Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: http://www.tandfonline.com/loi/ieds20

Hypomagnesemia and proton-pump inhibitors

Giuseppe Famularo, Laura Gasbarrone & Giovanni Minisola

To cite this article: Giuseppe Famularo, Laura Gasbarrone & Giovanni Minisola (2013) Hypomagnesemia and proton-pump inhibitors, Expert Opinion on Drug Safety, 12:5, 709-716, DOI: 10.1517/14740338.2013.809062

To link to this article: http://dx.doi.org/10.1517/14740338.2013.809062

Published online: 29 Jun 2013.

EXPERT OPINION

Hypomagnesemia and proton-pump inhibitors

Giuseppe Famularo[†], Laura Gasbarrone & Giovanni Minisola
San Camillo Hospital, Rome, Italy

Introduction: Proton pump inhibitors (PPIs) have been linked to clinically symptomatic hypomagnesemia.

Areas covered: We searched Medline database in all languages using 'proton-pump inhibitors, magnesium, hypomagnesemia and hypomagnesemic hypoparathyroidism' as search terms and other articles were identified through searches of the files of the authors and reference lists from relevant articles. All patients presented with hypomagnesemic hypoparathyroidism, however, they rarely had life-threatening conditions such as malignant ventricular arrhythmias associated with prolonged QT interval, tetany and generalized seizures. Hypomagnesemia was seen with different PPIs, which could suggest a class effect, and was refractory to Mg replacement until PPIs were stopped. Hypomagnesemia may recur after re-challenge with the same or a different PPI and is not clearly dose-related. Mechanisms are poorly understood but PPI-induced hypochlorhydria does not seem involved. Carriers of TRPM6/7 mutations could be at risk.

Expert opinion: Although mechanism and incidence rate remain unclear, there seems little doubt that PPIs may cause hypomagnesemia. We should obtain blood Mg levels prior to initiation of PPIs when patients are expected to be on treatment for long period of time and in those with other potential causes of hypomagnesemia. Use of H_2-blockers may be an appropriate alternative.

Keywords: hypomagnesemia, hypomagnesemic hypoparathyroidism, magnesium, proton-pump inhibitors

Expert Opin. Drug Saf. (2013) 12(5):709-716

1. Introduction

Proton-pump inhibitors (PPIs) are the mainstay in the treatment of acid-related disorders and as of today are one of the most commonly prescribed classes of drug worldwide also because they are often inappropriately prescribed [1]. Even though PPIs are usually well-tolerated, adverse effects have increasingly been described since their introduction into clinical practice, which has raised some concern about their safety profile. Adverse effects appear to be mainly related to the alkalization of the gastric acidity and range from hypergastrinemia to enteric infections including *Clostridium difficile*, pneumonia, osteoporosis and fracture risk, iron and vitamin B12 deficiency, and drug–drug interactions involving both the CYP system and the intestinal absorption which may ultimately alter the pharmacological activity, as well as the clinical response to, clopidogrel, warfarin, benzodiazepines, tricyclic antidepressants and phenytoin [2]. We discuss here the body of research in favor of a possible causal role of PPIs in hypomagnesemic hypoparathyroidism, a rare disorder recently linked with their long-term use.

2. Magnesium metabolism and hypomagnesemia

Mg, which is the second most abundant intracellular cation, is an essential factor implicated in many biochemical and physiological processes, and its homeostasis

informa
healthcare

Article highlights.

- Evidence is limited in favor of a clear-cut association between long-term PPI therapy and risk of hypomagnesemia.
- Severe presentations with malignant arrhythmias, tetany and generalized seizures associated with the lowest blood Mg levels.
- Close monitoring of blood Mg required only in patients with additional risk factors for hypomagnesemia
- H_2-blockers are a valuable alternative to PPIs in patients with hypomagnesemia who need long-term antacid therapy.

This box summarizes key points contained in the article.

is sophisticatedly regulated by intestinal absorption, renal excretion and other systems in the body [3]. It is an important cofactor for enzymatic reactions and plays a pivotal role in energy metabolism involving ATP, which explains the clinical syndromes that develop with deficiency [3].

Hypomagnesemia is an under-recognized problem at the population level. Almost 50% of the US population has been shown to consume less than the daily requirement of Mg from foods and the figure was down from 56% in 2001 – 2002 to 48% in 2005 – 2006 [4]. Furthermore, hypomagnesemia is found in up to 12% of hospitalized patients [5] and the incidence is as high as 60 – 65% in intensive care settings [6].

