The Impact of Proton Pump Inhibitors on the Human Gastrointestinal Microbiome

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KEYWORDS

• Proton pump inhibitors • Gastric acid suppression • Hypergastrinemia
• Human microbiome • Barrett's esophagus • *Helicobacter pylori*
• Small bowel bacterial overgrowth • *Clostridium difficile* infection

KEY POINTS

- Proton pump inhibitors (PPIs) have the potential to affect human health via interactions with the gastrointestinal microbiome.
- PPIs reduce esophageal gram-negative bacteria and may decrease risk for distal esophageal neoplasia.
- Given for *Helicobacter pylori* eradication, PPIs can prevent gastric cancer but may cause gastric dysbiosis after *H pylori* has been eradicated.
- PPIs may cause small intestinal bacterial overgrowth and are associated with the diagnosis of celiac disease.
- PPIs are associated with *Clostridium difficile* infection (CDI), although the mechanism linking PPIs and CDI is uncertain.

INTRODUCTION

For centuries, it has been known that dietary factors influence gastrointestinal bacteria; Dorlencourt and Lavaudon[1] hypothesized that pH differences between breast milk and cow's milk explained the higher proportions of *Lactobacillus* observed in the

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stools of breastfed children. The role of gastric acidity in the human gastrointestinal microbiome is now intertwined with the development and increasing use of proton pump inhibitors (PPIs). Other medications can alter the pH of the human gastrointestinal lumen. However, PPIs are the most potent, the most common, and have received the most attention. This article focuses on PPIs and covers the physiology of gastric acid production and suppression, and the evidence and clinical consequences of acid-related changes in the normal microbiome.

PROTON PUMP INHIBITORS AND GASTROINTESTINAL ACIDITY

Normal Gastrointestinal Acidity

Acidity within the human gastrointestinal tract varies by anatomic location and is part of essential physiologic processes, including digestion and nutrient absorption.[2] In the stomach, lumenal pH can approach 1.0; gastric acid plays a role in breakdown of food particles and the pH-dependent separation of intrinsic factor from R-protein.[3] Outside the stomach, lumenal pH is often discussed in the context of optimizing drug delivery. In general, pH tends to increase gradually from 6.5 in the small bowel to a high of 7.5, decrease in the cecum (to as low as 5.5), and again increase gradually in the left colon to a high of 6.5 to 7.0.[4] The invariant pattern of gastrointestinal pH seen between individuals suggests that pH plays crucial physiologic roles throughout the gastrointestinal tract. Local pH partially determines the absorption of biotin and folate in the small bowel,[5,6] vitamin B_{12} in the distal ileum,[7] and calcium and other electrolytes in the colon.[8] Thus, in addition to the influence that pH exerts on the microbiome, gastrointestinal acidity is important and tightly regulated.

Physiology of Gastric Acid Production

Food, stress, and other central and hormonal mechanisms stimulate gastric acid secretion acting via autonomic and paracrine signals. The primary signals are gastrin from pyloric and duodenal G cells, acetylcholine from postganglionic neurons in the gastric submucosa, and histamine from enterochromaffinlike cells; the common target of these signals and the acid-producing cells of the stomach is the parietal cell.[9] In response to stimuli, transmembrane H^+/K^+-ATPase pumps are translocated from tubulovesicles into parietal cell canaliculi, increasing their concentration on the cell surface by 10-fold. These powerful pumps then acidify the stomach by using ATP for energy to drive protons or hydronium ions against enormous concentration gradients.[10]

Proton Pump Inhibitors

PPIs were independently synthesized by 2 companies from 2-pyridylthioacetamide by screening modified compounds (**Fig. 1**); the first PPIs were omeprazole (1988) and lansoprazole (1991).[11] There were initial safety concerns surrounding omeprazole, which

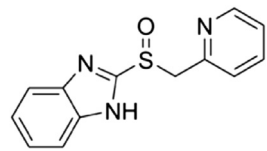

Fig. 1. Common structure of PPIs. All PPIs share a common backbone, with a pyridine linked to a benzimidazole.