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Delay in diagnosis of proton pump inhibitor induced hypomagnesaemia: A case series

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ABSTRACT

Proton pump inhibitor (PPI) induced hypomagnesaemia is an increasingly recognised side effect of these commonly used medications. We present a case series highlighting the delay in diagnosis of PPI induced hypomagnesaemia, in three patients who presented with symptomatic electrolyte abnormalities. Our first case depicts that, despite multiple presentations to an emergency department in a tertiary hospital, PPIs were not recognised as the underlying cause of hypomagnesaemia and hypocalcaemia. Our second case highlights the difficulty faced by primary case physicians in recognising this side effect. Similarly, our third case demonstrates these challenges in a patient that presented to hospital twice, before the offending agent was ceased. Given the widespread use of PPIs and the simplicity in treating this side effect, we aim to shed light on the incidence of PPI induced hypomagnesaemia. We suggest that a high index of suspicion must be maintained for patients on PPIs, who can present with potentially life threatening electrolyte derangement.

1. Case 1

Mrs TA was a 53-year-old female who presented to the emergency department of a tertiary hospital with paraesthesiae and carpo-pedal spasm. She had experienced involuntary muscle spasms, which had been progressive for three days. She reported diarrhoea and occasional vomiting for 24 hours prior to presentation. She had presented to the Emergency Department twice in the past year with similar symptoms. On both occasions, she was diagnosed with hypocalcaemia and treated with intravenous (IV) calcium replacement, but no further investigations were performed to elicit the cause of her electrolyte derangement. She had a background of gastro-oesophageal reflux disease (GORD), for which she had been on esomeprazole for 4 years. In addition, she also had asthma requiring daily budesonide/formoterol bronchodilators, hypercholesterolemia, requiring atorvastatin 40mg and depression, for which she was on fluoxetine 40mg. She was not on over the counter medications or vitamin supplements.

At presentation, she was haemodynamically stable. She had carpo-pedal spasm and a positive Trousseau's sign, but this resolved with administration of an IV calcium infusion. Her oxygen saturation on pulse oximetry was normal and she was afebrile, with a blood pressure of 133/96 mmHg. An electrocardiogram demonstrated normal sinus rhythm, with a normal QT interval of 385 milliseconds. Her serum laboratory results are reported below (Table 1), and demonstrate marked hypocalcaemia, hypomagnesaemia and inappropriately low PTH in the setting of hypocalcaemia.

Following this presentation, her third with these symptoms, the cause of her impaired electrolytes was recognised and esomeprazole therapy was ceased, following a significant delay in recognition and multiple hospital presentations. She received IV calcium and magnesium replacement and was commenced on oral calcitriol and calcium carbonate. Her corrected calcium and magnesium levels improved and she was discharged from hospital the following day.

Mrs TA had repeat pathology collected 2 weeks after ceasing the proton pump inhibitor (PPI), and again 2 months post presentation (see Fig. 1). Her blood results demonstrated normalisation of her serum calcium and magnesium levels, and an initial increase followed by normalisation of PTH levels after ceasing the PPI.

2. Case 2

Mr NY was a 52-year-old gentleman of Lebanese background who was referred to an endocrinology clinic by his general practitioner for management of hypomagnesaemia and hypocalcaemia. He reported symptoms of muscle cramps, perioral and acral paresthesia, and constipation.

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Table 1
Case 1 electrolytes.

	Baseline	2 weeks	2 months	Reference Range
Corrected calcium	1.86 mmol/L	2.07 mmol/L	2.38 mmol/L	2.15–2.55 mmol/L
Magnesium	0.3 mmol/L	0.45 mmol/L	0.75 mmol/L	0.70–1.10 mmol/L
25-OH vitamin D	28 nmol/L	33 nmol/L	61 nmol/L	50–140 nmol/L
1, 25-OH vitamin DPTH	8.1 pmol/L	14.4 pmol/L	5.7 pmol/L	1.6–7.5 pmol/L
ALP	97 U/L	N/A	N/A	30–110 U/L

