



# Can proton pump inhibitors cause intestinal inflammation in children?

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Proton pump inhibitors (PPIs) such as lansoprazole, esomeprazole, pantoprazole, and rabeprazole are currently among the most frequently prescribed medications in both adults and children. In the pediatric population, PPIs are indicated for the treatment of gastroesophageal reflux disease (GERD), erosive esophagitis, gastric ulcers, *Helicobacter pylori* infection, and eosinophilic esophagitis.<sup>1)</sup> Although evidence from most clinical trials of PPIs in children with GERD have demonstrated that adverse events do not significantly differ between PPI-treated and placebo groups, case control studies have revealed an increased risk of infections including necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and *Clostridium difficile* infection (CDI) with PPI use.<sup>2)</sup>

The underlying mechanism of these adverse events associated with PPI use is related to their acid inhibition effect, which is mostly observed during long-term treatment.<sup>3)</sup> PPIs increase gastric pH, which decreases the bactericidal effect of the gastric juices and can lead to a higher susceptibility to infections. In the gastrointestinal tract, the chance of infection and proliferation of acid-labile bacteria, such as *Salmonella*, *Campylobacter*, and the vegetative form of *C. difficile*, is increased when gastric acid secretion is suppressed by PPI administration.<sup>3)</sup> Recent studies investigating the gut microbiome using high throughput genomic sequencing have revealed significant decreases in the diversity of the normal gut flora within 1 month after initiating PPI administration.<sup>4)</sup> This may eliminate nutrient competition between the gut microbiome and enhance the proliferation of *C. difficile*.<sup>4)</sup> An association between CDI and PPI use in children was also demonstrated from a database of 2,531 pediatric cases of CDI.<sup>5)</sup> Therefore, PPI use may cause dysbiosis of the normal gut flora, leading to the proliferation of pathogenic bacteria, which may trigger the activation and recruitment of neutrophils to sites of intestinal inflammation.

Fecal calprotectin (FC), a sensitive biomarker of intestinal inflammation derived from neutrophils within the mucosa, is widely used in the discrimination between inflammatory bowel disease (IBD) and functional gastrointestinal disorders as well as monitoring mucosal activity in patients with IBD.<sup>6)</sup> The study by Kim et al.<sup>7)</sup> was novel in its attempt to investigate the effect of PPIs on intestinal inflammation using FC as a surrogate marker. Unfortunately, the results of this study showed no significant differences in FC levels between the PPI group and the control group at the end of the study period. These findings are inconsistent with the findings of studies conducted in adults.<sup>8,9)</sup> In a cross-sectional study of 599 adult patients, the use of PPIs was significantly associated with an elevated FC > 50 mg/kg (adjusted odds ratio, 3.843; confidence interval, 2.338–6.316).<sup>9)</sup> Owing to the small number of patients in the study of Kim et al.,<sup>7)</sup> comparable results may have been derived between the PPI and control groups. For instance, the proportion of patients with an increased calprotectin level >50 mg/kg was 24.3% (9 of 37) for the PPI group and 7.1% (1 of 14) for the control group ( $P=0.250$ ). These results could have been statistically significant in a larger number of patients. Another possible explanation for the discrepancy between the 2 studies is the duration of PPI usage.

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Although the adult study did not disclose the PPI usage duration, it is likely that the adults in this study had taken them for a long-term period, while children in the study by Kim et al.<sup>7)</sup> took them for only 1–2 months.

The prevalence of GERD in children is increasing in Western countries as well as in Korea.<sup>2,10)</sup> Hence, prescriptions of PPIs are likely to continuously increase. Meanwhile, PPIs are also used off-label in children to optimize pancrelipase therapy, stress ulcer prophylaxis, treatment of respiratory symptoms, and treatment of sleep disorders.<sup>3)</sup> The use of PPIs is also prevalent in the intensive care environment, and inappropriate uses of PPIs occur at all ages to treat gastroduodenal ulcers in low-risk patients, as low-dose steroid therapy without additional risk factors, to achieve systemic anticoagulation without additional risk factors in cases of gastroduodenal injury, and in cases of overtreatment of functional dyspepsia.<sup>4)</sup> Considering the potential risks of long-term PPI use, the recent GERD guideline from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition emphasizes that widespread unnecessary use of acid suppressive medications such as PPIs should be avoided and, if they must be used, unnecessarily long-term usage should be avoided whenever possible.<sup>2)</sup> The joint recommendation also states that regular assessment of the ongoing need for long-term acid suppression therapy is required.<sup>2)</sup>

In conclusion, intestinal inflammation is likely to increase with long-term PPI use in children as in adults. However, further evidence from large-scale prospective longitudinal studies is required in the pediatric population to better clarify whether and when PPIs induce intestinal inflammation.

## Conflicts of interest

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

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