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Severe Electrolyte Disturbances Due to Proton Pump Inhibitor Therapy: An Underrecognized Problem with Potentially Severe Sequelae

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 55-year-old
Final Diagnosis: Convulsions and confusion due to electrolyte disturbances
Symptoms: Confusion • convulsions
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Proton pump inhibitors are increasingly being recognized as a cause of multiple electrolyte disturbances, including hypomagnesemia, hypocalcemia, hypophosphatasemia, hypokalemia and hyponatremia, particularly in persons on long-term therapy. The mechanisms, consequences, and management of these electrolyte disturbances are discussed below.

Case Report: A 55-year-old woman was seen by various clinicians, with a variety of clinical presentations, over the space of a couple of years. During each visit, she had electrolyte disturbances and was on proton pump inhibitor therapy, which were either continued or changed to a different proton pump inhibitor. She had presented variously with diarrhea and weight loss due to microscopic colitis, confusion, and grand mal seizures on separate occasions. Changing the proton pump inhibitor did not alleviate her profound electrolyte disturbances, which completely resolved shortly after stopping drug therapy.

Conclusions: It is important for clinicians to be aware of the electrolyte disturbances that can be caused by these medications, and to actively monitor patients on long-term therapy for these disturbances, thus avoiding potentially severe consequences. Electrolyte disturbances are more likely to arise in patients who are prescribed concomitant diuretic treatment or who overuse alcohol. The incidental finding of hypocalcemia in persons on proton pump inhibitors may be secondary to hypomagnesemia, and hypomagnesemia may be a consequence of an underlying otherwise symptomless genetic disorders. Clinicians should be encouraged to deprescribe these drugs after 4 weeks of treatment in patients with mild symptoms or mild disease.

Keywords: Colitis, Microscopic • Confusion • Electrolytes • Hypomagnesemia 1, Intestinal • Proton Pump Inhibitors • Seizures

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Background

Proton pump inhibitors (PPIs) are widely prescribed drugs, used for the treatment of peptic ulcer disease. Their discovery has dramatically decreased the morbidity and mortality of peptic ulcer disease in the last decades of the 20th century. They are the most effective drugs currently available for suppressing gastric acid secretion and are as such are particularly effective drugs for treating gastric and duodenal ulcers, gastroesophageal reflux disease, and erosive esophagitis. They have been increasingly used to prevent symptoms derived from other medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin, which are both used widely. Additionally, they are unfortunately used to treat vague digestive problems, and are often used for longer than recommended and often inappropriately by self-medicating individuals [1].

The widespread use of PPIs has led to the adverse effects of this class of medications becoming increasingly common, particularly with prolonged use. It is important that prescribers keep in mind that these drugs have a number of important adverse effects, including electrolyte disturbances, which may on occasion be profound. These electrolyte abnormalities are often not ascribed to these drugs by clinicians. This case report draws attention to potential complications of proton pump inhibitors, including severe electrolyte disturbances, and highlights the potential for patient harm (which in this case included separate presentations with microscopic colitis, acute confusion, and convulsions) if these electrolyte abnormalities are not recognized and if these drugs are not adequately deprescribed.

Case Report

A 55-year-old woman was referred to the internal medicine clinic with diarrhea in June 2015. She had smoked half a packet of cigarettes daily for the preceding 35 years and drank 3 cans of beer most days. Her past medical history included hypertension, dyslipidemia, psoriasis, depression, endometriosis, and hypothyroidism.

She had been troubled by intermittent chronic diarrhea, up to 8 times a day, during the preceding year and had lost 12 kg in weight during the period. This started shortly after she was treated with ranitidine 150 mg daily for dyspepsia by her family physician. Her ranitidine was changed to omeprazole but her diarrhea persisted. Her medications at the time of her referral to the internal medicine service included omeprazole, venlafaxine, atenolol, losartan, trimebutine, atorvastatin, metoclopramide, and Imodium.

Physical examination of her chest, abdomen, cardiovascular system, and nervous system was unremarkable. She was subsequently scheduled for a colonoscopy, but unfortunately changed her contact details and was lost to follow-up.