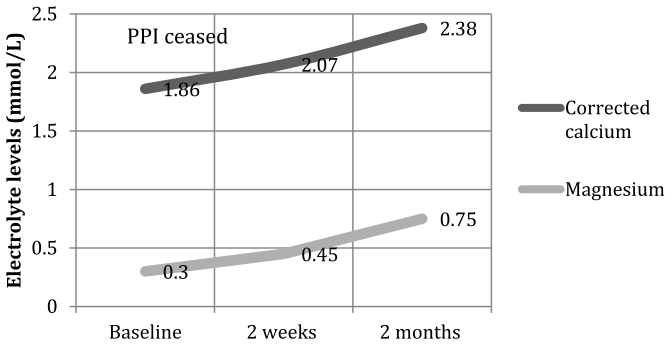

Fig. 1. Case 1 electrolyte levels.

He had a background of Crohn's disease limited to the terminal ileum, for which he had been on a disease-modifying agent. He also had a history of GORD, coronary artery disease, hypertension, and had undergone coronary artery bypass grafting earlier in the year. His medications included esomeprazole 20mg, which he had been taking for 15 years. Other medications included telmisartan 40mg daily, mesalazine MR 1 g BD, mercaptopurine 50mg daily, cephalexin 500mg BD, atorvastatin 40mg daily, metoprolol 50mg BD and aspirin 100 mg daily. He was not on over the counter medications or vitamin supplements on presentation.

On examination, he had a blood pressure of 120/80 mmHg. He had a negative Trousseau and Chvostek's sign. His bloods at the time of review demonstrated hypomagnesaemia (0.47 mmol/L), hypocalcaemia (1.82 mmol/L) and hypophosphatemia (1.57 mmol/L), as demonstrated in Table 2. He was commenced on calcium carbonate 1.2 g twice daily and magnesium aspartate dihydrate 1 tablet daily. His esomeprazole was ceased at the time of review and bloods were repeated 2 weeks later, showing normalisation of his electrolytes (Fig. 2).

3. Case 3

Mr RB was a 66-year-old male who presented to the emergency department of a tertiary hospital with bilateral paraesthesia in his extremities. He had experienced these symptoms for two days prior to presentation. He had a background of ischemic heart disease, myelodysplasia for which he underwent a bone marrow transplant 8 years prior, emphysema, type 2 diabetes mellitus and GORD.

His medications included empagliflozin, metformin, clopidogrel, aspirin, metoprolol, telmisartan, hydrochlorothiazide (HCT),

Table 2
Case 2 electrolytes.

	Baseline (24/8/2017)	2 weeks later (6/9/2017)	Reference Range
Corrected calcium	1.82 mmol/L	2.17 mmol/L	2.15–2.55 mmol/L
Magnesium	0.47 mmol/L	0.77 mmol/L	0.70–1.10 mmol/L
Phosphate	1.57 mmol/L	1.03 mmol/L	0.75–1.5 mmol/L
Vitamin D	20 nmol/L	33 nmol/L	50–140 nmol/L
PTH	N/A	8.3 pmol/L	1.6–7.5 pmol/L
ALP	79 U/L	76 U/L	30–110 U/L

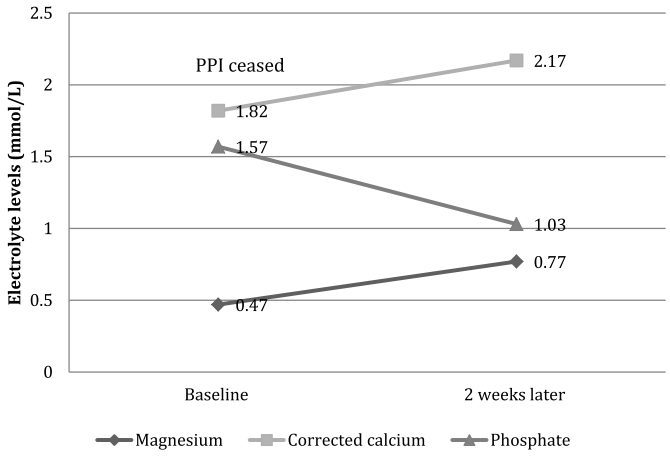

Fig. 2. Case 2 electrolyte levels.

