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EDITORIAL

Proton pump inhibitor-induced hypomagnesemia: A new challenge

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Abstract

Proton pump inhibitors (PPIs) are commonly used in clinical practice for the prevention and treatment of peptic ulcer, gastritis, esophagitis and gastroesophageal reflux. Hypomagnesemia has recently been recognized as a side effect of PPIs. Low magnesium levels may cause symptoms from several systems, some of which being potentially serious, such as tetany, seizures and arrhythmias. It seems that PPIs affect the gastrointestinal absorption of magnesium. Clinicians should be vigilant in order to timely consider and prevent or reverse hypomagnesemia in patients who take PPIs, especially if they are prone to this electrolyte disorder.

Key words: Hypocalcemia; Hypokalemia; Hypomagnesemia; Proton pump inhibitors; Transient receptor potential melastatin

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PROTON PUMP INHIBITOR-INDUCED HYPOMAGNESEMIA

Magnesium is an essential cation which is implicated in several physiological processes in the body[1,2]. Fifty to 60% of total magnesium is stored in bones, about 40% is intracellular (mainly in muscles) and only 1% is found in extracellular fluid[1]. Magnesium balance is tightly regulated through intestinal and renal absorption and excretion as well as exchange with bone. Approximately one third of the average daily magnesium intake (about 360 mg; 15 mmol) is absorbed in the small intestine through both a saturable transport system and passive diffusion, while another 20 mg (0.8 mmol) are absorbed in the large bowel. Conversely, almost 40 mg (1.7 mmol) of magnesium are excreted in intestinal secretions[1,3]. Overall, approximately 100 mg (4.1 mmol) of magnesium are absorbed and magnesium balance is maintained by their urinary excretion. As the body cannot readily mobilize magnesium stores (in fact, equilibration with bone stores takes place after several weeks), alterations in magnesium intake are balanced by changes in urinary magnesium reabsorption[1,4].

At this point magnesium renal handling will be briefly presented. In contrast with other ions, only 15%-25% of the filtered magnesium is passively reabsorbed in the proximal tubule[5]. The thick ascending limb of the loop of Henle seems to be the major site of magnesium transport, where the reabsorption of 60%-70% of the ultrafiltrable magnesium takes place[5]. Data suggests that magnesium transport in the loop of Henle is mainly passive *via* paracellular diffusion between the cells. This effect seems to be facilitated by a tight junction protein, claudin-16[6], which is encoded by the paracellin-1 gene[7].

Regarding the distal reabsorption of magnesium (5%-10% of the filtered magnesium), it has been suggested that it enters the tubular cells through magnesium channels in the luminal membrane, whereas the exit mechanism in the basolateral membrane occurs through sodium-magnesium exchange[5].

Hypomagnesemia is of particular clinical importance as it may cause neuromuscular disturbances (e.g., tetany, seizures), cardiac complications (mainly arrhythmias), hypoparathyroidism, osteomalacia (probably due to vitamin D deficiency), osteoporosis as well as concurrent metabolic disorders (mainly hypocalcemia and hypokalemia)[4,8-11].

Hypomagnesemia may be due to inadequate intake, increased entry into cells, as well as gastrointestinal or renal losses[11]. Several pathologic conditions and drugs lead to hypomagnesemia through one or more of these mechanisms. Drugs frequently associated with renal magnesium wasting include loop and thiazide diuretics, aminoglycosides, amphotericin, cisplatin, cyclosporine, pentamidine and foscarnet[12-14]. An increasing number of reports have recently identified proton pump inhibitors (PPIs) as a cause of hypomagnesemia[15-21]. This paper discusses the use of these drugs as an emerging cause of hypomagnesemia.

PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus, where they become protonated producing the activated sulphenamide form of the drug. The latter binds covalently and blocks the hydrogen-potassium adenosine triphosphatase enzyme system of gastric parietal cells thus irreversibly inhibiting acid secretion[22-24].

PPIs are indicated for the prevention and treatment of dyspeptic symptoms attributed to peptic ulcer, gastritis, esophagitis and gastroesophageal reflux[24,25]. Their use has increased greatly in recent years rendering them among the most commonly prescribed drugs; for example, PPIs now account for nearly 10% of the annual prescribing costs of £4.5 billion in England[26]. In fact, many patients take these drugs without an appropriate indication[26]. Therefore, even rare adverse effects associated with their use may be of clinical importance. PPIs are generally well tolerated with an overall incidence of side effects below 5%[27]. The most common side effects are headache, diarrhea, abdominal pain and nausea[27]. However, PPI use has been associated with some undesirable serious conditions, such as increased risk of clostridium difficile enterocolitis[28] and severe hypomagnesemia with significant ensuing morbidity[15-21].