Mg is widespread in foods and approximately one-third of dietary Mg is absorbed, that is about 120 mg daily, principally in the small bowel through both a carrier-mediated transport and simple diffusion [7]. Low gastric pH is important because Mg binds to ligand sites on dietary fibers and may be displaced by hydrogen ions, which facilitates the intestinal absorption; in addition, waves of acidity entering the small intestine from the stomach may help to keep Mg salts in solution until they are absorbed [7]. There is ileal secretion of approximately 40 mg Mg daily and absorption of another 20 mg daily in the large bowel [7]. One important point is that the blood Mg levels represent only 0.5% of total body Mg stores and the maintenance of circulating concentrations within the normal range largely depends on the net balance between the gastrointestinal absorption and the urinary excretion. There is no physiologic hormonal control and changes in Mg intake are balanced by changes in urinary Mg filtration and reabsorption in response to changes in blood Mg concentrations. This highlights the role of kidneys as highly efficient organs in tight regulation of Mg conservation and excretion. Mg is completely filtered by the glomerulus and then is reabsorbed in the proximal tubules (15 – 20%) and thick ascending loop of Henle (about 70%), both by passive, paracellular processes driven by positive luminal charge [7]. Moreover, fine-tuning of Mg reabsorption occurs in the distal convoluted tubule.

As in the intestine, transient receptor potential melastin 6/7 (TRPM6/7) channels located in the apical membrane of the distal convoluted tubule actively transport Mg from the lumen to the intracellular space and, once inside the cell, Mg crosses the basolateral membrane into peritubular capillaries [8]. Mg deficiency increases the expression of TRPM6/7 in the intestine and kidneys which enhances active Mg transport through these channels [8]. Ultimately, < 3% of filtered Mg is lost in the urine under physiological conditions.

There are many causes of hypomagnesemia (**Table 1**), gastrointestinal and urinary losses being by far the most common [7]. Depending on the severity of hypomagnesemia, patients may be asymptomatic or present with life-threatening ventricular arrhythmias or severe neuromuscular symptoms such as tetany and generalized convulsions.

Clinical symptoms of Mg deficiency relate to the central role of Mg in energy metabolism and neuromuscular transmission, but it is generally difficult to ascribe symptoms of hypomagnesemia solely to Mg deficiency because severely hypomagnesemic patients have coexistent hypokalemia and hypocalcemia that may remain refractory to treatment until the underlying Mg deficiency is corrected [7]. Potassium is lost into the extracellular fluids and then into the urine because Mg deficiency impairs the renal conservation of this cation.

Hypomagnesemic patients have normal or low, and in some cases undetectable, blood levels of parathyroid hormone (PTH) [7], which reflects the suppressive effect of hypomagnesemia on PTH secretion [9]. Further evidence comes from the observation that Mg supplementation leads to a rapid rise in plasma PTH levels in the majority of hypomagnesemic patients [7]. Most of them have tissue resistance to PTH action, which is postulated to be of greater importance than the diminished secretion of the hormone [10,11]. However, there are insufficient data to explain why a subset of hypomagnesemic patients have normal PTH levels in the context of the experimental evidence of the PTH-suppressing effect of decreased Mg concentrations. In particular, it is unclear if this depends on the severity of hypomagnesemia and it is unknown if the concomitant deficiencies of other ions also play a role. It would also be of interest to investigate whether the tissue resistance to PTH action in these patients can be reverted by Mg supplementation as no data are currently available. If no cause of hypomagnesemia is apparent, the distinction between gastrointestinal and renal losses is made by measuring the 24-h urinary Mg excretion or the fractional Mg excretion on a random urine specimen. Low fractional Mg excretion is an indirect measurement of total body Mg deficiency.

3. PPIs and hypomagnesemic hypoparathyroidism: the clinical impact

There is a wide spectrum of disorders that may cause hypomagnesemic hyporathyroidism that is parathyroid agenesia, surgery, radiation, infiltration by systemic diseases, autoimmune parathyroiditis and reduced parathyroid function

Table 1. Causes of hypomagnesemia.

Gastrointestinal losses
Acute and chronic diarrhea
Malabsorption syndromes
Small bowel by-pass surgery
Acute and chronic pancreatitis
Inborn metabolism errors
Renal losses
Loop and thiazide-type diuretics
Extracellular volume expansion
Chronic alcoholic hepatitis
Hypercalcemic syndromes
Nephrotoxins (aminoglycosides, amphotericin B, cisplatin, pentamidine, cyclosporine)
Acute tubular necrosis
Renal transplantation
Bartter syndrome
Post-obstructive diuresis
Primary renal magnesium wasting syndrome
Idiopathic hypercalciuria
Gitelmann's syndrome
Miscellaneous causes
Liver transplantation
Hungry bone syndrome
Diabetes
Transfusion of citrate-rich blood products
Tacrolimus
Digoxin
Calcium supplements

due to PTH gene defects and calcium sensitizing receptor mutations [12]. Exposure to PPIs has been recently added to the list.

