MAYO CLINIC

REVIEW

Nonsteroidal Anti-inflammatory Drugs, Proton Pump Inhibitors, and Gastrointestinal Injury: Contrasting Interactions in the Stomach and Small Intestine

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are among the most frequently prescribed groups of drugs worldwide. The use of NSAIDs is associated with a high number of significant adverse effects. Recently, the safety of PPIs has also been challenged. Capsule endoscopy studies reveal that even low-dose NSAIDs are responsible for gut mucosal injury and numerous clinical adverse effects, for example, bleeding and anemia, that might be difficult to diagnose. The frequent use of PPIs can exacerbate NSAID-induced small intestinal injury by altering intestinal microbiota. Thus, the use of PPI is considered to be an independent risk factor associated with NSAID-associated enteropathy. In this review, we discuss this important clinical problem and review relevant aspects of epidemiology, pathophysiology, and management. We also present the hypothesis that even minor and subclinical injury to the intestinal mucosa can result in significant, though delayed, metabolic consequences, which may seriously affect the health of an individual. PubMed was searched using the following key words (each key word alone and in combination): *gut microbiota*, *microbiome*, *non-steroidal anti inflammatory drugs*, *proton pump inhibitors*, *enteropathy*, *probiotic*, *antibiotic*, *mucosal injury*, *enteroscopy*, and *capsule endoscopy*. Google engine search was also carried out to identify additional relevant articles. Both original and review articles published in English were reviewed.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are among the most frequently prescribed and used medications.[1,2] Besides many proven benefits of NSAID therapy, its long-term use is associated with various complications and adverse effects (eg, upper and lower gastrointestinal [GI] tract bleeding or increased risk of adverse cardiovascular events).[3,4] A recent meta-analysis that included 31 trials and 116,429 patients revealed an increase in rates of myocardial infarction, stroke, and cardiovascular death in patients taking either selective or nonselective NSAIDs.[5] Clinical and endoscopic observations indicate that even short-term administration of NSAIDs in low doses frequently induces several adverse effects in the small intestine as increased gut permeability, gut inflammation, mucosal erosions, and ulcerations.[6] In accordance with the current guidelines of professional societies of gastroenterology,[7] cardiology,[8] and rheumatology,[9] NSAIDs are frequently coprescribed with PPIs to minimize NSAID-related adverse effects in the upper GI tract. Thus, the clinical benefit of NSAID/PPI coadministration is regarded as obvious and safe and has come to be viewed as standard medical practice.[10] However, more recent scientific evidence points toward unwanted and more dangerous adverse effects in the small intestine if PPIs are combined with NSAIDs.[11] PPIs, by suppressing gastric acid secretion, are very effective in reducing NSAID-induced damage in the stomach but are without proven benefit in preventing NSAID-related damage in the rest of the GI tract. Moreover, PPIs alter the small intestine microbiome.[12] This phenomenon augments the toxic effects of NSAIDs on the intestinal mucosa and may be responsible for clinically significant complications, such as anemia, that are difficult to manage.[13,14] Alterations in

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ARTICLE HIGHLIGHTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) are among the most frequently prescribed and used medications worldwide.
- Current guidelines from major professional medical societies advocate prescribing PPIs along with NSAIDs in all patients at risk of upper gastrointestinal tract bleeding. The clinical benefit of such coadministration is regarded as obvious and safe and has come to be viewed as standard medical practice.
- Recent scientific evidence points toward unwanted adverse effects in the small intestine if PPIs are combined with NSAIDs. PPIs, by altering the small intestine microbiome, can augment the injurious effects of NSAIDs on the intestinal mucosa.
- Medical practitioners should be aware of potential short- and long-term risks of combined PPI/NSAID therapy in high-risk patients and its effect on small-bowel mucosa.
- Strategies aimed at modulating the gut microbiota may offer the potential of lowering the risk of intestinal mucosal injury related to NSAID/PPI cotherapy.

the microbiota, together with impaired intestinal barrier function, could have pathophysiological consequences that reach beyond the GI tract; however, despite considerable scientific interest, these factors are currently rarely taken into consideration in everyday clinical practice. In this review, we shed light on this phenomenon, with the aim of opening up a lively debate among physicians, leading to more basic and clinical research in and more practical awareness on this hot topic. The authors searched PubMed and Google search engine using the following key words (each key word alone and in combination): *gut microbiota*, *microbiome*, *nonsteroidal anti-inflammatory drugs*, *proton pump inhibitors*, *enteropathy*, *probiotic*, *antibiotic*, *mucosal injury*, *enteroscopy*, and *capsule endoscopy* to identify relevant articles. Both original and review articles published in English were reviewed.