It was in 2006 when Epstein *et al*[18] first reported 2 patients currently treated with omeprazole who presented with carpopedal spasm, severe hypomagnesemia and hypocalcemia without an appropriate increase in parathyroid hormone (PTH) concentration[18]. The levels of magnesium in serum and urine normalized after omeprazole discontinuation and remained within normal range without supplementation. Of note, calcium levels were restored after PPI discontinuation before serum magnesium had been corrected, while PTH levels rose only after recovery. Although another case of PPI-induced hypocalcemia has been previously described[29], the levels of magnesium were not available; thus, this was the first case of PPI-induced hypomagnesemic hypoparathyroidism[18]. Similarly, Kuipers *et al*[20] described a 76-year-old woman with lethargy and muscle cramps in the abdomen and extremities which were attributed to hypocalcemia (with low PTH), hypomagnesemia and hypokalemia. The electrolyte abnormalities were restored with intravenous (iv) calcium, potassium and magnesium supplementation and the patient was discharged with oral magnesium. However, magnesium discontinuation resulted in a dramatic drop in calcium and magnesium levels, suggesting that hypomagnesemia was the leading disturbance[20].

Furthermore, a 43-year-old man on high-dose omeprazole developed symptomatic hypomagnesemia and hypocalcemia with headaches, dizziness and paresthesias in both hands. Electrolytes normalized and symptoms resolved only after omeprazole withdrawal and not with oral and parenteral magnesium replacement[30].

A 78-year-old woman currently taking omeprazole developed hallucinations and muscle excitability which were accompanied with severe hypokalemia, hypocalcemia, hypomagnesemia and hypophosphatemia[31]. Although she responded to iv treatment with magnesium sulphate, calcium gluconate and potassium, supplementation with oral magnesium and phosphate agents was not able to maintain calcium and magnesium levels. The electrolyte status was restored after omeprazole discontinuation without necessitating further magnesium supplementation[31].

Similar electrolyte disturbances, i.e., hypokalemia, hypomagnesemia and hypocalcemia with inappropriately low PTH concentration, were observed in an 81-year old man who presented with muscle cramps, paresthesia, Trousseau's sign, unsteady gait, atrial flutter and long pauses (4 s) in electrocardiogram[31]. All abnormalities were restored when omeprazole was stopped and the patient required no supplementation[31].

Two long-term users of PPI therapy presented with seizures due to severe hypomagnesemia and hypocalcemia with low PTH[17]. The levels of both electrolytes normalized with iv magnesium infusions. The investigators demonstrated avid renal magnesium retention during treatment, suggesting that renal wasting was not the cause of hypomagnesemia. The latter was only partially corrected with high doses of oral magnesium and resolved on PPI withdrawal[17].

Overall, at least 13 cases of PPI-induced hypomagnesemia have been recognized since 2006, when this was first described (Table 1). Since hypomagnesemia impairs several physiologic functions and concomitant electrolyte abnormalities may also cause different symptoms, the clinical presentation varied among the patients affected. Gastrointestinal disturbances (e.g., nausea, vomiting, diarrhea), paresthesias, cramps, dizziness, weakness, tetany were among the most common symptoms, while col-

Table 1 Symptoms and laboratory findings in patients with proton pump inhibitor-associated hypomagnesemia[1]

Proton pump inhibitor	Symptoms	Laboratory findings	Ref.
Omeprazole	Diarrhea, vomiting, hallucinations, muscular excitability	Hypomagnesemia, hypocalcemia, hypophosphatemia and low urinary magnesium and calcium levels	[31]
Omeprazole	Muscle cramps, paresthesia, Trousseau's sign, atrial flutter, pauses (4 s) in ECG	Hypomagnesemia, hypocalcemia and hypokalemia, PTH within the reference range	[31]
Omeprazole	Carpopedal and truncal spasm	Hypomagnesemia and hypocalcemia without an appropriate increase of PTH	[18]
Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole (4 cases)	ECG abnormalities (QT interval prolongation, ST depression, Q waves)	Hypomagnesemia and hypocalcemia without an appropriate increase of PTH, hypokalemia, very low magnesium and calcium and increased potassium urinary levels	[19]
Omeprazole	Grand mal seizures	Hypomagnesemia, hypocalcemia, low urine magnesium levels	[17]
Esomeprazole	Lethargy, muscle cramps in extremities and abdomen	Hypomagnesemia, hypocalcemia, hypokalemia and low serum PTH levels, low urine magnesium levels	[20]
Omeprazole	Paresthesia, numbness, limb weakness	Hypomagnesemia, hypocalcemia, low vitamin D levels	[21]

[1]We should note that not all cases described in the literature are presented in the Table because not all data was available. ECG: Electrocardiogram, PTH: Parathormone.

lapse, arrhythmias, seizures, pulmonary and glottic edema and postanoxic encephalopathy (after collapse probably due to arrhythmia) were the most serious ones[15,19].