atorvastatin and esomeprazole. He was not on any vitamin supplementation or over the counter medications. He was admitted to hospital at the time and his empagliflozin and hydrochlorothiazide were ceased. He received IV calcium and magnesium replacement. On discharge, he had improved electrolytes (Table 3). His empagliflozin was recommenced, but HCT was permanently ceased. During admission, it was not identified that his electrolyte derangements may be caused by his PPI use, and he was discharged home with ongoing esomeprazole.

His general practitioner again referred him to the emergency department 2 weeks later, when he noticed that Mr RB had ongoing hypomagnesaemia despite oral magnesium replacement (see Fig. 3). His esomeprazole was ceased and he was discharged from hospital, with repeat blood tests planned in a few days time.

4. Discussion

We present three cases in which patients have presented with hypomagnesaemia in the context of PPI use, specifically esomeprazole. In each of the three cases, there was a significant delay between the onset of symptoms and the recognition of the role of PPIs in inducing electrolyte derangements. In Case 1, the patient had presented twice to the emergency department of a tertiary hospital, and had received symptomatic treatment only, without further investigations into the cause of her marked hypomagnesaemia and hypocalcaemia. There was no diagnosis made as to the underlying mechanisms responsible for the electrolyte derangement and the offending agent, namely the PPI she was on, was continued as per her usual medication regime. In case 2, the patient was referred to an endocrinology clinic by his GP with ongoing electrolyte derangements. In Case 3, the patient presented with electrolyte derangements and was admitted. Despite this, the offending agent was not identified and ceased, and he subsequently re-presented with ongoing symptoms.

While they have a considerably good safety profile, the side effects of PPIs have increasingly come to light in recent years. With their increasing use in the primary care setting, there is a need to promptly recognise common side effects associated with their use. Reports suggest that the prevalence of hypomagnesaemia while on a PPI is 1% [1].

Table 3
Case 3 electrolytes.

	Baseline	Discharge	Re-presentation	Reference Range
Corrected calcium	1.67 mmol/L	2.29 mmol/L	2.019 mmol/L	2.15–2.55 mmol/L
Magnesium	0.13 mmol/L	0.59 mmol/L	0.32 mmol/L	0.70–1.10 mmol/L
Phosphate	1.4 mmol/L	0.81 mmol/L	0.89 mmol/L	0.75–1.5 mmol/L
25-OH Vitamin D	64 nmol/L	N/A	N/A	> 50 nmol/L
PTH	2.0 pmol/L	N/A	N/A	1.6–7.5 pmol/L

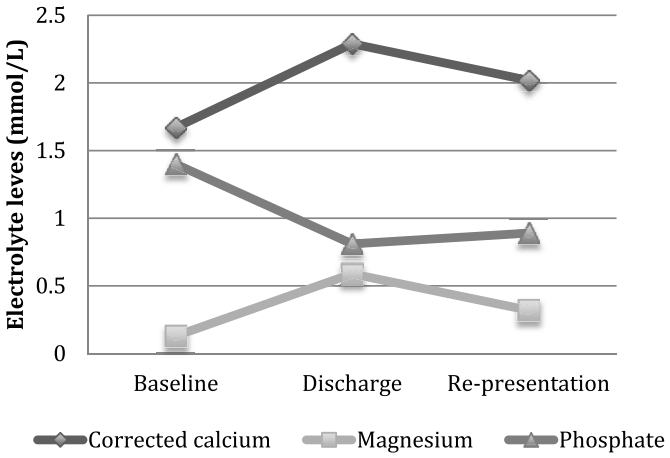

Fig. 3. Case 3 electrolyte levels.

