

Long-term use of proton pump inhibitors: many a little makes a mickle?

Takakazu Higuchi

Blood Transfusion Department, Dokkyo Medical University Saitama Medical Center, Koshigaya, Japan

RELATED ARTICLE

by Kaczmarczyk et al,
see p. 179

Proton pump inhibitors (PPIs) have taken the place of histamine H₂ receptor antagonist in the treatment of peptic ulcer disease, mainly due to their superior gastric acid suppression effect. Today, they are approved in many countries for not only the management of a variety of gastrointestinal disorders, such as gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), reflux esophagitis, and Barrett esophagus, but also *Helicobacter pylori* eradication, prophylaxis for bleeding associated with nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin, and pathologic hypersecretory conditions.¹ Consequently, they are currently one of the most widely prescribed drugs worldwide.

In addition to their superior gastric acid suppression effect, PPIs have other advantages over H₂ receptor antagonists. For example, PPIs are metabolized by the liver and do not require dose-adjustment based on renal function, and they are usually given as once-a-day prescription. These advantages and the early impression that they had encouraging safety profiles have contributed to the increased prescription of PPIs.

When PPIs are prescribed for peptic ulcer disease or *H. pylori* eradication, the duration of PPI-therapy is usually limited and short-term (<8 weeks); however, when used for GERD, Barrett esophagus, prophylaxis for bleeding associated with NSAIDs or low-dose aspirin, and pathologic hypersecretory conditions, PPIs are usually prescribed for long periods without specified treatment goal. Also, with recent introduction of combination preparation of low-dose aspirin and a PPI, patients with ischemic heart disease and/or cerebral vascular diseases may continue a PPI for indefinite period, possibly lifelong.

Proton pump inhibitors were first introduced in 1989 and as their use has become prevalent and the restriction of the treatment periods has been less strict or abolished, adverse effects associated with their long-term use have been recognized. Although the evidence level of most of

the studies on the potential adverse effects associated with long-term PPI are not high enough to evaluate the causative association, comprehensive reviews on the safety of long-term PPI use have been published.¹⁻³ Long-term use of PPIs is reported to be associated with conditions such as osteoporosis and bone fracture, *Clostridioides difficile* (formerly *Clostridium difficile*) infection, small intestinal bacterial overgrowth, collagenous colitis, chronic kidney disease, pneumonia, dementia, and deficiencies of micronutrients such as calcium, iron, magnesium, and vitamin B₁₂, and the list of such conditions is increasing. Among these associations, the relationships between PPIs with hypomagnesemia, vitamin B₁₂ deficiency, and small intestinal bacterial overgrowth appear likely; however, others are unclear due to lack of high-quality evidence, confounding factors, and unclear pathophysiological causality. Moreover, PPI treatment for patients involved in the previous studies is necessarily limited and may not be long enough to evaluate the real long-term adverse effects of treatments that will be continued for decades. It is possible that longer observation period may reveal causative associations. In particular, accumulation of continuous small deficit of micronutrients may eventually reach the level which can cause clinically significant consequences associated with long-term PPI treatment. As the decrease in absorption of micronutrients is subtle or minimal and the progress of the deficit may be insidious, it may take years for a micronutrient to decrease to a clinically meaningful level. In such case, it is likely that signs and symptoms related to the deficit are not overt or are not noticed until the deficiency becomes profound. We still do not know what happens to patients who have taken PPIs for longer than 30 years. In fact, we experienced a case of iron deficiency anemia which developed after 25 years of PPI use.⁴ Further extended use of PPIs may prove that conditions whose association with long-term PPIs is suggested but not clear have in

Correspondence to:

Takakazu Higuchi, MD, FACP,
Blood Transfusion Department,
Dokkyo Medical University
Saitama Medical Center, 2-1-50,
Minami-Koshigaya, Koshigaya,
Saitama 343-8555, Japan,
phone: +81 48 965 1111,
email: thiguchi@dokkyomed.ac.jp

Received: February 21, 2020.

Accepted: February 22, 2020.

Published online: March 27, 2020.

Pol Arch Intern Med. 2020;

130 (3): 174-175

doi:10.20452/pamw.15259

Copyright by Medycyna Praktyczna,
Kraków 2020

fact a causative relation. It should be mentioned here that the effects of PPIs may differ among individuals possibly due to the interindividual variability of *CYP2C19* gene and the composition of daily diet. Interaction with other drugs may also have to be taken into consideration. Thus, there might be considerable differences in the long-term effects of PPIs among individuals, making generalized conclusion rather difficult.

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Kaczmarczyk et al.⁵ describe another aspect of long-term effects of PPIs. They report higher prevalence of anemia and leucopenia, lower serum iron level, and higher copper and zinc levels among long-term PPI users, with the data on the serum selenium level, and correlations of the findings. While it should be noted that the duration of PPI therapy is between 3 and 10 years and may not be long enough to determine the true long-term effects as discussed earlier, they have already observed emerging effects of “long-term” PPIs and present a new insight that longer-term PPI use may lead to disturbance or imbalance of micronutrients which are not known to be affected by long-term PPI use so far. Larger and more comprehensive studies with longer treatment periods are expected to confirm or refute their findings and also to verify the observation that suppression of gastric acid is not the only factor associated with long-term adverse effects.

Newer and more potent PPIs have been successively developed, achieving more profound suppression of gastric acid. We are going into an unknown realm of long-term use of more potent PPIs and should be prepared to encounter unexpected adverse effects. A recommendation for routine monitoring and prophylaxis is proposed for some of the adverse effects.³ However, as prospective studies in which a large number of individuals are followed for decades are not realistic and we will hardly know the true “long-term” effect of PPIs, they should be prudently prescribed only when necessary and at the lowest dose for the shortest term possible, balancing the benefits and adverse effects.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution NonCommercial ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

HOW TO CITE Higuchi T. Long-term use of proton pump inhibitors: many a little makes a mickle? *Pol Arch Intern Med.* 2020; 130: 174-175. doi:10.20452/pamw.15259

REFERENCES

- 1 Nehra AK, Alexander JA, Loftus CG, et al. Proton pump inhibitors: review of emerging concerns. *Mayo Clin Proc.* 2018; 93: 240-246. [↗](#)
- 2 Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from

the American Gastroenterological Association. *Gastroenterology.* 2017; 152: 706-715. [↗](#)

3 Malfertheiner P, Kandulski A, Venerio M. Proton-pump inhibitors: understanding the complications and risks. *Nature Rev Gastroenterol Hepatol.* 2017; 14: 697-710. [↗](#)

4 Imai R, Higuchi T, Morimoto M, et al. Iron deficiency anemia due to the long-term use of a proton pump inhibitor. *Intern Med.* 2018; 57: 899-901. [↗](#)

5 Kaczmarczyk O, Przybylska-Feluś M, Piątek-Guziewicz A, et al. Effect of long-term proton pump inhibitor therapy on complete blood count parameters and selected trace elements: a pilot study. *Pol Arch Intern Med.* 2020; 130: 179-186. [↗](#)