In an effort to explain the mechanism of hypomagnesemia, some investigators assessed urinary magnesium excretion and performed diagnostic tests for malabsorption or other gastrointestinal problems. Urinary magnesium was low in all studies suggesting that renal magnesium handling remained intact with PPI use[15,17,20,31]. Gastrointestinal investigations identified no structural cause of hypomagnesemia or malabsorption syndromes including sprue[15,18,21]. Therefore, it is highly likely that PPIs impair intestinal magnesium absorption.

As already mentioned magnesium intestinal absorption is achieved through both passive diffusion and an active transport system[3]. Approximately 90% of magnesium is absorbed passively *via* paracellular pathways between the enterocytes. Specifically, a constant fraction of ingested magnesium is absorbed by simple diffusion in such a way that absorption increases linearly with luminal concentrations[32,33]. The transcellular active transport mechanism operates through transient receptor potential melastatin (TRPM) cation channels, in particular TRPM6 and TRPM7, which are composed of linked channel and protein kinase domains. These channels conduct divalent cations (magnesium and calcium) into the cell following the transmembrane electrochemical gradient[3]. Importantly, this system allows adaptation to low magnesium intake by increasing fractional magnesium reabsorption[34]. TRPM6 is expressed along the entire gastrointestinal tract, in kidney, testis and lungs, while TRPM7 is ubiquitous in tissues. In some of the previously presented cases hypomagnesemia was partially corrected with high doses of oral magnesium, suggesting that PPI treatment does not affect passive magnesium transport but rather the active transport pathway[15,17]. The mechanism by which PPIs reduce intestinal magnesium absorption has not been elucidated, while it remains unknown whether all PPI users are potentially susceptible or if it is an idiosyncratic reaction. It could be speculated that PPIs affect the enzyme and/or the channel functions of the active transport system either directly or *via* intestinal pH changes. Alternatively, susceptibility to reduced intestinal magnesium absorption could be attributed to TRPM6 mutations[35]. Indeed, a mutation in the TRPM6 gene has been identified in familial cases of hypomagnesemia with secondary hypocalcemia[35]. We should note, though, that clinical manifestations have only been described in homozygous and not in heterozygous carriers of TPRM6/7 mutations. Whether variants in TRPM6/7 genes predispose to PPI-induced hypomagnesemia warrants further research.

It appears that PPI-associated hypomagnesemia is a class effect as this disorder has been described with several PPIs, while substitution of one PPI for another resulted in electrolyte derangement and symptom recurrence[16]. Long treatment duration and high adherence rates are probable risk factors[16]. Although most cases of hypomagnesemia occurred after 1 year of treatment, this has also been reported in patients taking PPIs for at least 3 mo[36].

CONCLUSION

To conclude, commonly used drugs, such as PPIs, may induce deleterious clinical manifestations. Thus, it would be prudent to prescribe these agents only when there is a clear indication for their use. The Food and Drug Administration recommends that clinicians consider checking serum magnesium levels before PPI initiation, especially in cases of long-term therapy ($\geq$ 1 year) and/or concomitant administration of other agents that may lower magnesium levels (e.g., diuretics, digoxin)[37].

REFERENCES

1 **Allgrove J**. Physiology of calcium, phosphate and magnesium. *Endocr Dev* 2009; **16**: 8-31
2 **Saris NE**, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta* 2000; **294**: 1-26

