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Review Article

Proton pump inhibitor-induced hypomagnesaemia and hypocalcaemia: case review

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Abstract: Proton pump inhibitor (PPI)-induced hypomagnesaemia is a rare but serious adverse effect of a widely prescribed medication. It has become an increasingly recognised complication since 2006, with the U.S. Food and Drug Administration issuing a warning for this risk with regards to long-term PPI use. We present the case of PPI-associated hypomagnesaemia and hypocalcaemia. A 91 year old male presented with tetany from severe hypomagnesaemia and hypocalcaemia. This condition occurred in the context of 18 months of PPI use, and resolved following cessation of PPI therapy and the replenishment of magnesium and calcium stores. Monitoring of magnesium, calcium and potassium levels is crucial in patients prescribed PPIs long-term; especially the elderly patient.

Keywords: PPI, hypomagnesemia

Introduction

Proton pump inhibitors (PPIs) are widely used for the treatment and prevention of acid-related gastrointestinal disorders, with current guidelines recommending them for gastroesophageal reflux disease [1], non-steroidal anti-inflammatory drug (NSAID)-associated peptic ulcer prevention [2], Helicobacter pylori eradication [3], and Zollinger-Ellison syndrome [4]. PPIs are generally well tolerated with a favourable safety profile, and have superior efficacy to histamine-2 receptor antagonists [5-9]. They have become one of the most commonly prescribed drug classes in both primary and specialty care [10]. In the United States, from the introduction of PPIs in the 1980s to the 1990s, their use has risen dramatically with an increase of up to 456% [11]. Although approved for long-term use, long-term safety concerns have been raised with regards to the risk of hypomagnesaemia.

PPI-induced hypomagnesaemia was first recognised in 2006, with a report of two patients developing severe magnesium deficiency, in addition to hypocalcaemia and hypokalaemia, whilst on long-term PPI treatment [12]. Since then, our knowledge of this risk has largely been generated by observational studies, with no more than 40 cases being published to date [13]. In 2011, the US Food and Drug Administration (FDA) issued a drug safety warning regarding the potential association of hypomagnesaemia as a long-term side-effect of PPIs, based on accumulating reports [14-17]. The Australian Therapeutic Goods Administration (TGA) released a similar alert in June 2011 [18]. The underlying pathogenesis for this, however, is still under investigation.

We report a case of severe hypomagnesaemia and hypocalcaemia secondary to PPI exposure. This article reviews the relevant literature of this condition, and discusses the potential mechanism of PPI-induced hypomagnesaemia and hypocalcaemia.

Clinical case

A 91 year old male from home was admitted to hospital with a history, for several months, of involuntary muscle twitches that had worsened recently. These twitches had affected function of his hands and speech, and led to recurrent falls in the two months prior to his admission. He also reported a three week history of watery diarrhoea with no other infective symptoms present.

Table 1. Initial serum laboratory values on presentation

Specimen Type	Result	Specimen Type	Result
Sodium (137-145)	140 mmol/L	Ionised Calcium (1.10-1.30)	0.76 mmol/L
Potassium (3.5-4.9)	4.1 mmol/L	Magnesium (0.70-0.95)	0.24 mmol/L
Urea (2.7-8.0)	7.0 mmol/L	Albumin (34-48)	34 g/L
Creatinine (50-120)	122 mmol/L	eGFR	44 mL/min/1.73 m^2
Phosphate (0.65-1.45)	1.29 mmol/L	25-OH Vitamin D (60-160)	49 ng/mL
Calcium (2.10-2.55)	1.41 mmol/L	PTH (0.8-5.5)	15.7 pmol/l

eGFR-Estimated glomerular filtrated rate; PTH-Parathyroid hormone.

Table 2. Calcium, magnesium and creatinine

Specimen Type	PPI Started	Day 1	Day 2	Day 3	Day 4
Calcium (2.10-2.55)	2.18 mmol/L	1.41 mmol/L	1.96 mmol/L	1.94 mmol/L	2.12 mmol/L
Ionised Calcium (1.10-1.30)	1.17 mmol/L	0.76 mmol/L	1.02 mmol/L	1.03 mmol/L	1.11 mmol/L
Magnesium (0.70-0.95)		0.24 mmol/L	1.02 mmol/L	0.86 mmol/L	0.82 mmol/L
Creatinine (50-120)	138 mmol/L	122 mmol/L	130 mmol/L	137 mmol/L	143 mmol/L