The first two cases of hypomagnesmic hypopathyroidism linked to the long-term use of PPIs were in 2006 from Epstein *et al.* [13] and thereafter several other case reports have been described [14-28]. Whether these cases represent the 'tip of the ice-berg' is unclear, however, it is reasonable to speculate this side effect could be under-diagnosed and under-reported because of the large-size worldwide prescription of PPIs and the low frequency of Mg measurement in routine clinical analysis. Available data are insufficient to exactly quantify the incidence rate for hypomagnesemia with PPI therapy.

Table 2 summarizes the key clinical and laboratory findings reported in patients with PPI-associated hypomagnesemia. Hypomagnesemia has been described in adult patients taking PPIs for at least 3 months but in most cases after > 1 year of treatment and some of them were given PPI therapy for 5 or more years. No case has been reported among children.

All patients had the typical features of hypomagnesemic hypoparathyroidism (i.e., hypomagnesemia, hypocalcemia, inappropriately low to normal PTH and normal levels of vitamin D). Since hypomagnesemia also produces impaired PTH secretion which may lead to hypocalcemia, the concomitant finding of hypocalcemia and normal or low PTH levels confirms hypomagnesemia as the primary deficiency.

Patients were asymptomatic or complained of non-specific symptoms (nausea, vomiting, diarrhea) and mild neuromuscular manifestations such as paresthesias, carpopedal spasm, muscle cramps and positive Chvostek and Trousseau signs. Some of them, however, were severely ill and presented with life-threatening conditions such as malignant ventricular arrhythmias associated with prolonged QT interval, tetany and generalized seizures. Underlying host characteristics, comorbidities, concomitant therapy with other drugs and individual pharmacogenetics could contribute to the ultimate severity of clinical symptoms of hypomagnesemia. Furthermore, there is a high probability that milder cases of PPI-associated hypomagnesemia can go undetected.

What constitutes a clinically important hypomagnesemia remains to be defined but it is notable that the majority of patients with PPI-associated hypomagnesemia had no clinical symptoms, which, therefore, were not linearly dependent on the blood Mg levels. In general, clinical symptoms of hypomagnesemia were more likely when blood Mg concentrations fell below 1.0 mEq/l (0.5 mmol/l or 1.2 mg/dl). However, no lowest threshold limit of magnesemia for clinical symptoms to occur has been established and no clear-cut linear relationship has been quantified between blood Mg levels and the probability of overt clinical manifestations of hypomagnesemia. One problem in discussing the clinical relevance of PPI-associated hypomagnesemia is that different criteria have been proposed to define hypomagnesemia. For example, various units, that is mEq/l, mmol/l, mg/dl at least, have been used in previous reports, which is a not negligible confounding factor in the context. Further confusion is generated by the recently raised problem of Chronic Latent Magnesium Deficit (CLMD), a subtle chronic negative magnesium balance in a large number of people who appear healthy [29]. As a consequence, many researchers agree that the standard 0.70 mmol/l as the lowest limit of the normal range for blood Mg is probably too low for the proper diagnosis of hypomagnesemia and that the 0.85 mmol/l threshold would be more appropriate under a biological and clinical perspective to identify patients with true hypomagnesemia [30].

Hypomagnesemia was refractory to oral or parenteral Mg replacement irrespective of high doses of supplemented Mg, that is up to 480 mg elemental Mg daily in the patients reported by Epstein *et al.* [13]., and the response failure was also independent of the elimination of other plausible confounding causes of hypomagnesemia, such as for example diuretics or other drugs. In turn, Mg and PTH levels quickly normalized after PPI cessation and remained stable once Mg replacement was withdrawn. The median time required for Mg to normalize was 1 week after discontinuing the PPI. In the patient reported from Shabajee hypomagnesemia persisted for 21 months despite Mg supplementation but blood Mg levels quickly returned to the normal range within 2 weeks after PPI therapy was discontinued [15].

Patients may have other conditions that make hard to understand the causal relationship, if at all, between exposure

Table 2. Key clinical and laboratory features of patients with PPI-induced hypomagnesemia.

