



Overprescribing Proton Pump Inhibitors & A Glimpse on its Side Effects



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Mini Review

Proton pump inhibitors are one of the most frequently prescribed classes of drug in the world because they combine a high level of efficacy with low toxicity. In 2006, expenditure on these drugs was £7bn globally [1]. Yet studies consistently show that proton pump inhibitors are being overprescribed worldwide in both primary and secondary care [2]. Between 25% and 70% of patients taking these drugs have no appropriate indication. This means that, at the very least, £100m from the National Health Service (NHS) budget and almost £2bn worldwide is being spent unnecessarily on proton pump inhibitors each year.

The first generic proton pump inhibitor (omeprazole) was introduced in 2002 and now comprises more than four fifths of all prescriptions for proton pump inhibitors in India. In the five years since the introduction of omeprazole, prescriptions for proton pump inhibitors have doubled, although the reasons for this rise are not obvious [3]. Despite this substantial increase in drug usage, the decrease in price means that overall expenditure on proton pump inhibitors has been falling in recent years.

Effective and less expensive alternative drugs, such as H2 receptor antagonists are available for many patients. Yet prescriptions for proton pump inhibitors have superseded those for all other acid inhibiting agents and now account for over 90% of the NHS drug budget for treating dyspepsia. Proton pump inhibitors cost more than other agents, which is partly why prescribing guidelines have been drafted in several countries. The National Institute for Health and Clinical Excellence (NICE) published its guidelines on proton pump inhibitors in 2000. Its recommendations for using these drugs particularly in the long term are relatively selective [4]. If prescriptions were restricted to the recommended indications, expenditure on proton pump inhibitors would be far less than 90% of the total dyspepsia drug budget.

Proton pump inhibitors have been a tremendous therapeutic advance. Especially in the long term, they have transformed the lives of patients with previously intractable symptoms of gastro-oesophageal reflux with its associated complications, and they have also proved valuable for patients who are at risk of iatrogenic upper gastrointestinal pathology. A short term trial of a proton pump inhibitor is also a good option for treating a wide range of acid-peptic conditions. But the drugs are clearly being overused. Some people will point to their combination of superior efficacy and high safety as a justification for using them in preference to drugs such as H2 receptor antagonists. Yet, side effects should not be overlooked. An increase in the prevalence of pneumonia and *Campylobacter* enteritis is reported, as well as a doubling of the risk of infection with *Clostridium difficile* [5]. Acute interstitial nephritis and osteoporosis are unusual but recognised consequences of treatment with proton pump inhibitors. Such effects are fortunately rare. The adverse effect of over prescription on drug budgets around the world is the real problem. Quite how to motivate doctors to follow guidelines is a matter of considerable importance

Proton pump inhibitors & hypomagnesemia

Proton pump inhibitors (PPIs) were introduced to the market for peptic ulcer disease in 1989. Hypomagnesemia was reported for the first time in medical literature as a potential side effect of this class of drugs in 2006. The US Food and Drug Administration released a warning in 2011 [6] about low serum magnesium levels associated with long-term use of PPIs. An analysis of the Food and Drug Administration's Adverse Event Reporting System shows that approximately 1% of patients experienced hypomagnesemia while on PPIs [7]. Symptoms include seizures, arrhythmias, hypotension, tetany, and death [8]. Despite the evidence, hypomagnesemia related to chronic PPI use was not

addressed in the 2013 American College of Gastroenterology guidelines [9].

PPIs are widely used, both through prescription and over the counter, and are believed to be safe; however, one of the rare but serious complications is hypomagnesemia. It is well reported in nephrology journals [10]. However, the paucity in the internal medicine literature is amazing and prompted us to present this case. To our knowledge, there have been only 4 case reports of PPI-induced hypomagnesemia resulting in seizures [11]. Magnesium is excreted via renal and gastrointestinal routes. The prime culprit in PPI-induced hypomagnesemia is impaired intestinal absorption [12]. In patients with gastrointestinal malabsorption, H₂ antagonists should be the first-line therapy, or if PPI use is essential, then the patient should be monitored closely for hypomagnesemia, especially for cardiac patients who might have a propensity for arrhythmia. There is a clear correlation between long-term use of PPI and hypomagnesemia, and clinicians need to be aware of it.

Proton pump inhibitors & in high risk cardiovascular subsets

Proton-pump inhibitors (PPIs) have been demonstrated to reduce rates of gastrointestinal events in patients requiring dual antiplatelet therapy (DAPT). Data are limited regarding the efficacy and safety of PPIs in high-risk cardiovascular subsets after acute coronary syndrome or percutaneous coronary intervention. PPI therapy attenuates gastrointestinal bleeding risk without significant excess in major cardiovascular events in high-risk cardiovascular subsets, regardless of indication for DAPT. Future studies will be needed to clarify optimal gastroprotective strategies for higher-intensity and longer durations of DAPT.

Hypomagnesemic hypoparathyroidism may develop during long-term PPI therapy [1,2]. Patients can be asymptomatic or present with life-threatening arrhythmias and neuromuscular symptoms; furthermore, hypomagnesemia is refractory to magnesium supplementation until PPIs are withdrawn [13]. Dietary magnesium is largely absorbed in the small bowel, and kidneys play a highly efficient role in its conservation, with 3% of filtered magnesium lost in the urine, most of which is reabsorbed in the thick ascending limb of the loop of Henley. Mechanisms by which the intestinal and renal handling of magnesium is affected by PPIs are unknown. PPI-induced hypochlorhydria is postulated to impair magnesium solubilization and absorption in the small intestine, ultimately depleting its body stores [14]. Variant alleles of active magnesium transport ion channel TRPM6/7 are associated with subtle malabsorption or persistent leak through the kidneys, which may be further aggravated by PPIs [15]. This might explain why only a minority of PPI-treated patients develop Hypomagnesemic Hypoparathyroidism. However, the lack of any report of hypomagnesemia associated with H₂-blockers does not support a mechanistic role of hypochlorhydria in PPI-induced hypomagnesemia.

Hypomagnesemic hypoparathyroidism has been reported with different PPIs, and our patient had ongoing hypomagnesemia with both omeprazole and pantoprazole. The potential to trigger a subclinical magnesium depletion or an overt deficiency status seems to be a class effect that may apply to all PPIs [16]. If PPI-associated hypomagnesemia is dose-related and if it can recur with rechallenge remains unclear [17]. We underscore the need for close monitoring of blood magnesium levels during long-term PPI therapy. PPI therapy is a rare but fully reversible cause of unexplained hypoparathyroidism

Proton pump inhibitors and risk of fractures

Concerns have been raised about the risk of fractures with acid-suppressive medications, such as proton pump inhibitors and histamine₂-receptor antagonists. In this meta-analysis of observational studies, proton pump inhibitors modestly increased the risk of hip, spine, and any-site fractures, whereas histamine₂-receptor antagonists were not associated with fracture risk. The possibility of residual confounding cannot be excluded. Further skeletal evaluation should be considered for patients who are taking proton pump inhibitors and also at risk for osteoporotic fracture.

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