She then presented to the emergency room on the 7 July 2016 with diarrhea, nausea, and occasional vomiting. On blood testing, she was found to have acute kidney injury (urea 21.5 mmol/l, creatinine 157 µmol/l) and hypokalemia (**Table 1**). Magnesium and calcium levels were not checked during that admission. She was on omeprazole at the time and an upper GI endoscopy was carried out, which was reported as normal. She was hydrated, and her creatinine levels improved to 61 µmol/l. Her omeprazole was continued and she was sent home on metoclopramide and Imodium. She then re-presented with vomiting, diarrhea, and confusion on 25 July 2016. During that visit, her magnesium levels were profoundly low, and her calcium and potassium levels were also low (**Table 1**). Following intravenous correction of her electrolyte derangement, she was discharged on oral calcium, magnesium, and potassium supplements. She stopped drinking alcohol after that admission.

An out-patient colonoscopy and biopsy were then carried out 1 month later. Endoscopic appearances were unremarkable except for a single polyp, which was removed. The pathologist's report was consistent with microcytic colitis and a hyperplastic polyp. She was put on budesonide 6 mg daily and

Table 1. Reported electrolyte levels on blood testing.

	Normal range	Date				
		7/7/16	25/7/16	6/5/17	16/08/17	14/02/22
Sodium	136-145 mmol/l	136	144	135	143	138
Chloride	98-107 mmol/l	99	108	101	102	101
Potassium	3.6-5.2 mmol/l	3.3	3.2	3.3	4.5	3.8
Magnesium	0.66-1.07 mmol/l	–	0.1	0.24	0.88	0.76
Calcium	2.10-2.70 mmol/l	–	1.71	1.97	2.46	2.37
Phosphate	0.81-1.58 mmol/l	–	–	0.73	0.98	1.32

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her diarrhea resolved. In the meantime, her omeprazole was changed to rabeprazole 20 mg twice daily for continued dyspeptic symptoms, despite normal upper gastrointestinal endoscopy results.

She then presented on 6 May the following year with a grand mal epileptic seizure associated with incontinence of urine and feces and had bitten her tongue. Her serum magnesium, calcium, potassium, and phosphorous levels were all low, and her sodium levels were mildly reduced (**Table 1**). She denied diarrhea or vomiting and had not drunk alcohol for 1 year. Her MCV was 91.7 fl and her liver function tests were normal (gamma-glutamyl transferase 39 U/L, aspartate transaminase 13 U/L, alanine transaminase 12 U/L, and alkaline phosphatase 98 U/L). Her rabeprazole was stopped and her electrolytes were corrected with intravenous therapy. Unfortunately, her parathyroid hormone levels were not checked on her presentation until 4 days after stopping her rabeprazole, when the levels were normal at 4.01 pmol/l. Her serum electrolytes remained normal with intermittent serial testing over the next 2 years. She had no further episodes of diarrhea, vomiting, confusion, or seizures since her PPIs were stopped.

She was again started on pantoprazole for atypical chest discomfort in January 2022, despite her electronic records indicating an adverse reaction to proton pump inhibitors. Within 1 month of restarting pantoprazole, her serum magnesium levels (0.76 mmol/l) were 0.06 mmol/l lower than her average (0.82 mmol/l, n=13) in the 2 years following her prior discontinuation of PPIs. Following her reassessment, the pantoprazole was again permanently discontinued.

Discussion

Proton pump inhibitors are substituted benzimidazole derivatives, available as enteric-coated tablets or capsules that pass through the stomach intact and are absorbed in the proximal small bowel. They inhibit the action of enzyme H+/K+-ATPase in the canaliculi of the parietal cells of the stomach and prevent the exchange of K+ for H+, thus increasing the pH of the gastric juice. PPIs have a relatively short plasma half-life (about 1-2 h), but covalently bind to cysteine residues within the gastric parietal cell canaliculus, causing irreversible inhibition and effective acid suppression for 24 to 48 h [1]. Rabeprazole uniquely forms a partially reversible bond with the proton pump and is activated at a broader range of gastric pH and may thus have a more sustained acid-suppressing effect than other PPIs [2].