WHAT ARE THE POTENTIAL LONG-TERM HEALTH CONSEQUENCES OF DRUG-INDUCED SMALL-BOWEL MUCOSAL INJURY?

Long-term treatment with NSAIDs and PPIs disturbs the intestinal microbiota and frequently results in intestinal mucosal injury.[15] There is mounting evidence that disturbances in the interplay between bacteria and host at the mucosal level in the gut affect the gut-liver axis and contribute to the development of low-grade inflammation, metabolic endotoxemia, obesity, metabolic liver disorders (nonalcoholic fatty liver disease [NAFLD] and nonalcoholic steatohepatitis),[16,17] and some cancers.[18]

The association between chronic low-grade inflammation, metabolic liver disease, and colon neoplasia has been well documented. Hwang et al[19] studied the association between the occurrence of NAFLD and the incidence of adenomas in the colon. Patients diagnosed with NAFLD had more frequent adenomas in the colon than did healthy individuals. Wong et al[20] found that active steatohepatitis was an independent risk factor for the presence of advanced neoplasia in the colon. Patients diagnosed with type 2 diabetes mellitus and metabolic syndrome are at greater risk for the development of advanced colon neoplasia at a younger age.[21] Of note, these groups of patients have several fold higher levels of circulating endotoxins than do healthy individuals.[22] These and other data provide the evidence that human metabolic status can be influenced by the level of gut mucosal integrity and the diversity of the GI microbiota.[23] These observations are supported by further examples not limited to the digestive tract.[24-32]

LOOKING OUTSIDE OF THE GI TRACT

Metabolic endotoxemia has been associated with (1) the development and progression of cardiovascular and liver diseases, increased susceptibility to infection, and fibrogenesis[2,25]; (2) increased mortality in patients with chronic kidney disease[26]; (3) the development of carotid atherosclerosis[27]; (4) edematous exacerbations in the course of chronic heart failure[28]; (5) increased risk of developing serious life-threatening complications (eg, variceal bleeding or spontaneous bacterial peritonitis) in patients with liver cirrhosis[17,25,29]; (6) deviations in serum lipid concentration resulting in the acceleration of atherosclerosis[30]; (7) behavioral and mood fluctuations as well as neurocognitive changes[31]; and (8) lowering of the pain threshold and changes in pain perception.[32]

An altered microbiota may affect the response of cancer patients to chemotherapy.[33] In light of

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these recent data, it is evident that clinical effects of NSAIDs and PPIs depend on not only the pharmacokinetic properties of different drugs but also their ability to induce alterations in the microbiota in the gut.[34] This phenomenon might be of greater clinical importance than previously thought. As a consequence, the development or progression of chronic diseases that may seriously affect the health of an individual might be initiated. A simplified scheme presenting the potential long-term health consequences of drug-induced small bowel mucosal injury with regard to microbiota alterations and metabolic endotoxemia is presented in Figure 1.

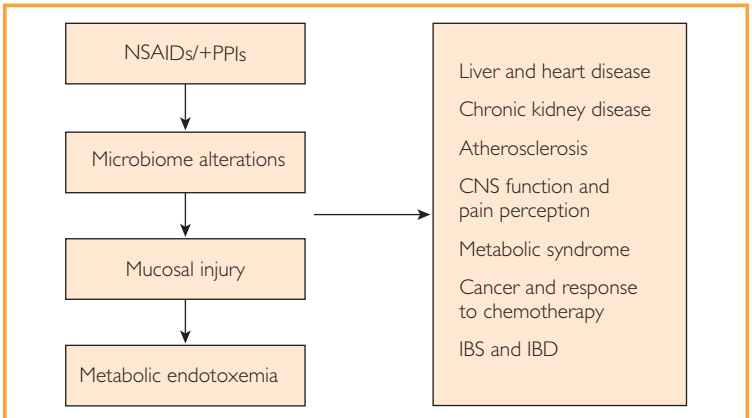

FIGURE 1. Simplified scheme presenting the potential long-term health consequences of drug-induced small-bowel mucosal injury related to alterations in the microbiome and metabolic endotoxemia. CNS = central nervous system; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors.

