported a case of 3 years of omeprazole treatment developing hypomagnesemia and hypocalcemia which magnesium and calcium replacement would not resolve symptoms and serum level.

Oral supplement of magnesium and calcium were only partially effective while PPI treatment is maintained. Mackay et al.[3] reported that symptoms due to hypocalcemia was more prominent than hypomagnesemia. Moreover, hypocalcemia was more predominant complication of PPI than hypomagnesemia, suggested by observation that initial hypomagnesemia coexi-sted with hypocalcemia was recovered to a normal range with continuous oral supplement of magnesium along with sustained hypocalcemia. In addition, it has been noted that hypomagnesemia has additive effect on the general adverse effects of PPI[2, 3, 6, 8-11].

Recent reports demonstrated that PPI induced hypomagnesemia and hypocalcemia with tetany, and the withdrawl of PPIs normalized the metabolic abnormalities[2-4]. PPI for treatment of dyspeptic symptoms, in association with peptic ulcer disease, gastritis, and esophagitis, are well tolerated with rare complication when used chronic[2, 3]. In this case, the first day

after withdrawal of PPI, the level of serum calcium (from 6.1 mg/dL to 8.4 mg/dL) and magnesium (from 0.55 mmol/L to 0.74 mmol/L) was normalized in this patient. Both serum levels maintained within normal range until and after discharge with while steadily tapering oral calcium and vitamin D supplement.

In addition, our patient has been taking phenobarbital for prophylaxis of seizure and lansoprazole for gastro-esophageal reflux. Both drugs are reported to have potential risk for decreasing serum level of calcium and magnesium. Since the first admission, phenobarbital was continuously administered for 1 year with EEG monitoring after withdrawal of lansoprazole. Serum calcium level was maintained within normal limit during this period and was not influenced by phenobarbital. Moreover, normalization of serum calcium and magnesium levels after discontinuation of lansoprazole suggests the PPI was the primary cause of hypocalcemia and hypomagnesemia rather than phenobarbital.

In this report, we summarize as cessation of PPI is necessary when symptoms induced by hypomagnesemia and/or hypocalcemia are present.

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Proton–Pump Inhibitor 제재로 유발된 저칼슘혈증과 저마그네슘혈증

최새롬 · 변정희 · 권아름 · 김예진 · 김용혁 · 채현욱 · 김호성
연세대학교 의과대학 세브란스 어린이병원 소아과학교실

저자들은 저칼슘혈증과 경련을 주소로 내원한 생후 7일된 여자 신생아에서 정주 및 경구 칼슘 제재를 투여 후 회복되었으나 치료 중 복용한 Proton–Pump Inihibitor (PPI) 제재로 다시 유발된 저칼슘혈증과 저마그네슘혈증에 대한 증례를 보고한다.