3 **Quamme GA**. Recent developments in intestinal magnesium absorption. *Curr Opin Gastroenterol* 2008; **24**: 230-235
4 **Shils ME**. Experimental human magnesium depletion. *Medicine* (Baltimore) 1969; **48**: 61-85
5 **Quamme GA**. Renal magnesium handling: new insights in understanding old problems. *Kidney Int* 1997; **52**: 1180-1195
6 **Kausalya PJ**, Amasheh S, Günzel D, Wurps H, Müller D, Fromm M, Hunziker W. Disease-associated mutations affect intracellular traffic and paracellular Mg2+ transport function of Claudin-16. *J Clin Invest* 2006; **116**: 878-891
7 **Simon DB**, Lu Y, Choate KA, Velazquez H, Al-Sabban E, Praga M, Casari G, Bettinelli A, Colussi G, Rodriguez-Soriano J, McCredie D, Milford D, Sanjad S, Lifton RP. Paracellin-1, a renal tight junction protein required for paracellular Mg2+ resorption. *Science* 1999; **285**: 103-106
8 **Flink EB**. Magnesium deficiency. Etiology and clinical spectrum. *Acta Med Scand Suppl* 1981; **647**: 125-137
9 **Fatemi S**, Ryzen E, Flores J, Endres DB, Rude RK. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25-dihydroxyvitamin D metabolism. *J Clin Endocrinol Metab* 1991; **73**: 1067-1072
10 **Freitag JJ**, Martin KJ, Conrades MB, Bellorin-Font E, Teitelbaum S, Klahr S, Slatopolsky E. Evidence for skeletal resistance to parathyroid hormone in magnesium deficiency. Studies in isolated perfused bone. *J Clin Invest* 1979; **64**: 1238-1244
11 **al-Ghamdi SM**, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis* 1994; **24**: 737-752
12 **Bashir H**, Crom D, Metzger M, Mulcahey J, Jones D, Hudson MM. Cisplatin-induced hypomagnesemia and cardiac dysrhythmia. *Pediatr Blood Cancer* 2007; **49**: 867-869
13 **Shetty AK**, Rogers NL, Mannick EE, Aviles DH. Syndrome of hypokalemic metabolic alkalosis and hypomagnesemia associated with gentamicin therapy: case reports. *Clin Pediatr* (Phila) 2000; **39**: 529-533
14 **Laniado-Laborín R**, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. *Rev Iberoam Micol* 2009; **26**: 223-227
15 **Mackay JD**, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. *QJM* 2010; **103**: 387-395
16 **Cundy T**, Mackay J. Proton pump inhibitors and severe hypomagnesaemia. *Curr Opin Gastroenterol* 2011; **27**: 180-185
17 **Cundy T**, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. *Clin Endocrinol* (Oxf) 2008; **69**: 338-341
18 **Epstein M**, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med* 2006; **355**: 1834-1836
19 **Hoorn EJ**, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. *Am J Kidney Dis* 2010; **56**: 112-116
20 **Kuipers MT**, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors--a review. *Neth J Med* 2009; **67**: 169-172
21 **Fernández-Fernández FJ**, Sesma P, Caínzos-Romero T, Ferreira-González L. Intermittent use of pantoprazole and famotidine in severe hypomagnesaemia due to omeprazole. *Neth J Med* 2010; **68**: 329-330
22 **Williams MP**, Pounder RE. Review article: the pharmacology of rabeprazole. *Aliment Pharmacol Ther* 1999; **13** Suppl 3: 3-10
23 **Playford RJ**, Podas T, Modlin I. Pantoprazole, Prout and the proton pump. *Hosp Med* 1999; **60**: 500-504
24 **Welage LS**, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc* (Wash) 2000; **40**: 52-62; quiz 121-3
25 **DeVault KR**, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999; **94**: 1434-1442
26 **Choudhry MN**, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with Clostridium difficile-associated disease. *QJM* 2008; **101**: 445-448
27 **Reilly JP**. Safety profile of the proton-pump inhibitors. *Am J Health Syst Pharm* 1999; **56**: S11-S17
28 **Aseeri M**, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008; **103**: 2308-2313
29 **Subbiah V**, Tayek JA. Tetany secondary to the use of a proton-pump inhibitor. *Ann Intern Med* 2002; **137**: 219
30 **Druce MR**, Thomas JDJ, Gorrigan RJ, Kelly PA, Coppack SW, Akker SA. Hypomagnesaemia and hypocalcaemia with proton-pump inhibitors: an under-recognised phenomenon. *Endocrine Abstracts* 2009; **19**: P50
31 **Shabajee N**, Lamb EJ, Sturgess I, Sumathipala RW. Omeprazole and refractory hypomagnesaemia. *BMJ* 2008; **337**: a425
32 **Fine KD**, Santa Ana CA, Porter JL, Fordtran JS. Intestinal absorption of magnesium from food and supplements. *J Clin Invest* 1991; **88**: 396-402
33 **Voets T**, Nilius B, Hoefs S, van der Kemp AW, Droogmans G, Bindels RJ, Hoenderop JG. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption. *J Biol Chem* 2004; **279**: 19-25
34 **Schlingmann KP**, Waldegger S, Konrad M, Chubanov V, Gudermann T. TRPM6 and TRPM7--Gatekeepers of human magnesium metabolism. *Biochim Biophys Acta* 2007; **1772**: 813-821
35 **Schlingmann KP**, Weber S, Peters M, Niemann Nejsum L, Vitzthum H, Klingel K, Kratz M, Haddad E, Ristoff E, Dinour D, Syrrou M, Nielsen S, Sassen M, Waldegger S, Seyberth HW, Konrad M. Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet* 2002; **31**: 166-170
36 Long-term PPI use associated with low magnesium. 2011. Available from: URL: http://www.medscape.org/viewarticle/738492
37 FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). Available from: URL: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm

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