The patient had a history of chronic renal failure of uncertain duration and aetiology, hypertension and an episode of transient ischaemic attack. He was admitted to hospital 18 months prior to this admission, due to duodenal ulcers secondary to NSAID use, for which he was prescribed oral pantoprazole 40 mg three times-a-day, a dose that was subsequently titrated to 40 mg once daily by his local doctor. His other medical treatment included candesartan (8 mg daily) for hypertension, diltiazem (240 mg) daily for hypertension, aspirin (100 mg daily) for acute coronary syndrome risk, risedronate (35 mg weekly) for osteoporosis, and a combination tablet of calcium carbonate/cholecalciferol (1200 mg/25 mcg daily) for vitamin D deficiency. The patient reported very poor compliance with the latter tablet due to its size making swallowing difficult.

At presentation, the patient was alert and oriented. He appeared well with a blood pressure of 154/75 mmHg, pulse rate of 74/min, temperature of 37.1°Celsius, and a percutaneous oxygen saturation level of 94% when breathing room air. He had notable tetany on observation and a positive Trousseau's sign, but otherwise had an unremarkable neurological examination.

An electrocardiogram demonstrated normal sinus rhythm. Remarkable serum laboratory values are reported in **Table 1**. Stool specimen microscopy and culture determined no underlying enteric infection or inflammation.

The diarrhoea was considered a complication of the electrolyte derangement rather than a contributing cause to it. Our clinical suspicion was that this patient's symptoms were attributable to hypocalcaemia secondary to PPI-induced hypomagnesaemia, in the setting of secondary hyperparathyroidism given his comorbidities of chronic renal failure and vitamin D deficiency. His hypocalcaemia was further exacerbated by bisphosphonate use in the context of poor compliance to calcium carbonate/cholecalciferol medication. The patient recorded a Naranjo score of 6, demonstrating a probable causal relationship between PPI intake and hypomagnaesemia [19].

Pantoprazole therapy was ceased and replaced by ranitidine, a histamine-2 receptor antagonists. The patient received supplementation with intravenous calcium and magnesium-2 g of intravenous magnesium sulfate over 20 minutes, and 1 g of intravenous calcium gluconate over 20 minutes, followed by further repeat doses of intravenous calcium gluconate during admission. The patient noted symptomatic improvement, as his magnesium level quickly normalised, though the positive Trousseau's sign persisted for longer as his calcium level took four days to correct (**Table 2**). Prior to discharge, he was re-commenced on regular oral calcium

and cholecalciferol supplementation. Since the discontinuation of PPI, his serum magnesium level has remained normal.

Discussion

Magnesium is the second most abundant intracellular cation and its homeostasis is intricately regulated by intestinal absorption and renal excretion [20]. There is no known hormonal axis dedicated to normalising this electrolyte and changes in its serum concentration poorly reflect matters in the much larger skeletal muscle intracellular pool which contains over 99% of total body magnesium [21].

Hypomagnesemia in association with PPI use is considered rare, with the FDA reporting it as an occurrence in less than 1% of all PPI-induced side-effects [22]. Magnesium deficiency as a result of PPI use can produce an array of cardiovascular features, the most concerning of which is life-threatening arrhythmias [23, 24], as well as neuromuscular symptoms in the form of tremors, weakness, tetany, and convulsions [13]. However, one study reports that symptoms tend to only occur when plasma concentrations are lower than 0.5 mmol/L as in our subject [17]. Concurrent electrolyte abnormalities, including hypocalcaemia, typically accompany severe hypomagnesemia, which may also lead to cardiovascular and neuromuscular instability [21, 25-27].

Since the initial report in 2006 [12], clinical observations have accumulated to support the association between PPIs and symptomatic hypomagnesaemia. Comparative studies to assess this relationship have not yet elucidated whether there is a causal role of proton pump inhibitors in the development of hypomagnesaemia. A meta-analysis of the available studies to date demonstrated a statistically significant association between PPI use and the risk of hypomagnesemia, whilst also noting the significant heterogeneity among the included studies prevented a definitive conclusion from being reached [28]. This risk, however, only appears to exist in patients with PPI use of over 1 year [10, 15, 17, 29, 30]. Studies also note that the potential for this symptomatic hypomagnesaemia to occur in these patients appears to be heightened in the elderly [27, 31], and those with concurrent diuretic use [20, 29, 32]. Our patient demonstrated the former of these risk factors, and while the age-dependent risk of PPI-induced hypomagnesaemia is still unclear, it is likely to be multifactorial.

