RISKS ASSOCIATED WITH LONG-TERM USE OF PROTON PUMP INHIBITORS

ANTHEA BRINCAT & NEVILLE AZZOPARDI

ABSTRACT

Proton pump inhibitors (PPIs) are widely used in the management of upper gastrointestinal disorders. In recent years, concerns have been raised on the potential adverse effects of long-term PPI use. This article reviews the published evidence of the effect of long-term PPI use on the absorption of minerals and vitamins, risk of infections, chronic kidney disease and dementia.

INTRODUCTION

Proton pump inhibitors (PPIs) are amongst the most commonly prescribed drugs globally, widely used for the prevention and treatment of acid-related disorders such as gastroesophageal reflux disease and peptic ulcer disease. Studies have however, shown that PPIs are often overprescribed or used inappropriately, with 25% - 70% of patients taking these drugs without having an appropriate indication.[1] Although PPIs are well tolerated and have been approved for long-term use, concern and evidence on the potential long-term adverse effects are increasingly emerging. This article reviews published information on adverse effects associated with long-term PPI use.

ABSORPTION OF VITAMINS AND MINERALS

PPIs block the hydrogen-potassium adenosine triphosphatase enzyme system of the gastric parietal cell, leading to inhibition of gastric acid secretion. This in turn, can lead to decreased absorption of minerals such as calcium, magnesium and iron as well as vitamins such as vitamin B12.

Gastric acid suppression by PPIs has been postulated to result in altered calcium metabolism, causing low bone density and an increased risk of fractures. The mechanism is related to both decreased absorption of calcium compounds in the presence of achlorhydria and primary hyperparathyroidism. The latter results from parathyroid hyperplasia secondary to the hypergastrinaemia caused by profound acid suppression.[2] Several studies have investigated the association of PPIs to fracture risk; however the results have been inconsistent. The latest meta-analysis of observational studies, published in 2016, has shown that PPI use modestly increased the risk of hip, spine, and any-site fracture, but with no evidence of duration effect in subgroup analysis.[3] Thus, in patients with increased risk of bone fractures, caution should be exercised when prescribing long term PPIs. Adequate dietary calcium intake with vitamin D and calcium supplementation should be considered, ideally in forms that are not influenced by gastric acid for absorption, such as calcium citrate.[2,4]

Iron and vitamin B12 absorption can be hindered by the low gastric acid levels produced by PPIs. Dietary iron is present in food as non-haem (66%) or haem iron (32%). Gastric acid assists food sources containing non-haem iron to dissociate and to solubilize the iron salts. These salts can then form complexes with sugars and amines, facilitating absorption.[5] The data on the effect of PPIs on iron absorption is inconsistent. There are case reports showing iron deficiency anaemia which resolved when PPI therapy was stopped[6] and a retrospective cohort study showing a significant decrease in haemoglobin in PPI users.[7] Patients with hereditary haemochromatosis were shown to require less frequent phlebotomies when given PPIs.[8] On the other hand, two small studies did not show any significant change in iron levels in patients on short or long-term PPIs[9,10] whilst a cohort of patients with Zollinger-Ellison Syndrome who received treatment with PPIs for over 10 years did not demonstrate a clinically significant iron deficiency.[11] As yet, there are no recommendations to monitor patients on long-term PPI therapy for iron deficiency anaemia and patients shown to be anaemic should be investigated as per published guidelines.

Vitamin B12 is a protein-bound vitamin that requires the presence of gastric acid and pepsin for it to be released in the stomach.[12] Once again, studies have shown conflicting data with a recent, large, case-control study showing that the use of PPIs for two years or more was significantly associated with a new diagnosis of vitamin B12 deficiency.[13] On the other hand, a cross-sectional study failed to show a significant difference in serum B12 levels in patients on PPIs, compared to their partners who were not on PPIs[14]. In a systematic review, the authors concluded that PPI therapy does not statistically affect the absorption of vitamin B12.[5]

In 2011, the FDA released a warning that long-term PPI use may cause hypomagnesaemia, including clinically serious adverse events. In approximately one-quarter of the cases reviewed, magnesium supplementation did not improve the low magnesium level and the PPI had to be discontinued. Whilst the true incidence of PPI-induced hypomagnesaemia is unknown, FDA recommends checking magnesium levels periodically in patients expected to be on prolonged PPI treatment or who take PPIs with other medications that may cause hypomagnesemia (such as diuretics) or digoxin.[4]