Adult patients with prolonged (at least 3 months; in most cases > 1 year and up to > 5 years) exposure to PPIs
No case described among children
All patients had the features of hypomagnesemic hypoparathyroidism (i.e., hypomagnesemia, hypocalcemia, low to normal PTH, normal vitamin D)
Clinical symptoms depending in most cases on the severity of hypomagnesemia
Life-threatening presentations (malignant ventricular arrhythmias with prolonged QT interval, tetany, generalized seizures) common among those with the lowest blood Mg levels
Subclinical cases often unrecognized
Hypomagnesemia refractory to oral or parenteral Mg replacement but quick normalization after discontinuing PPIs
Hypomagnesemia reported with different PPIs (class-effect) and relapse after re-challenge with the same or a different PPI
Unclear relationship between hypomagnesemia and PPI dose
Use of H_2-blockers appropriate therapeutic alternative if patients need prolonged antacid treatment
Other more common causes of hypomagnesemia need to be ruled out

Mg: Magnesium; PPIs: Proton-pump inhibitors; PTH: Parathyroid homone.

to PPIs and the occurrence of hypomagnesemia. For example, the case described by Quasdorff *et al.* was a 30-year-old woman with Crohn's disease whose history included a partial ileal resection and newly detected recto-vaginal fistula [26]. On the other hand, we should be warned that use of PPIs could exacerbate other Mg-lowering conditions so caution in prescribing or maintaining a patient on PPIs must also be in play. Furthermore, the health implications of low Mg status and CMLD are largely unrecognized and often go undetected whereas, in fact, they can predict serious health issues [31-33].

Hypomagnesemic hypoparathyroidism has been reported with different PPIs [13-28], for example our own patient had long-standing hypomagnesemia while on treatment with both omeprazole and pantoprazole [28]. The finding of recurrent hypomagnesemia after re-challenge with the same or a different PPI in several cases so far published is in agreement with the hypothesis. In these patients, the median time to suffer a new episode of hypomagnesemia on re-challenge was 2 weeks after re-starting the PPI.

One crucial issue is that published reports of PPI-dependent hypomagnesemia include just one [14,19,20,24-28], two [15,16], four [21] or ten [23] patients, therefore, we should use great caution in lending support to the view that hypomagnesemia could reflect a class-effect that may so apply to all PPIs until results from large studies comparing different PPIs in homogeneous cohorts will be available. In contrast with the little information available, in 2011 the US FDA warned that long-term use of PPIs has the potential reduce the blood Mg levels and that hypomagnesemia did not improve in spite of Mg supplememntation in about 25% of cases reviewed [34]. On this background, FDA recommended to obtain blood Mg levels before initiating long-term therapy with PPIs, particularly in patients concomitantly receiving drugs capable to cause Mg depletion such as diuretics and digoxin [34].

The important question if PPI-associated hypomagnesemia is dose-related is unanswered. Even though most reports have shown that the PPI-associated hypomagnesemia may be 'non-dose related', nonetheless in at least one report a linear dose–response curve between Mg levels and PPI dose has been found [20]. It is also unknown if the intermittent use of PPIs could help to reduce the probability of hypomagnesemia as suggested by Fernández-Fernández and colleagues [24].

Most of the evidence for a causal relationship between PPI use and hypomagnesemia is gathered from case reports or small case series and the lack of controlled epidemiologic data in larger sample sizes is an important problem in the context. A recent cross-sectional study by Gau and colleagues [35] examined the association between PPIs and blood Mg levels or hypomagnesemia in a cohort of hospitalized adults. Among study patients, PPI users (n = 207) had a mean Mg level of 1.91 (SD = 0.34) mg/dl, and non-users (n = 280) 2.00 (0.30) mg/dl, (p = 0.004). After adjusting for confounders (age; sex; diagnosis of diabetes mellitus and past medical history of congestive heart failure, use of diuretics, supplementation of potassium and Mg, discharge diagnosis of any acute gastrointestinal illness, and levels of serum albumin, potassium and creatinine), the authors demonstrated that PPI use was independently associated with lower blood Mg levels and also with clinically significant hypomagnesemia. In this cohort study patients used different types of PPIs (omeprazole, lansoprazole, esomeprazole) and both standard and high defined daily dose units of PPI therapy were associated with hypomagnesemia. Despite several methodological biases (i.e., enrolled subjects were only acutely ill patients requiring hospitalization, blood Mg levels were not routinely measured for all hospitalized patients, and data about the duration of PPI use were not provided), Gau and colleagues concluded that PPI use prior to hospitalization for an acute illness was associated with lower blood Mg levels by approximately 0.1 mg/dl and with a 2.5-fold increased risk of hypomagnesemia as compared to non-users. Overall, their findings indicate that long-term PPI use could be associated with both sub-clinical Mg insufficiency or an overt deficiency status. It is also noteworthy that the great majority of their patients did not have any symptoms of Mg deficiency, which raises some concern about the net clinical impact of the impaired Mg handling caused by PPI use.

