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EDITORIAL

What are the effects of proton pump inhibitors on the small intestine?

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Abstract

Generally, proton-pump inhibitors (PPIs) have great benefit for patients with acid related disease with less frequently occurring side effects. According to a recent report, PPIs provoke dysbiosis of the small intestinal bacterial flora, exacerbating nonsteroidal anti-inflammatory drug-induced small intestinal injury. Several meta-analyses and systematic reviews have reported that patients treated with PPIs, as well as post-gastrectomy patients, have a higher frequency of small intestinal bacterial overgrowth (SIBO) compared to patients who lack the aforementioned conditions. Furthermore, there is insufficient evidence that these conditions induce *Clostridium difficile* infection. At this time, PPI-induced dysbiosis is considered a type of SIBO. It now seems likely that intestinal bacterial flora influence many diseases, such as inflammatory bowel disease, diabetes mellitus, obesity, non-alcoholic fatty liver disease, and autoimmune diseases. When attempting to control intestinal bacterial flora with probiotics, prebiotics, and fecal microbiota transplantation, *etc*., the influence of acid suppression therapy, especially PPIs, should not be overlooked.

Key words: Proton-pump inhibitors; Nonsteroidal anti-inflammatory drug; Small intestine; Dysbiosis; Small intestinal bacterial overgrowth

Core tip: Proton-pump inhibitor (PPI) administration provokes dysbiosis of small intestinal bacterial flora, which exacerbates nonsteroidal anti-inflammatory drug-induced small intestinal injury. Dysbiosis is considered part of small intestinal bacterial overgrowth. Both PPI administration and gastrectomy increase the frequency of small intestinal bacterial overgrowth. Intestinal bacterial flora influence a number of systematic diseases. The influence of acid suppression therapy, especially PPIs, on small intestinal bacterial flora is worth noting.

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Proton-pump inhibitors (PPIs) induce strong acid suppression in the stomach and are used to treat upper gastrointestinal ulcerative lesions, including reflux esophagitis. Generally, PPIs are highly beneficial for patients with acid-related disease, and side effects from PPIs are infrequent. Recently, Wallace *et al*[1] reported that PPIs exacerbate nonsteroidal anti-inflammatory drug (NSAID)-induced small intestine injury in rats. In their study, omeprazole and lansoprazole caused "dysbiosis", or a microbial imbalance, which exacerbated NSAID-induced small intestinal injury. These results are important for researchers who investigate NSAID-associated small intestinal injuries. Because PPIs are co-administered with NSAIDs to prevent NSAID-induced gastroduodenal injury, many studies have evaluated NSAID-induced small intestinal injury in healthy volunteers[2-4]. Until recently, most studies on NSAID-associated injury have focused on the upper gastrointestinal tract because the stomach and duodenum are common sites of major morbidity and mortality in the clinical setting. As a result, PPIs and prostaglandin analogs are the currently established treatments against NSAID-induced gastroduodenal injuries[5]. However, PPIs can affect the small intestinal bacterial flora. On the other hand, the examination protocol for evaluating NSAID-associated small intestinal injuries has not changed since the Wallace *et al* study was published.

As mentioned above, many studies have evaluated healthy volunteers who were treated with the combination of NSAIDs and PPIs. These studies have shown that the preventive effect of PPIs does not extend to the small intestine[4]; after taking NSAIDs and PPIs for two weeks, > 50% of subjects had small intestine injuries. If PPIs do indeed exacerbate small intestinal injury, most capsule endoscopy studies that evaluated NSAID-induced small intestinal injury with the concomitant administration of PPIs likely over-estimated the frequency of NSAID-induced small intestinal injury. Accordingly, it is very important that we appropriately interpret the results of these studies by evaluating NSAID-associated small intestinal injury while considering whether or not PPIs have been co-administered.

Recently, the concept of dysbiosis, also called dysbacteriosis, has received substantial attention in various biomedical fields. Since the 1960s, the word "dysbiosis" has been used in research on intestinal bacteria flora in infants and post-gastrectomy patients in Germany. "Dysbiosis" was first used in a manuscript written in English in 1985[6]. Afterwards, the term was used in a 1987 study of patients with ulcerative colitis whose intestinal flora had increased levels of Proteus, a genus of Gram-negative proteobacteria[7]. Since then, "dysbiosis" has become established, and its use in publications written in English has increased. However, previous publications only evaluated approximately 10 species of bacteria, as closely as possible, using the available technology[8]. In the beginning, "dysbiosis" was mostly used in research on inflammatory bowel disease[9,10]. However, it has recently been posited that intestinal bacterial flora influence many diseases, such as diabetes mellitus[11], obesity, non-alcoholic fatty liver disease[12,13], and autoimmune diseases[14]. While 150 manuscripts that were published between 1960 and 2009 and included in PubMed used the word "dysbiosis", in the period from 2010 to 2014, an additional 800 manuscripts of that type were published. Clearly, the field of dysbiosis has attracted attention in recent years.

What does it mean for PPIs to induce dysbiosis? The first report of a possible association between PPIs and small intestinal bacterial overgrowth (SIBO) was published in 2008[15]. Recently, a meta-analysis reported on the statistical relationship between PPIs and SIBO[16]. In addition, numerous reports have stated that the number of patients with SIBO increases after total gastrectomy[17]. According to one report, the frequency of patients with *Clostridium difficile* (*C. difficile*) diarrhea increased during PPI administration in 2003[18]. Several other reports describe an association between PPI administration and *C. difficile* infection. However, there was no clear association between PPI administration and *C. difficile* infection in a recent systematic review[19]. Additionally, there are no reports of an increase in the number of patients with *C. difficile* diarrhea following total gastrectomy. Therefore, at this time, it is doubtful that PPI administration triggers *C. difficile* infection, while the frequency of SIBO is likely increased by PPI administration. Presumably, SIBO is closely related to dysbiosis. Currently, PPI-induced dysbiosis is considered part of SIBO.

In the near future, intestinal bacterial flora will be controlled by probiotics (viable micro-organisms with beneficial physiologic or therapeutic properties) and prebiotics (dietary components that foster the growth of beneficial bacteria). In addition, fecal microbiota transplantation is a promising therapy for controlling intestinal bacterial flora; its effectiveness has been reported in patients with inflammatory disease as well as in patients with *C. difficile* infection[20,21]. When attempting to control intestinal bacterial flora, the influence of acid suppression therapy, especially PPIs, should not be overlooked.

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