NSAID THERAPY LEADS TO THE GENERATION OF MUCOSAL LESIONS IN THE SMALL BOWEL

Gastrointestinal adverse effects are common and affect a significant number of patients receiving NSAID therapy. Patients with visible small-bowel mucosal lesions at the time of endoscopic examination are now seen frequently in clinical practice. Pictures obtained at the time of endoscopic examinations performed at the Department of Gastroenterology, Pomeranian University of Medicine, are presented in Figure 2. NSAIDs generate mucosal lesions in every part of the GI tract, most commonly in the stomach and the small intestine. The mechanism leading to gastric mucosal damage after exposure to NSAIDs is well known and beyond the scope of this article. In addition, routine upper GI endoscopy allows for easy and rapid diagnosis of such lesions. However, the clinical challenge is the diagnosis and management of lesions caused by NSAIDs in the small intestine. Recent advances in small-bowel imaging, together with the availability of capsule endoscopy (CE) and enteroscopy, have made this problem more clinically relevant. Data based on CE studies revealed that even low doses of NSAIDs can lead to the generation of erosions and ulcerations in the small intestine. Maiden et al[35] reported small-bowel mucosal injury in 68% to 75% of the volunteers after 2 weeks of therapy with 75 mg of slow-release diclofenac taken twice daily. Goldstein et al[36] documented that a 2-week course of therapy with 500 mg of naproxen twice daily resulted in small intestinal mucosal lesions in 55% of the patients.

The lesions in the small intestine tend to persist whether NSAID therapy is continued[37] or discontinued.[38] Tachecí et al[37] reported the prevalence of small-bowel enteropathy among patients diagnosed with rheumatoid arthritis and suffering from chronic occult GI bleeding who had been treated for several months with various selective (cyclooxygenase-2) and nonselective (eg, ibuprofen, diclofenac, and ketoprofen) NSAIDs. The prevalence of mucosal lesions in patients treated with NSAIDs

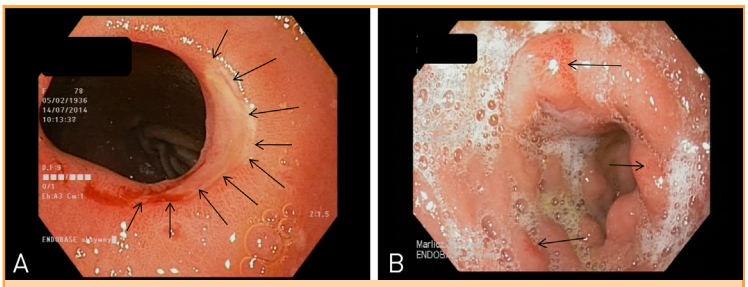

FIGURE 2. Yin and Yang of PPI therapy. Endoscopic features of 2 patients treated in the long term with NSAIDs alone (A) or with NSAIDs + PPIs (B). A, Pyloric channel ulcer in a patient with rheumatoid arthritis treated with 100 mg of diclofenac daily without regular PPI intake. In this case, PPIs, in an acid-dependent manner, could have effectively prevented NSAID toxicity. B, Multiple small erosions and mucosal breaks in the jejunum in a patient treated with NSAIDs and PPIs. In this case, PPIs did not prevent NSAID toxicity in the small intestinal mucosa and, in fact, augmented NSAID-related mucosal injury through a mechanism that involves interaction with the microbiota. NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors. Endoscopy performed by Wojciech Marlicz, MD, PhD, using Evis Exera III Olympus GIF-HQ190 endoscopic equipment.

presenting with anemia and/or positive fecal occult blood tests was 68%. Of interest, no statistically significant difference in prevalence was noted between the various NSAIDs.[37] Similarly, 75% of the patients diagnosed with osteoarthritis receiving chronic NSAID therapy (diclofenac, dexibuprofen, or inbuprofen) and evaluated with CE had mucosal lesions in the small bowel.[38]

Leung et al[39] documented that the administration of low-dose acetylsalicylic acid (ASA) resulted in injury to the small-bowel mucosa similar to that observed with NSAIDs. The lesions reported by Leung et al[39] were located in the ileum and tended to persist for up to 3 months after the discontinuation of ASA.

Studies from Japan have provided further endoscopic evidence of a high prevalence of small-bowel mucosal lesions in relation to low-dose ASA administration.[40,41] Endo et al[40] studied 22 patients on low-dose ASA with obscure GI bleeding with CE and found that more than 95% of the patients had some small-bowel mucosal injury. The enteropathy was characterized by multiple petechiae and loss of villi. Among the patients studied, 66% had visible erosions in the small bowel at the time of CE. In some patients, circumferential ulcers with strictures were noted. The lesions found in the small bowel were multifocal, evenly distributed throughout the small intestine, and probably responsible for clinically evident anemia.[40] It is important to note that the use of selective or enteric-coated NSAIDs is also responsible for mucosal damage in the small bowel.[41-49] For example, Shiotani et al[41] observed large erosions and ulcers in 60% of young healthy volunteers after 7 days of ingestion of 100 mg of enteric-coated aspirin.

