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.

PROTON PUMP INHIBITOR-INDUCED HYPOMAGNESEMIA

Magnesium is an essential cation which is implicated in several physiological processes in the body\(^1\). 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\(^2\). 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\(^3,4\). Overall, approximately 100 mg (4.1 mmol) of magnesium are absorbed and magnesium balance is maintained by their urinary reabsorption\(^3,4\).

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 ultrafilterable 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[8].

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)[18-21].

Hypomagnesemia may be due to inadequate intake, increased entry into cells, as well as gastrointestinal or renal losses[22]. 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 foscarner[23-25]. 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 canalculus, 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[19]. 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[28], 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[28].

A 78-year-old woman currently taking omeprazole developed hallucinations and muscle excitability which were accompanied with severe hypokalemia, hypocalcemia, hypomagnesemia and hypophosphatemia[30]. 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[31].

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-
Diarrhea, vomiting, hallucinations, muscular excitation.

Hypomagnesemia, hypocalcemia, low urine magnesium levels.

Lethargy, muscle cramps in extremities and paresthesia.

Symptoms

Hypomagnesemia, hypocalcemia, hypophosphatemia and low urinary magnesium and calcium levels.

Hypomagnesemia, hypocalcemia and hypokalemia, PTH within the reference range.

Hypomagnesemia and hypocalcemia without an appropriate increase of PTH.

Hypomagnesemia and hypocalcemia without an appropriate increase of PTH, hypokalemia, very low magnesium and calcium and increased potassium urinary levels.

Hypomagnesemia, hypocalcemia, low urine magnesium levels.

Hypomagnesemia, hypocalcemia, hypokalemia and low serum calcium levels.

Hypomagnesemia, hypocalcemia, low urine magnesium levels.

Hypomagnesemia, hypocalcemia, low vitamin D levels.

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.

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 (≥ 1 year) and/or concomitant administration of other agents that may lower magnesium levels (e.g., diuretics, digoxin).

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Florentin M et al. PPI-induced hypomagnesemia

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