INFECTIONS

Gastric acid secretion is part of the local defence system against orally ingested pathogens and its suppression could, theoretically, lead to an increased risk of enteric infections. In addition, a twin study has shown a significant impact of PPIs on the gut microbiome.[15]

Infection with *Clostridium difficile* is of particular importance due to its morbidity. A meta-analysis of 42 observational studies has shown a probable association between PPI use and incident and recurrent *Clostridium difficile* infection.[16] This resulted in the FDA issuing a safety announcement on the increased risk in PPI users of *Clostridium difficile*-associated diarrhoea, especially in elderly patients with chronic underlying medical conditions or on broad spectrum antibiotics.[4] A systematic review has also shown that PPI use increases patient susceptibility to other enteric infections such as Salmonella, *Campylobacter jejuni* and small intestinal bacterial overgrowth.[17]

Long-term PPI treatment has also been linked to pneumonia. The mechanism with this association may be due to upper gastrointestinal bacterial overgrowth, resulting in an increased susceptibility to respiratory infections by potential micro-aspiration or translocation into the lungs. Data is inconsistent, with some recent meta-analyses suggesting that PPI use is associated with an increased risk of both community and hospital-acquired pneumonia[18] and others failing to show an association.[19]

RENAL DISEASE

Over the years, concerns have been raised about the adverse renal effects of PPIs, with acute interstitial nephritis being the most frequently observed acute kidney damage in PPI users. The proposed mechanism is thought to be secondary to deposition of PPIs or their metabolites in the kidney's tubulo-interstitium compartment and direct stimulation of an immune response.[20] Three large population-based studies in Canada, the United States and New Zealand have all shown a higher risk of acute interstitial nephritis in patients on PPIs compared to controls. In some cases, this acute injury goes unrecognized and therefore uncorrected. While most patients recover kidney function, many are left with some level of chronic kidney injury.[12,20] Several studies have shown an association of PPI use with chronic kidney disease.[21] Caution should therefore be exercised when prescribing PPIs to patients who have other risk factors for renal disease and patients on long-term treatment should have their renal function monitored.

... IN PATIENTS WITH INCREASED RISK OF BONE FRACTURES, CAUTION SHOULD BE EXERCISED WHEN PRESCRIBING LONG TERM PPIS... CALCIUM SUPPLEMENTATION SHOULD BE CONSIDERED, IDEALLY IN FORMS THAT ARE NOT INFLUENCED BY GASTRIC ACID FOR ABSORPTION, SUCH AS CALCIUM CITRATE

DEMENTIA

PPIs were shown to lead to higher levels of amyloid-beta in the brains of mice in a manner similar to the extracellular deposition of amyloid-beta peptides seen in the pathogenesis of Alzheimer's disease. This lead to the hypothesis that PPI use can be associated with an increased risk of dementia. A systematic review looking at 11 studies showed a positive association between PPI use and dementia (three out of four studies) or acute cognitive impairment; however, the authors pointed out several methodological problems and conflicting results.[22] Further longitudinal studies are needed to confirm this association.

CONCLUSION

Although PPIs are safe and effective drugs, their long-term use carries potential risks. As with all medications, there should be a clear indication when prescribing PPIs, with the lowest effective dose being used. It is recommended to weigh the benefits of PPI therapy against the risks, especially in patients with multiple co-morbidities and in the elderly. As clinical situations may change over time, patients should be regularly reviewed as to whether acid suppression is still required.