Tamura and colleagues [36] evaluated the reports submitted to the Adverse Event Reporting System of US FDA from 2004 to 2009 to assess the use of omeprazole and esomeprazole, the S-isomer of omeprazole, in terms of susceptibility to hypomagnesemia. Both omeprazole and esomeprazole were linked with a greater risk of hypomagnesemia compared to no use of PPIs, however, the association was statistically more significant for omeprazole compared to esomeprazole. The authors stated that sufficient evidence was not provided to recommend systematic monitoring of Mg blood levels in all PPI users but long-term exposure to PPIs can lead, at least in the context of certain settings, to severe and potentially life-threatening hypomagnesemia.

Recently, Dazinger and colleagues have published the results of a study conducted in 11,490 consecutive hospitalized intensive care unit patients at a tertiary medical center over 7 years [37]. They found that patients taking PPIs, compared with those receiving H_2-blockers or no acid-suppressive medications, had a decline in serum Mg after adjusting for several clinical and laboratory factors. However, the effect was seen only in those concomitantly receiving diuretics; in fact, among diuretic users (n = 3286), PPIs were associated with a lower serum Mg concentration (0.028 ± 0.007 mg/dl lower) and an odds ratio of 1.54 (95% CI 1.22–1.95) for hypomagnesemia (< 1.6 mg/dl). In other words, users of PPIs were not at higher risk of hypomagnesemia compared to non-users after adjustment for major confounders such as the concomitant use of diuretics. In fact, no association with hypomagnesemia was found among 'lone' PPI-users; however, this fits what is seen in reported cases. In reality, as noted by Perazella in the accompanying commentary, most patients have other co-morbidities (vomiting, diarrhea, diabetes mellitus, potential TRPM6/7 mutations) or are also receiving concomitant medications (diuretics, stool softeners and so on) that can exacerbate hypomagnesemia [38]. In conclusion, the study by Danzinger and colleagues underscores that the majority of patients given PPIs will not develop clinically significant hypomagnesemia but a proportion of them are at risk of hypomagnesemia during PPI therapy. Furthermore, in this study H_2-blockers were not associated with hypomagnesemia irrespective of the concomitant use of diuretics.

3.1 What are the mechanisms of PPI-induced hypomagnesemia?

Many drugs can cause abnormalities in blood Mg concentration and most cases of drug-induced hypomagnesemia derive from a loss of the mineral in the urine by facilitated renal secretion [39]. However, the mechanisms by which Mg intestinal and renal handling is affected by PPIs are poorly understood.

The finding that almost all patients with PPI-associated hypomagnesemia have a low urinary Mg excretion indicates adequate renal handling and rather suggests that Mg uptake is disturbed. No evidence of urinary Mg wasting has been found in patients with PPI-induced hypomagnesemia except one report suggesting that a reduced efficiency of renal Mg conservation might have been involved [22]. PPI-induced hypochlorhydria has been postulated to impair Mg solubilization and absorption in the small intestine which could ultimately deplete Mg body stores [16].

A better knowledge of the biological and physiological mechanisms involved in Mg metabolism and handling may help to target the main factors responsible for PPI-dependent hypomagnesemia. Modeling experiments are in agreement with the hypothesis that a PPI-induced decrease in intestine luminal pH of 0.5 (a 3.5-fold increase in protons) alters TRPM6/7channel affinity for Mg [40]. In TRPM6/7 channel pore-forming regions, two ionized carboxyl side chains of both glutamic and aspartic acid residues are important to Mg binding and electrical conductivity. These findings indicate that increased intestinal protons as seen with PPIs reduce the ionized/un-ionized ratio for these residues, which decreases channel affinity for Mg and reduces absorption suggesting that PPIs can impair active Mg transport through TRPM6/7 channels and lead to hypomagnesemia over time. This can be quantified in the terms that short-term PPI therapy may cause about 5% reduction in blood Mg level, which seems to reflect a 1% reduction in Mg absorption after 1 week of therapy in humans [40]. However, the lack of any report of hypomagnesemia associated with H_2-blockers does not support a mechanistic role of hypochlorhydria in the pathophysiology of PPI-associated hypomagnesemia. This view is indirectly lent support by the finding that the least effective PPI in decreasing gastric pH, that is pantoprazole, was found to be associated with hypomagnesemia as reported with other PPIs. In addition, blood Mg concentration and urinary excretion have been shown to quickly increase when PPI therapy was withdrew and H_2-blockers given in turn. In addition, a study performed in patients with the short bowel syndrome clearly demonstrated that omeprazole as well the H_2-blocker ranitidine had no effect on the intestinal absorption of Mg and other electrolytes [41]. To the best of our knowledge, there is no report of hypomagnesemia associated with the use of antacids other than PPIs or H_2-blockers.