While this is not a common side effect, the consequences can be potentially life threatening, with profound hypoparathyroidism with hypocalcaemia induced by the hypomagnesaemia. PPI related hypomagnesaemia was first reported by Epstein et al., in 2006 [2]. Since then, several case reports have been published, linking long term PPIs to episodes of symptomatic hypomagnesaemia. While this side effect is now well established, our case series demonstrates that this is still not well recognised by physicians and there was a delay in diagnosis. A systematic review and meta-analysis published in 2014 analysed 9 studies to assess the association between hypomagnesaemia and PPI use [3]. The authors found that among patients taking PPIs, the median proportion of patients with hypomagnesaemia was 27.1%, compared to 18.4% in those not taking PPIs. The pooled odds ratio was 1.775 (95% CI 1.077–2.924). However, definitive conclusions were not reached due to significant heterogeneity between studies (I^2 = 98%).

Additionally, several studies have demonstrated the association between PPIs and hypomagnesaemia [2,4,5]. One case control study conducted in Ontario, Canada, found that among 366 patients hospitalised with hypomagnesaemia, PPI use was associated with a 43% increased risk of hypomagnesaemia (adjusted odds ratio, 1.43; 95% CI 1.06–1.93). The risk was particularly increased among patient's receiving diuretics (adjusted odds ratio, 1.73; 95% CI 1.11–2.70) [6]. In our case series, 1 of the 3 patients was receiving diuretics (case 2), placing them at higher risk of developing this side effect. Hess et al. identified 36 cases of PPI induced hypomagnesaemia, with an aim to determine the changes in serum magnesium upon withdrawal and subsequent re-challenge of PPIs [7]. They found that a normal serum magnesium level was reached 4 days after withdrawal of the PPI. Upon re-challenge with a PPI in 7 different cases, the serum magnesium level in 70% of cases had fallen below their 0.6mmol/L cut off. The authors suggested that once PPI induced hypomagnesaemia is established; it persists with use and has a high likelihood of recurring when re-challenged. They also concluded this was likely to be a class effect, as all three medications omeprazole, pantoprazole and esomeprazole were implicated. Additionally, they found that the time to hypomagnesaemia was highly variable, ranging from 14 days to up to 13 years, with a mean of 5.5 years. The authors did find in their series, that in 75% of cases, omeprazole was implicated, 25% esomeprazole and 14% pantoprazole.

The pathogenesis underlying electrolyte derangement lies in profound hypoparathyroidism with hypocalcaemia mediated by PPI induced hypomagnesaemia. While this has not been definitively described, it is postulated that impaired absorption of intestinal magnesium, due to PPIs, may be the underlying mechanism [4]. Additionally, hypomagnesaemia may induce hypocalcaemia by interfering with calcium sensing reception transduction, inhibition of PTH release, end-organ resistance to PTH and increased breakdown of PTH into inactive metabolites [2,8]. Further, decreased luminal pH in the intestines may alter the affinity of the TRPM6/7 channel for magnesium, reducing active transport of magnesium. In case 1, the PTH level that was only mildly raised, which could be considered as an inappropriately near-normal level for the given corrected calcium.

The question then arises about how clinicians can recognise the signs and symptoms associated with electrolyte derangement when using PPIs. The signs and symptoms of hypocalcaemia and hypomagnesaemia are quite similar and include cognitive changes such as apathy, depression, delirium and coma. On an ECG, patients may present with a prolonged QT and PR interval, widened QRS complex or multifocal atrial tachycardia. Neuromuscular symptoms include weakness, tremor, convulsions, tetany and paraesthesia. Given the non-specific symptoms, the key marker of identifying PPI induced electrolyte derangements lies in the biochemistry. Ensuring that physicians are aware of this side effect, both in the primary and secondary care setting, remains crucial in patient care. As evidenced by Case 1, the patient presented to the emergency department twice before the correlation between PPI use and hypomagnesaemia was identified. In Case 3, this common side effect of PPIs was not initially recognised during the patient's first admission. Thus, improving the education of physicians and ensuring monitoring of blood tests is essential to improve the morbidity and potential mortality associated with these electrolyte disturbances.

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Declaration of conflict of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2019.01.001.

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