This case report highlights a 55-year-old woman with non-ulcer dyspepsia who developed multiple adverse effects of proton pump inhibitors, causing multiple visits to clinicians and multiple investigations. The adverse effects she developed included microscopic colitis, profound electrolyte disturbances with hypomagnesemia, hypokalemia, hypocalcemia, and hypophosphatasemia, which led to separate admissions for acute confusion and for convulsions. Despite her severe adverse effects and minimal dyspeptic symptoms, her PPIs were either continued or changed. Additionally, despite this being highlighted in her medical records, some clinicians continued to prescribe these drugs to this patient after they had been deprescribed. This report aims to discuss the adverse effects of PPIs to improve awareness of these potential problems. This single case is representative of a common problem of electrolyte disturbances caused by prolonged use of PPIs, which is discussed further below.

The most common adverse effects of PPIs include headache, nausea, constipation, flatulence, diarrhea, skin rash, and dizziness. Other adverse effects less frequently connected to PPIs include bone fractures, pneumonia, dementia, and hypomagnesemia [1].

Chronic diarrhea is an important adverse effect and may be due to microscopic colitis, which has been described with several PPIs, including omeprazole and lansoprazole [3,4], and with other acid-suppressing drugs like ranitidine [5]. Microscopic colitis has also been associated with several other drugs, including aspirin, NSAIDs, acarbose, clozapine, entacapone, flavonoids, sertraline, ticlopidine, Cyclo 3 Fort, carbamazepine, vinburnine, tardyferon, simvastatin, cimetidine, and flutamide [3,6,7]. The risk of developing microscopic colitis is higher when NSAIDs are taken with PPIs [8].

Microscopic colitis is not an entirely benign condition and has been associated with severe electrolyte disturbances such as hypokalemia, which has in turn rarely caused severe symptoms, including cardiac arrhythmias and cardiac arrest [7]. Microscopic colitis should be managed by stopping the offending drugs and reducing excessive intake of dairy products, caffeine, and alcohol. Celiac disease and bile acid malabsorption should be excluded. If symptoms are debilitating, budesonide, a glucocorticoid with low systemic effect due to its substantial elimination by first-pass hepatic metabolism, has been proven to be effective [9].

Additionally, PPIs have important renal adverse effects, including acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, kidney failure, and increased risk for all-cause mortality and mortality due to chronic kidney disease [10].

In a study involving 9818 individuals, there was an increased risk of hypomagnesemia, but only after prolonged use of PPIs (range, 182-2618 days; OR, 2.99; 95% CI, 1.73-5.15). PPI use was associated with an increased risk of hypomagnesemia (n=36;

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OR, 2.00; 95% CI, 1.36-2.93) compared to no use. Additionally, the overall serum magnesium level was 0.022 mEq/L lower in PPI users (n=724; 95% CI, -0.032 to -0.014 mEq/L) than in non-users. In participants using loop diuretics (n=270), PPI use was associated with a further increased risk of hypomagnesemia (n=5; OR, 7.22; 95% CI, 1.69-30.83) compared to no use [11].

The exact mechanism of hypomagnesemia is not fully understood. However, renal magnesium handling is normal in patients on PPIs; as such, diminished intestinal absorption is thought to play the main role. It is uncertain if the defective absorption of magnesium is through the active or passive transport processes, or alternatively due to increased gut losses [12]. Hypomagnesemia can in turn cause urinary potassium wasting leading to hypokalemia [13]. Hypocalcemia may develop following hypomagnesemia and is thought to be caused by the inhibitory effect of hypomagnesemia on parathyroid gland hormone secretion [14]. The observation of asymptomatic hypokalemia or hypocalcemia in patients treated with PPIs is often indicative of hypomagnesemia [15].

In a recently published case report, normal renal calcium and magnesium conservation was demonstrated in a patient prone to hypocalcemia and hypomagnesemia due to esomeprazole. This patient had normal vitamin D levels and low parathyroid hormone levels, which returned to normal after discontinuing esomeprazole. Treatment with oral magnesium supplements in this patient corrected the hypomagnesemia, suggesting a normal passive paracellular pathway and a problem with active transcellular magnesium absorption. When this patient was rechallenged with esomeprazole after a 2-year break, her serum magnesium levels dropped by 0.4 mmol/l in 4 weeks. Normally, 90% of magnesium absorption is passive and linear with dietary magnesium content. The authors theorized that magnesium availability in patients on PPIs may be reduced as a consequence of the failure of H+ ions competing with and liberating metal ions from ligand binding sites in food. The authors postulated that there may be symptomless genetic defects in certain patients that can make them more prone to hypomagnesemia. Potential genetic defects include defects in TRPM6 (expressed along the kidney and gastrointestinal tract) and TRPM7 channels (omnipresent in tissues) and other genetic defects [16]. A mutation in the TRPM6 gene has been specifically identified as being responsible for primary hypomagnesemia and secondary hypocalcemia [16]. This patient had no known genetic predisposition to low magnesium levels.