Genetic factors might result in increased susceptibility to PPI-induced hypomagnesemia. It is unknown if the prolonged use of PPIs could cause an altered regulation of the transient receptor potential melastin 6/7 (TRPM 6/7), which is an active transcellular channel present in the gastrointestinal tract and kidneys involved in driving cations such as Mg and calcium into the cells [42,43]. TRPM6/7 mutations are postulated to impair kidney function and, possibly, also the urinary excretion of Mg. TRPM6/7 mutations have been shown in human disease only in association with Mg urinary wasting [44] or hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder characterized by diminished intestinal absorption and increased renal excretion of magnesium that is uniformly manifested in early infancy with generalized convulsions, muscle spasms or tetany [45].

It has been also postulated that variant alleles of TRPM6/7 are associated with subtle malabsorption and/or persistent

leak trough the kidneys which may be further aggravated by PPIs thus being responsible for hypomagnesemia in susceptible patients. This might explain why only a minority of PPI-treated patients develop hypomagnesemic hypoparathyroidism which implicates that heterozygous carriers of TRPM6/7 mutations could be at a greater risk of PPI-induced hypomagnesemia. Search for mutations of the TRPM6/7 gene was negative in one patient with PPI-induced hypomagnesemia [18].

Furthermore, no disturbances in the urinary Mg wasting have been found in long-term PPI users with hypomagnesemia. In summary, the available body of evidence indicates that the pathophysiology behind PPI-induced hypomagnesemia remains elusive. However, the PPI-induced hypochloridria is unlikely to be the main factor responsible for hypomagnesemia in these patients. Even though the accepted physiological control points for body Mg are absorption and excretion of the cation we should acknowledge that only considering these two control points may be simplistically based on lack of research and knowledge on mechanisms of Mg metabolism and handling.

4. Conclusion

To date, several case reports [7-22] and only two observational studies [23,24] have suggested the association of long-term PPI therapy with the risk of symptomatic severe hypomagnesemia. Hypomagnesemia might be under-diagnosed in the context of PPI therapy because of several reasons but, even though the strength of the evidence linking PPIs with an increased risk of hypomagnesemia is limited and the potential mechanisms elusive, it is still possible that published data could actually represent the tip of the iceberg of an under-recognized and potentially serious side effect.

5. Expert opinion

Although the mechanism and the incidence rate remain unclear, there seems little doubt that PPIs may cause hypomagnesemia at least in certain patients. Before definitely linking in the individual patient the occurrence of hypomagnesemia with PPI use, other more common causes need to be ruled out on history and clinical and laboratory findings. PPIs should be viewed as a possible cause of hypomagnesemia particularly in those who are clinically symptomatic and when no other obvious cause is apparent. We should consider obtaining blood Mg levels prior to initiation of PPIs when patients are expected to be on treatment for long periods of time, that is for 3 months or more, and in those who take PPIs in association with medications such as digoxin, diuretics, calcium supplements or drugs that by themselves have the potential to cause hypomagnesemia. In these settings, it could be reasonable and cost-effective to monitor Mg levels periodically. PPI treatment should not be withheld from patients who genuinely require it, but the PPI should be taken in the lowest effective dose and only for as long as clinically indicated. Use of H_2-blockers may be an appropriate therapeutic alternative when hypomagnesemia occurs during PPI therapy and patients need prolonged antiacid treatment. Recognition and management of subclinical cases are a challenge, nonetheless no evidence exists to support systematic PPI withdrawal in all subclinical cases. Patients on prolonged PPI therapy should be advised of the potential risk of hypomagnesemia as well as to seek medical care if they will experience clinical symptoms and signs consistent with hypomagnesemia. However, despite these problems and the probable under-recognition of this side-effect the benefits of PPI therapy are likely to outweigh the risk of hypomagnesemia. According to research findings available at this time, we need to know much more about the relationship linking exposure to PPIs and Mg metabolism.