REFERENCES
1. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008; 336(7634):2-3.
2. Yang Y-X. Chronic PPI Therapy and Calcium Metabolism. Current gastroenterology reports 2012; 14(6):473-479.
3. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016; 27:339-347.
4. US Food and Drug Administration (FDA). FDA Drug Safety Communication. Available from: http://www.fda.gov/Drugs/default.htm.
5. Ito T, Jensen RT. Association of Long-term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium. Current gastroenterology reports 2010; 12(6):448-457.
6. Sharma V, Brannon M, Carloss E. Effect of omeprazole on oral iron replacement in patients with iron deficiency anemia. South Med J 2004; 97:887–889.
7. Sarzynski E, Puttarajappa C, Xie Y, Grover M, Laird-Fick H. Association between proton pump inhibitor use and anemia: a retrospective cohort study. Dig Dis Sci 2011; 56:2349.
8. Hutchinson C, Geissler C, Powell J, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. Gut 2007; 56:1291–1295.
9. Koop H, Bachem MG. Serum iron, ferritin, and vitamin B12 during prolonged omeprazole therapy. J Clin Gastroenterol 1992; 14(4):288-92.
10. Tempel M, Chawla A, Messina C, Çeliker MY. Effects of Omeprazole on Iron Absorption: Preliminary Study. Turkish Journal of Hematology 2013;30(3):307-310.
11. Stewart C, Termanini B, Sutliff V, et al. Iron absorption in patients with Zollinger–Ellison syndrome treated with long-term gastric acid antisecretory therapy. Aliment Pharmacol Ther 1998;12:83-98.
12. Eusebi LH, Rabitti S, Artesiani ML, et al. Pump Inhibitors: Risk of Long-term Use. Journal of Gastroenterology and Hepatology. 2017. (Epub ahead of print).
13. Lam JR, Schneider JL, Zhao W, Corley DA. Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B12 Deficiency. JAMA 2013; 310(22):2435-2422.
14. Den Elzen WP, Groeneveld Y, De Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Alimentary Pharmacology & Therapeutics 2008; 27:491–497.
15. Jackson MA, Goodrick JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016; 65:749–56.
16. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. American Journal of Gastroenterology 2012; 107(7):1011-1019.
17. Bavishi C, DuPont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Alimentary Pharmacology & Therapeutics 2011; 34:1269–1281.
18. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of Community-Acquired Pneumonia with Outpatient Proton-Pump Inhibitor Therapy: A Systematic Review and Meta-Analysis. PLoS ONE 2015; 10(6):e0128004.
19. Filion KB, Chateau D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut 2014; 63(4):552-558.
20. Moledina DG, Perazella MA. PPIs and kidney disease: from AIN to CKD. J Nephrol 2016; 29:611.
21. Arora P, Gupta A, Golzy M, et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC Nephrology 2016; 17:112.
22. Batchelor R, Gilmartin JF, Kemp W, Hoppler I, Liew D. Dementia, cognitive impairment and proton pump inhibitor therapy - a systematic review. J Gastroenterol Hepatol 2017 Jan 27. (Epub ahead of print).

RESEARCH

WASP (WRITE A SCIENTIFIC PAPER) AGAIN IN MALTA AND LONDON

VICTOR GRECH

The ability to write up research in a paper that can withstand peer-review is a crucial and critical requisite for all academics, not only to disseminate their work, but also to further their careers. The skills required are manifold and are usually acquired piecemeal. WASP (Write a Scientific Paper) is an intensive and comprehensive 3-day course that covers all requisite paper-writing skills.

Core subjects include: literature appraisal, proposals, ethics and data protection, seeking materials for publication, preparing a compelling abstract, an attractive poster and a captivating presentation, how to lay out a paper, which journals to target (and why), editors' viewpoints, tackling editors, the difference between a paper and a thesis, and statistics. Almost a third of WASP includes statistical analysis using the familiar Microsoft Excel environment. The WASP faculty comprises experienced researchers and journal editors. WASP's purpose is to impart the lecturers' collective experience to the delegates in this crucial aspect of career progress.

WASP courses include soft copies of all talks, all papers discussed as examples, all spreadsheets including actual data used in published papers, as well as spreadsheets that extend Excel's native capabilities. WASP also has a half day of statistics exercises using Microsoft Excel. The author is well suited to impart the statistics lectures, having co-written the statistics chapter in *The Science of Paediatrics: MRCPCH Mastercourse*.[1]

WASP has been held in Malta almost annually since 2010. After each iteration, feedback has been used for fine-tuning WASP. The course was held in London, for the first time, at the Royal College of Paediatrics and Child Health at the end of January 2017. This is a unique course worldwide and feedback has been excellent (table 1). The modus operandi for WASP has also been published.[2]

This event is suitable for all individuals in the sciences field who wish to enhance their paper writing skills by acquiring sound competences in academic writing. WASP will once again be held in Malta (2-4/10/2017) and in London (23-25/10/2017). The WASP faculty looks forward to meeting you. Registration is available at www.ithams.com/wasp.

REFERENCES
1. Fine-Golden M, Grech V. Statistics. In: Lissauer T, Carrol W (eds). *The Science of Paediatrics MRCPCH Mastercourse* (1st edition). London: Elsevier, 2016. (p. 723-738).
2. Grech V. WASP – Write a Scientific Paper course: Why and how. *J Vis Comm Med* – in press.