EDITORIAL

Gut and Liver, Vol. 10, No. 6, November 2016, pp. 865-866

Does Long-Term Proton Pump Inhibitor Therapy Affect the Health of Gut Microbiota?

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See "Impact of Long-Term Proton Pump Inhibitor Therapy on Gut Microbiota in F344 Rats: Pilot Study" by Cheol Min Shin, et al. on page 896, Vol. 10. No. 6, 2016

Proton pump inhibitors (PPIs) are among the most widely sold medications in the world and are generally considered safe. PPIs are frequently prescribed or taken for long periods without evidence-based indication.[1] However, long-term use of PPIs has not been studied in depth, and several side effects have recently been identified, including an increased risk of enteric infections such as small intestinal bacterial overgrowth and *Clostridium difficile* infections.[2,3] The increased risk of enteric infections can be caused by the changes in the PPI-user's gut microbiome, which result from the reduced acidity of the stomach and the subsequent survival of more bacteria that are ingested with food and oral mucus. Gut microbiota can resist or promote the colonization of *C. difficile* and other enteric infections through mechanisms that directly inhibit bacterial growth or enhance the immune system.[4]

Through the fecal microbiome analysis of 1,815 individuals spanning three cohorts, PPI use was associated with decreased bacterial richness and profound changes in the gut microbiome.[5] Oral bacteria and potential pathogenic bacteria were increased in the feces of PPI users. In addition, the alterations of fecal microbiota in PPI users were more prominent than individuals who had used antibiotics or other drugs.[5] A recently published, large, healthy twin cohort study identified significant associations between the composition of gut microbiota in feces and PPI use.[6]

The best way to confirm that long-term PPI use altered gut microbiota composition is to conduct double-blinded, randomized, placebo-controlled trials; however, this study may not be feasible due to ethical concerns. Animal models should be investigated to determine the impact of long-term PPI therapy on gut microbiota and to set up preclinical trials to resolve the problem associated with long-term PPI therapy.

Until recently, few studies have confirmed the effects of long-term PPI treatment on the gut microbiota in animal models.[7] In this issue of *Gut and Liver*, the article "Impact of long-term proton pump inhibitor therapy on gut microbiota in F344 rats: pilot study" by Shin *et al*.[8] investigated compositional changes in gut microbiota due to long-term PPI use in F344 rats treated with lansoprazole for 50 weeks. The gut microbiota in rats' terminal ileum was profiled using 16S rRNA sequencing. Shin *et al*.[8] found that the profile of gut microbiota in the terminal ileum of F344 rats treated with lansoprazole for 50 weeks was quite different than that of the control group. Terminal ileal microbiota profiles showed a predominance of *Proteobacteria* (93.9%) due to the abundance of *Escherichia* or *Pasteurella* genera in control rats, whereas lansoprazole-treated rats showed an increased population of *Firmicutes* (66.9%) due to an increased ratio of *Clostridium g4* or *Lactobacillus genera*. This study was performed underregulated conditions to define the effect of long-term PPI use on gut microbiota, which suggests the results of this study may be more reproducible than those of previous studies. This study provided good additional evidence to support the alteration of gut microbiota induced by long-term PPI use.

In addition, this study suggested a new correlation between the alteration of small intestinal microbiota and changes in body weight in long-term PPI-treated animal models. PPIs induce strong acid suppression in the stomach to treat upper gastrointestinal ulcerative lesions, including reflux esophagitis, which results in symptom-related food abstinence. PPI therapy promotes patients' weight gain. However, it was reported that

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pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl16438

PPI treatment induced weight loss in patients who had already had bariatric surgery.[9] Previous mouse and human studies have associated *Firmicutes* with obesity and *Bacteroidetes* with weight loss.[10] PPI may have another regulatory mechanism responsible for the regulation of body weight and the alteration of gut microbiome; this requires further study.

Although the animal models are a different size and have different physiologies compared to humans, the role of animal models is to gain preclinical data of the responses and safety of interventions. Alteration of gut microbiome may be controlled using probiotics and/or prebiotics in the near future. The changes in gut microbiome due to PPI depend on the species and intestinal sampling site. Shin and colleagues established the rodent model for long-term PPI use and this model is thought be applicable to further preclinical trials to alleviate the adverse effects of long-term PPI use. Fecal microbiota transplantation may be another promising therapy for controlling gut microbiota.

To date, microbiota changes in terminal ileum due to PPI administration may be summarized as an increase in *Firmicutes* and/or a decrease in *Bacteroidetes*. Given the widespread use of PPI, adverse effects, including enteric infections, should not be overlooked. The studies investigating the impact of PPIs on the gut microbiome consistently indicate that PPI use affects the alteration of gut microbiome. Therefore, healthcare practitioners should consider the influence of PPI on gut microbiome.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (number: 2014R1A2A11052136).

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