6. Addendum

A recent cross-sectional study of the FDA Adverse Event Reporting System database suggests that hypomagnesemia could account for about 1% of all adverse effects of PPIs, with elderly females taking pantoprazole being at the highest risk [46]. However, a retrospective, nested case-control failed to find any association between out-of-hospital PPI use and hypomagnesemia at the time of hospital admission [47].

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Forges I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008;336:2-3
2. Abraham NS. Proton pump inhibitors: potential adverse effects. Curr Opin Gastroenterol 2012;28:615-20
3. Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev 2003;24:47-66
4. Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the United States: are the health consequences underestimated? Nutr Rev 2012;70:153-64
5. Wong ET, Rude RK, Singer FR. A high prevalence of hypomagnesemia in hospitalized patients. Am J Clin Pathol 1983;79:348-52
6. Ryzen E. Magnesium homeostasis in critically ill patients. Magnesium 1989;8:201-12
7. Agus ZS. Hypomagnesemia. J Am Soc Nephrol 1999;10:1616-22
8. Rondon LJ, Tiel Groenestege WM, Rayssiguier Y, Mazur A. Relationship between low magnesium status and TRPM6 expression in the kidney and large intestine. Am J Physiol Regul Integr Comp Physiol 2008;294:R2001-7
9. Chase LR, Slatopolsky E. Secretion and metabolic efficiency of parathyroid hormone in patients with severe hypomagnesemia. J Clin Endocrinol Metab 1974;38:363-71
10. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone and organ resistance in human magnesium deficiency. Clin Endocrinol (Oxf) 1976;5:209-24
11. Freitag JJ, Martin KJ, Conrades MB. Skeletal resistance to parathyroid hormone in magnesium deficiency: studies in isolated perfused bone. J Clin Invest 1974;64:1238-44
12. Thakker RV. Parathyroid disorders and diseases altering calcium metabolism. In: Warrell DA, Cox TM, Firth JD, editors. 5th Edition. Oxford textbook of medicine. Oxford University Press; Oxford; 2010. p. 1850-68
13. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med 2006;355:1834-6

• **This is the first report of hypomagnesemic hypoparathyroidism associated with long-term use of PPIs. In both patients Mg levels rose rapidly to the normal range when PPIs were discontinued.**

14. Metz DC, Sostek MB, Ruszniewski P, et al. Effects of esomeprazole on acid output in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. Am J Gastroenterol 2007;102:2648-54
15. Shabajee N, Lamb EJ, Sturgess I, et al. Omeprazole and refractory hypomagnesaemia. BMJ 2008;337:a425
16. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin Endocrinol 2008;69:338-41
17. Broeren MA, Geerdink EA, Vader HL, et al. Hypomagnesemia induced by several proton-pump inhibitors. Ann Intern Med 2009;151:755-6
18. Doornebal J, Bijlsma R, Brouwer RM. An unknown but potentially serious side effect of proton pump inhibitors: hypomagnesaemia. Ned Tijdschr Geneeskd 2009;153:A711
19. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors: a review. Neth J Med 2009;67:169-72
20. Swaminathan K, Wilson J. Elusive cause of hypomagnesaemia. BMJ 2011;343:d5087
21. Hoorn EJ, van der Hoek J, de Man RA, et al. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis 2010;56:112-16
22. Regolisti G, Cabassi A, Parenti E, et al. Severe hypomagnesemia during long-term treatment with a proton pump inhibitor. Am J Kidney Dis 2010;56:168-74
23. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibi-tor therapy: a clinical case series. QJM 2010;103:387-95
24. Fernandez-Fernandez FJ, Sesma P, Cainzos-Romero T, Ferreira-Gonzalez L. Intermittent use of pantoprazole and famotidine in severe hypomagnesaemia due to omeprazole. Neth J Med 2010;68:329-30

• **This is the only case of PPI-associated hypomagnesemia in whom search for mutations of the TRPM6/7 gene was performed. Findings were negative.**

