Tzu Chi Medical Journal 27 (2015) 175–176

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Case Report

Refractory hypocalcemia and hypomagnesemia associated with the use of an oral proton-pump inhibitor in a patient with hypoparathyroidism

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ARTICLE INFO

Article history:
Received 19 March 2014
Received in revised form
15 April 2014
Accepted 21 April 2014
Available online 11 June 2014

Keywords:
Hypocalcemia
Hypomagnesemia
Hypoparathyroidism
Proton-pump inhibitor

ABSTRACT

The human body physiologically requires gastric acid for efficient absorption of calcium through the small intestine. A proton-pump inhibitor reduces acidity in the stomach, and impairs the absorption of food and therapeutic preparations of calcium salts in the small intestine. Hypomagnesemia is a rare adverse effect of a proton-pump inhibitor. We report a 64-year-old man with a malignant neoplasm of the hypopharynx. After a total pharyngolaryngectomy, bilateral selective neck dissection (levels II, III, and IV), and right thyroidectomy, he developed hypocalcemia, hypomagnesemia, and hypoparathyroidism. After the administration of calcium and magnesium supplements, the patient's serum calcium and magnesium levels were still abnormal. The patient was later found to be taking an oral proton-pump inhibitor (esomeprazole) to treat a peptic ulcer. After discontinuing the oral proton-pump inhibitor, the patient was found to have normal serum calcium and magnesium levels under supplementation with oral calcium and 1,25-dihydroxyvitamin D.

1. Introduction

Proton-pump inhibitors (PPIs) have been used widely since their introduction in the late 1980s because they are highly effective for the treatment of gastric acid-related diseases [1]. PPIs act by inhibiting the proton pump or H^+/K^+ adenosine triphosphatase found on gastric mucosal parietal cells, and reduce the secretion of gastric acid [2]. Therefore, PPIs contribute to changes in the gastric and intestinal pH environments, which may impact the absorption of nutrients with some clinical consequences. The notion that PPIs interfere with the absorption of calcium and magnesium has often been discussed. We report a patient with a malignant neoplasm of the hypopharynx who received a total pharyngolaryngectomy, bilateral selective neck dissection (levels II, III, and IV), and right thyroidectomy. The patient had hypocalcemia, hypomagnesemia, and very low levels of parathyroid hormone.

2. Case Report

A 64-year-old man with a malignant neoplasm of the hypopharynx, T_1N_0Mx, stage I, was admitted to the otolaryngology ward for a total pharyngolaryngectomy, bilateral selective neck dissection (levels II, III, and IV), and right thyroidectomy. On the 3rd postoperative day, the patient developed paresthesia and muscle cramps in the four limbs. Laboratory studies revealed hypocalcemia (serum calcium: 1.35 mmol/L), hypomagnesemia (serum magnesium: 1.3 mg/dL), and very low levels of parathyroid hormone (serum intact parathyroid hormone: 1.5 pg/mL). Primary hypoparathyroidism was diagnosed. The patient's symptoms, as well as serum calcium and magnesium levels improved after continuous administration of intravenous calcium gluconate and oral magnesium oxide. However, the patient repeatedly developed severe hypocalcemia when shifted to oral calcium carbonate and 1,25-

Conflicts of interest: None.

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http://dx.doi.org/10.1016/j.tcmj.2014.05.003

Table 1
Clinical course and laboratory examinations.

April 15, 2011	Prior to surgery	Ca: 2.29 (2.12–2.52) mmol/L; albumin: 3.5 (3.4–5.0) g/dL
April 27, 2011	Surgery for hypopharynx cancer	1. Total pharyngolaryngectomy 2. Bilateral selective neck dissection (levels II, III, IV) 3. Right thyroidectomy
April 30, 2011	Symptoms of paresthesias and muscle cramps	Ca: 1.35 mmol/L; P: 3.5 (2.5–4.9) mg/dL; Mg: 1.3 (1.8–2.4) mg/dL; albumin: 2.0 g/dL; Na: 136 mmol/L; K: 3.5 mmol/L; i-PTH: 1.5 (14–72) pg/mL
	Intravenous injection calcium gluconate	Calcium gluconate (0.898 meq/mL, 5 mL/amp) 5 amp in 500 mL normal saline run 20 mL/h (0.014 meq/mL/min)
	Oral magnesium oxide	Magnesium oxide 250 mg/tab 1# t.i.d.
May 5, 2011		Ca: 1.69 mmol/L; calcium gluconate intravenous injection form shift to $CaCO_3$ (500 mg/tab) oral form 3# q6h; calcitriol 0.25 μg/cap 1# q12 h
May 7, 2011	Intravenous injection calcium gluconate	Ca: 1.39 mmol/L; calcium oral form shift to calcium gluconate intravenous injection form
May 11, 2011	Oral thyroxin	TSH: 28.6 μIU/mL; free T4: 0.79 ng/dL
June 3, 2011		Ca: 1.60 mmol/L; calcium gluconate intravenous injection form shift to $CaCO_3$ oral form 3# q4h; calcitriol 0.25 μg/cap 1# q8h
June 5, 2011	Intravenous injection calcium gluconate	Ca: 1.45 mmol/L; P: 5.9 mg/dL; Mg: 3.4 mg/dL; albumin: 2.8 g/dL; Na: 135 mmol/L; K: 3.9 mmol/L
June 7, 2011	Stop esomeprazole	Esomeprazole was started on Apr 29, 2011
June 10, 2011		Ca: 1.78 mmol/L; P: 4.3 mg/dL
June 17, 2011		Ca: 2.04 mmol/L; P: 6.1 mg/dL; albumin: 2.9 g/dL
	Oral agents after hospital discharge	Calcium citrate (950 mg/tab) 5# q8h; calcitriol 0.25 μg/cap 1# q8h; thyroxine 100 μg/tab 8#/qw
August 27, 2012		Ca: 2.2 mmol/L; P: 4.1 mg/dL; albumin: 4.0 g/dL; Na: 140 mmol/L; K: 3.7 mmol/L; TSH: 1.093 (0.25–4.0) μIU/mL; free T4: 1.266 (0.8–2.0) ng/dL

