NSAID–PPI Enteropathy in Humans

Dear Sir:

The comprehensive studies by Wallace et al[1] strongly support a co-enhancement by nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) in the development of enteropathy in rats, with the PPI contribution largely mediated through its alteration of small intestinal bacterial flora.

A variety of observations support the presence of similar phenomena in human subjects, and suggest that NSAID–PPI enteropathy may be a frequent, but unappreciated, illness in clinical practice.

Compare et al[2] reported diarrhea, often associated with other prominent gastrointestinal symptoms, in 53% of 42 patients after 6 months of PPI therapy, with small intestinal bacterial overgrowth in 62% of them. Lombardo et al[3] reported similar phenomena among 40%–50% of 200 adults who had consumed PPI medications for an average of 36 months, with diarrhea eliminated or improved in 94% after 2 weeks of oral rifaximin therapy. In neither study was the use of NSAIDs by their subjects analyzed. Both Goldstein et al[4] and Hawkey et al[5] have independently reported more frequent small intestinal injury in healthy volunteers consuming a combination of NSAID and omeprazole for 14–16 days, in comparison with those consuming a selective cyclooxygenase (COX)-2 inhibitor, supporting the presence of an independent PPI contribution to their injury, since multiple other studies have demonstrated similar small bowel damage induced by therapeutic doses of conventional NSAIDs and COX-2 inhibitors. Microscopic colitis is reported to be more common among both PPI and NSAID consumers[6–8] with its strongest association among older adults consuming both classes of medication concurrently.[8]

Both classes of medications are widely prescribed and also available without prescription. In my small, solo practice of general internal medicine, over a recent 2-month interval, 6 patients were identified with apparent NSAID–PPI diarrhea of 2–12 months' duration, each of whom responded dramatically within 2 weeks to withdrawal of the offending medications without other medicinal or dietary therapy. Additional studies exploring these associations on humans should receive high priority, and patients with diarrhea, abdominal distention, flatulence, or abdominal pain while consuming medications of both classes should undergo reassessment of their diagnoses and therapy.

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Conflicts of interest:
The authors disclose no conflicts.

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Reply. We thank Dr Daniell for his insightful remarks about our paper on the exacerbation of NSAID-induced enteropathy in rodents by proton pump inhibitors (PPIs).[1] He has provided references to several studies in which data were generated that are consistent with our hypotheses that PPIs can worsen NSAID-induced small intestinal injury, and that the underlying mechanism is the PPI-induced shift in quantity and types of bacteria in the small intestine. Two additional studies are worthy of mention. Poullis et al[2] reported that fecal levels of calprotectin, a marker of gut inflammation, were significantly elevated in patients taking PPIs. Similarly, Andreasson et al[3] reported an association between elevated fecal calprotectin levels and use of PPIs in patients with systemic sclerosis.

It is important to bear in mind that, in addition to PPIs, patients taking NSAIDs are also often encouraged to take low-dose aspirin once daily to provide protection against the cardiovascular toxicity of the NSAIDs.[4] Low-dose aspirin has been reported to cause significant small intestinal damage/bleeding in humans.[5] In rat models, we have observed that low-dose aspirin, although not producing intestinal damage on its own at the anti-thrombotic dose used, did significantly augment naproxen- or celecoxib-induced small intestinal damage.[6] When either NSAID was administered together with both a PPI and low-dose aspirin, even greater small intestinal damage was observed.

The combined use of a PPI and an NSAID is common, and with the introduction of combination tablets containing both of these drugs, such use may increase. The clinical evidence on combined PPI and NSAID use, as separate or combination tablets, supports the notion of reduced gastroduodenal injury versus use of an NSAID alone. However, careful consideration needs to be given to the impact of this combination therapy on the intestine distal to the ligament of Treitz.

PPIs markedly suppress gastric acid secretion and this leads to significant changes in the numbers and types of bacteria in the small intestine. Histamine H2 receptor antagonists, by suppressing gastric acid secretion, can also alter the small intestinal microbiota, as well as producing changes in bile acid metabolism that may contribute to alterations in intestinal mucosal integrity.[7] It is possible that use of histamine H2 receptor antagonists will augment NSAID-induced small intestinal injury in a similar manner to that observed with use of PPIs. This requires further study in a clinical setting, particularly because combination tablets of NSAIDs plus H2 receptor antagonists are at an advanced stage of development.

Prevention of NSAID enteropathy is a challenge, especially because the pathogenesis of this injury remains