25. Furlanetto TW, Faulhaber GAM. Hypomagnesemia and proton pump inhibitors. Arch Intern Med 2011;171:1391-2
26. Quasdorff M, Mertens J, Dinter J, Steffen HM. Recurrent hypomagnesemia with proton-pump inhibitor rechallenge. Ann Intern Med 2011;155:405-7
27. Matsuyama J, Tsuji K, Doyama H, et al. Hypomagnesemia associated with a proton pump inhibitor. Intern Med 2012;51:2231-4
28. Famularo G, Minisola G, Bravi MC, et al. Tetany, hypomagnesemia and proton-pump inhibitors. Am J Med 2012;125:e7-8
29. Elin RJ. Assessment of magnesium status for diagnosis and therapy. Magnes Res 2010;23:194-8
30. Elin RJ. Re-evaluation of the concept of chronic, latent, magnesium deficiency. Magnes Res 2011;24:225-7
31. Leone N, Courbon D, Ducimetiere P, et al. Zinc, copper, and magnesium and risks for all-cause, cancer, and cardiovascular mortality. Epidemiology 2006;17:308-14
32. Peacock JM, Ohira T, Post W, et al. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2010;160:464-70
33. Chiuve SE, Korngold EC, Januzzi JL Jr, et al. Plasma and dietary magnesium and risk of sudden cardiac death in women. Am J Clin Nutr 2011;93:253-60
34. PPI's and hypomagnesemia. Med Lett Drugs Ther 2011;53:25
35. Gau JT, Yang YX, Chen R, Kao TC. Uses of proton pump inhibitors and hypomagnesemia. Pharmacoepidemiol Drug Saf 2012;21:553-9

• **In this study, PPI use was associated with lower Mg levels and hypomagnesemia in a population of hospitalized adult patients. Findings support the general notion that long-term PPI use could be associated**

with sub-clinical Mg insufficiency or deficiency status.

36. Tamura T, Sakaeda T, Kadoyama K, Okuno Y. Omeprazole- and esomeprazole-associated hypomagnesaemia: data mining of the public version of the FDA adverse event reporting system. Int J Med Sci 2012;9:322-6

• **The data obtained in this study do not provide sufficient evidence to recommend systematic monitoring of Mg levels in all long-term PPI users, however it shows that chronic exposure to a PPI can lead to severe hypomagnesemia. The strength of the evidence was more noteworthy for omeprazole than for esomeprazole.**

37. Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. Kidney Int 2013;83:692-9

•• **This study demonstrates the association of PPIs with hypomagnesemia in patients hospitalized at a tertiary medical center. Patients taking PPIs, compared with those receiving histamine-2 antagonists or no acid-suppressive medications, had a decline in blood Mg concentrations after adjusting for several clinical and laboratory factors. The effect, however, was seen only in those concomitantly receiving diuretics.**

38. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. Kidney Int 2013;83:553-6

39. Kawamura Y. Drugs affecting serum magnesium concentration. Clin Calcium 2012;22:1211-16

• **Many drugs can cause abnormalities in blood Mg concentration and most cases of drug-induced hypomagnesemia derive from a loss of the mineral in the urine by facilitated renal secretion, however patients with PPI-associated hypomagnesemia have no evidence of urinary Mg wasting.**

40. Bai JP, Hausman E, Lionberger R, Zhang X. Modeling and simulation of the effect of proton pump inhibitors on magnesium homeostasis. 1. Oral absorption of magnesium. Mol Pharm 2012; in press

41. Jeppesen PB, Staun M, Tjellesen L, Mortensen PB. Effect of intravenous ranitidine and omeprazole on intestinal absorption of water, sodium, and macronutrients in patients with intestinal resection. Gut 1998;43:763-9

42. Quamme GA. Recent developments in intestinal magnesium absorption. Curr Opin Gastroenterol 2008;24:230-5

43. Voets T, Nilius B, Hoefs S, et al. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption. J Biol Chem 2004;279:19-25

44. Costa A, Tejpar S, Prenen H, Van Cutsem E. Hypomagnesaemia and targeted anti-epidermal growth factor receptor (EGFR) agents. Target Oncol 2011;6:227-33

45. Schlingmann KP, Sassen MC, Weber S, et al. Novel TRPM6 mutations in 21 families with primary hypomagnesemia and secondary hypocalcemia. J Am Soc Nephrol 2005;16:3061-9

46. Luk CP, Parsons R, Lee YP, et al. Proton pump inhibitor-associated hypomagnesemia: what do FDA data tell us? Ann Pharmacother 2013: In press

47. Koulouridis I, Alfayez M, Tighiouart H, et al. Out-of-hospital use of proton pump inhibitors and hypomagnesemia at hospital admission: a nested case-control study. Am J Kidney Dis 2013: In press

Affiliation

Giuseppe Famularo[†], Laura Gasbarrone & Giovanni Minisola
[†]Author for correspondence
San Camillo Hospital,
Rome, Italy
E-mail: gfamularo@scamilloforlanini.rm.it