The risk of PPI-induced hypomagnesemia may be magnified in the elderly population due to the prevalence of polypharmacy, and multiple comorbidities with potential to impair renal function or affect serum magnesium levels. Several reports have expressed concern of the very high incidence of inappropriate prescriptions for PPIs in the elderly population [33, 34]. Furthermore, while the use of PPIs is expanding rapidly, this appears to be most substantial within the older population group [35]. This high consumption of PPIs, and in a considerable number of cases, unnecessary consumption, is what also perpetuates the dander of PPI-induced adverse effects, including hypomagnesaemia.

While initial case reports on PPI-induced hypomagnesaemia were demonstrated with omeprazole and esomeprazole [12], recently published cases of numerous PPI formulations have proposed that this is a true drug class effect that's applies to all PPI agents [30, 36]. Interestingly, our patient was under treatment with pantoprazole which is considered the least potent PPI with the lowest risk of inducing hypomagnesaemia [17, 37]. Often, as partly seen in our case, PPI-associated hypomagnesemia has potential to cause other electrolyte disturbances, specifically hypocalcaemia and hypokalaemia [10, 12, 14, 27, 30]. Our patient demonstrated a normal potassium level, and it is likely that an underlying hypokalaemia may have been masked by his long-standing treatment with candesartan, an angiotensin II receptor antagonist.

While the exact underlying pathogenesis for PPI-induced hypomagnesaemia is still unclear, several reports have recently proposed PPI-induced impairment of gastrointestinal magnesium absorption. While majority of oral magnesium is absorbed passively through paracellular pathways between enterocytes, it is believed that PPIs influence the action of a second magnesium transport system, the transient receptor potential melastatin (TRPM) cation channels, specifically TRPM6 and TRPM7 [36]. These TRPM channels are transcellular active transport mechanisms that permits adaptation to a low magnesium intake by increasing frac-

tional magnesium absorption [15]. It is thought that chronic PPI use impairs this adaptive intestinal response to a low dietary magnesium intake [29, 32, 38, 39]. However, it is important to note that recent research brings into question the role of TRPM7 in the magnesium homeostasis, as Jin et al. demonstrated that the absence of TRPM7 in their own study did not impact of acute uptake of Mg2+ or the maintenance of total cellular Mg2+ [40]. While hypomagnesaemia develops over years, the fact that the passive paracellular pathways are still intact allows for remission to occur relatively quickly within days of discontinuing PPI therapy [41]. The phenomenon of hypocalcaemia secondary to hypomagnesaemia is due to functional hypoparathyroidism because parathyroid hormone release is a magnesium-dependent process [42-44]. This hypocalcaemia is typically refractory to correction until the magnesium deficit has been corrected [45]. A second mechanism of hypocalcaemia in the setting of PPI use relates to the decrease in calcium bioavailability in the presence of gastric achlorhydria, given that calcium absorption is a pH-dependent process [13, 46, 47].

In our patient's case, several other contributing factors toward his hypocalcaemia are apparent. Chronic kidney disease causes hypocalcaemia alongside impairment in mechanisms that maintain phosphate homeostasis. Associated with this is decreased vitamin D synthesis which further impairs intestinal calcium absorption, and as seen in this case report, secondary hyperparathyroidism arises [48]. Another additional consideration is the patient's adherence to bisphosphonates, with severe hypocalcaemia having an association with this medication when used in vitamin D deficient patients [49, 50].

The reversible effect of PPI-induced hypomagnesaemia has been validated with previous reviews that reveal rapid improvement following magnesium supplementation and discontinuation of PPI therapy [51, 52]. Reports describe resolution of hypomagnesaemia within 4 days of ceasing PPIs [53], as seen with our case, and conversely a rechallenge of PPI therapy is known to result in recurrence of hypomagnesaemia within days [10, 23].

The decision to switch our patient to ranitidine, a histamine-2 receptor antagonist, has been supported by previous studies that determined no associated risk of hypomagnesaemia with this medication [23, 52].

Conclusion

Hypomagnesemia induced by PPI treatment can be a serious clinical condition. We recommend routine serum magnesium level monitoring be performed in elderly patients on prolonged PPI therapy.

Disclosure of conflict of interest

None.

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