$CaCO_3$ = calcium carbonate; free T4 = free thyroxine; i-PTH = intact parathyroid hormone; TSH = thyroid-stimulating hormone.

dihydroxyvitamin D. After reviewing the patient's medications, we found that he was taking an oral PPI (oral administration of 20 mg esomeprazole per day) for a peptic ulcer. After discontinuation of the oral PPI, the patient achieved normal serum calcium and magnesium levels under supplementation with oral calcium and 1,25-dihydroxyvitamin D.

3. Discussion

It is well established that calcium must be in a soluble, ionized form to be absorbed. In normal circumstances, prior to food chyme reaches the small intestine, gastric acid and the slightly acidic environment help in the dissolution of calcium, leading to the formation of calcium ions that can be absorbed. PPIs are powerful gastric acid suppressors that may reduce the bioavailability of calcium for gastric and intestinal absorption. Gastric acid is necessary to facilitate effective absorption of calcium in the intestine. In 1967, Ivanovich et al [3] showed that calcium was not absorbed from carbonate when basal stomach acid secretion was zero. A study by Recker [4] in 1985 found that calcium absorption from carbonate is impaired in achlorhydria. The inhibition of gastric acid secretion by dietary omeprazole (a PPI) in male Wister rats decreased calcium absorption from calcium carbonate. Chonan et al [5] reported that dietary lactic acid prevented calcium absorption in rats fed with omeprazole.

O'Connell et al [6] measured intestinal calcium absorption in humans using a radiolabeled calcium isotope. They reported that women who were aged 65 years and older and taking omeprazole at a dose of 20 mg once a day for 7 days had a significant reduction in the absorption of calcium carbonate taken under fasting conditions. This study showed that omeprazole therapy decreased calcium absorption from calcium carbonate significantly when ingested by elderly women after an overnight fast and on an empty stomach [6]. Calcium carbonate and calcium citrate are the most common calcium supplements. Calcium carbonate should be taken with a meal to ensure optimal absorption. Calcium citrate can be taken without food, and is the supplement of choice for individuals with achlorhydria and those who are taking histamine-2 blockers or PPIs [7].

Hypomagnesemia is a rare but serious adverse effect of PPI. The first case of PPI-associated hypomagnesemia was reported in 2006 [8]. Two patients presented with carpopedal spasms in association with severe hypomagnesemic and hypocalcemic hypoparathyroidism when they were treated with PPIs [8]. In the United States Food and Drug Administration database, only 1% of the 66,102 patients who experienced various adverse effects due to PPI use presented with hypomagnesemia [9]. Patients with hypomagnesemia often develop secondary hypocalcemia and hypokalemia. According to the United States Food and Drug Administration data, there is a strong association between PPI-associated hypomagnesemia and hypocalcemia. More than 60% of the patients who had hypomagnesemia also had hypocalcemia [9]. Our patient also developed hypomagnesemic and hypocalcemic hypoparathyroidism associated with the use of oral PPIs. After discontinuing the oral PPI, the levels of calcium and magnesium in the serum normalized (Table 1).

In conclusion, we suggest that serum magnesium and calcium levels be checked regularly in patients with hypoparathyroidism who take PPIs or histamine-2 blockers. Calcium carbonate should be taken with a meal for its effective absorption. Calcium citrate, which can be ingested without food, is the supplement of choice for individuals who are taking PPIs or histamine-2 blockers.

References

[1] Yang YX. Chronic proton pump inhibitor therapy and calcium metabolism. Curr Gastroenterol Rep 2012;14:473–9.
[2] Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. Eur J Clin Pharmacol 2008;64:935–51.
[3] Ivanovich P, Fellows H, Rich C. The absorption of calcium carbonate. Ann Intern Med 1967;66:917–23.
[4] Recker RR. Calcium absorption and achlorhydria. N Engl J Med 1985;313:70–3.
[5] Chonan O, Takahashi R, Yasui H, Watanuki M. Effect of L-lactic acid on calcium absorption in rats fed omeprazole. J Nutr Sci Vitaminol (Tokyo) 1998;44:473–81.
[6] O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med 2005;118:778–81.
[7] Strau DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract 2007;22:286–96.
[8] Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med 2006;355:1834–6.
[9] Luk CP, Parsons R, Lee YP, Hughes JD. Proton pump inhibitor-associated hypomagnesemia: what do FDA data tell us? Ann Pharmacother 2013;47:773–80.