Excessive alcohol intake can be associated with hypomagnesemia. This could be due to multiple mechanisms, including decreased magnesium intake, increased gastrointestinal Mg losses in patients with chronic diarrhea, increased Mg entry into cells due to both respiratory alkalosis and excessive catecholamine release in alcohol withdrawal syndrome, inappropriate urinary losses due to alcohol-induced tubular damage, alcohol-related metabolic acidosis, and acute pancreatitis [17,18].

Hypomagnesemia has been reported to cause carpopedal spasm, tetany, convulsions, cardiac arrhythmias, hypoparathyroidism, hypocalcemia, hypophosphatasemia, muscle cramps or weakness, vertigo, ataxia, seizures, depression, and psychosis [16,18]. Hypomagnesemia typically recurs following replacement of one proton pump inhibitor with another [19].

Hyponatremia has also been described in association with PPIs and may be due to the associated vomiting [20]. The syndrome of inappropriate antidiuretic hormone secretion secondary to the use of omeprazole and pantoprazole causing hyponatremia has been described [21]. Possible urinary sodium losses following omeprazole administration have been cited as contributing to hyponatremia [22].

Pancreatitis is a rare complication of proton pump inhibitor therapy and has been reported with omeprazole [23,24] and pantoprazole [25]. It has been suggested that patients with acute pancreatitis and hypocalcemia commonly have magnesium deficiency and that magnesium deficiency can play a significant role in the pathogenesis of hypocalcemia in patients with acute pancreatitis [26].

It is important for clinicians to appreciate the need to deprescribe PPIs in adults who have completed a minimum of 4 weeks of treatment for heartburn, mild to moderate gastroesophageal reflux disease or esophagitis, and whose symptoms have resolved. This may include reducing the dose, stopping use, or using “on-demand” dosing. These recommendations do not apply to those who have or have had Barrett esophagus, severe esophagitis grade C or D, or a documented history of bleeding gastrointestinal ulcers [27]. Hypergastrinemia can result from therapy with PPIs. This can cause rebound symptomatic dyspepsia due to hyperacidity when PPIs are abruptly discontinued. As such, tapering these drugs may be the easiest way to deprescribe them [28]. A survey in Sarjah in the United Arab Emirates showed that 52% of patients on PPIs did not receive guidance about deprescribing these drugs, and 50% of patients purchased these drugs without a prescription [29].

Conclusions

Hypomagnesemia due to proton pump inhibitors is not uncommon and may on occasion be profound. Hypomagnesemia is more common in patients taking concomitant loop diuretics and in alcoholic patients. Hypomagnesemia may lead to secondary hypokalemia, hypophosphatasemia, and hypocalcemia. Hyponatremia can be a rare complication of proton pump inhibitor use. Serum magnesium levels should be checked in

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patients with hypocalcemia associated with pancreatitis, especially if they are on proton pump inhibitors. Ranitidine and proton pump inhibitors can cause diarrhea and microcytic colitis, which can cause or further exacerbate these electrolyte abnormalities. Electrolyte disturbances typically persist if proton pump inhibitors are changed. Our patient presented with profound electrolyte abnormalities and was treated with electrolyte supplements while proton pump inhibitors were continued. This strategy was inadequate to correct her deficiencies, leading to a number of admissions with severe adverse effects, and although there were opportunities to deprescribe these drugs, this was not done. We hope this case report will increase clinicians' awareness of the need to deprescribe proton pump inhibitors to avoid adverse effects and not to simply attempt to correct electrolyte deficiencies. Additionally, patients started on long-term proton pump inhibitors should have baseline magnesium, potassium, calcium, and phosphate levels checked, followed by periodic monitoring.

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