How clinically important are mucosal lesions observed in the small bowel of patients chronically treated with NSAIDs? This question is important because similar although less advanced intestinal lesions were described in healthy volunteers not taking NSAIDs.[42] In light of these data, it might be reasonable to assume that mucosal lesions observed in persons not taking NSAIDs were caused by other, as yet, undisclosed factors such as stress,[43] diet and lifestyle (eg, vitamin D deficiency),[44] or infectious agents.[45]

Clinical evidence points, however, to several important consequences related to the effects of NSAIDs on the small intestine: (1) occult GI bleeding and microcytic anemia,[15,41,46] (2) worsening of underlying disease (chronic liver and kidney diseases),[17,25,26] (3) diverticulitis and diverticular bleeding,[47] (4) inflammatory bowel disease,[48] and (5) symptoms consistent with dyspepsia and irritable bowel syndrome (IBS).[49,50] However, the effect of NSAID-related damage might be subclinical, resulting only in anti-inflammatory reaction limited to the mucosal surface and increased intestinal permeability, phenomena that are not routinely measured in clinical practice.

THE MECHANISM AND RELEVANCE OF NSAID-INDUCED MUCOSAL TOXICITY IN THE SMALL BOWEL

NSAID-induced small intestinal mucosal damage, in contrast to gastric damage, occurs in an acid-independent mechanism. Although bile acids[51] and inhibition of cyclooxygenase activity[52] are important factors in the pathogenesis of NSAID enteropathy, current concepts relating to the pathogenesis of NSAID-induced mucosal damage in the small intestine revolve around alterations in the gut microbiota and pathological activation of the innate inflammatory cascade.[53] Diverse experimental and clinical observations support the centrality of these factors. Thus, Kent et al[53] reported 100% protection from indomethacin-induced ulcerations in experimental animals pretreated with neomycin, polymycin B, and bacitracin. Uejima et al[54] studied the role of intestinal bacteria in the induction and suppression of small-bowel ulcer formation in experimental animals treated with various NSAIDs. Of importance, germ-free as well as antibiotic-treated animals were resistant to ulcer formation. In contrast, the numbers of gram-negative facultatively anaerobic bacteria in the ulcerated intestine were increased. These authors concluded that gram-negative bacteria were associated with ulcer formation in animals treated with NSAIDs. Moreover, gram-positive bacteria (genera *Lactobacillus* and *Bifidobacterium*) were able to repress the growth of ulcer-inducing bacteria and inhibit ulcer formation in the small intestine.[54]

It is possible that NSAID-induced mucosal damage allows for deeper microbial penetration and subsequent interaction with components of the innate immune system through activation of the Toll-like receptor 4 intestinal pathways.[55] As

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a consequence, mast cell degranulation, neutrophil activation, and cytokine release follow, leading to mucosal inflammation and damage. In particular, the role of the proinflammatory cytokines tumor necrosis factor-alpha and monocyte chemoattractant protein-1 in NSAID-mediated intestinal damage has been elegantly studied.[55] Monoclonal antibodies against neutrophils, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1 resulted in the attenuation of mucosal lesions. Similarly, the administration of broad-spectrum antibiotics, by reducing the number of gram-negative, lipopolysaccharide-secreting bacteria in the small bowel, resulted in an inhibition of ulcer formation. Of interest, these protective effects were lost when antibiotics with no activity against gram-negative bacteria were administered.[55] NSAID therapy alters the intestinal barrier and leads to increased intestinal permeability. However, the consequence of this phenomenon for the immune and endocrine systems is not completely understood and requires further study. It is possible that despite a deleterious impact on the gut barrier and the potential of NSAIDs to initiate the state of metabolic endotoxemia, NSAIDs, through their stimulation or suppression of cyclooxygenase—dependent and cyclooxygenase—independent pathways, counteract intestinal damage. The well-known fact that chronic NSAID therapy has been associated with anti-inflammatory and antitumor activity supports this notion.[56] Epidemiologic studies suggest that the chronic use of NSAIDs reduces the risk of several GI cancers.[57] In addition, it is difficult to exclude that the effect of NSAIDs on the intestinal mucosa might result in enhancement of the innate immunity components, allowing for better adaptation to stressful stimuli.[58]

NSAIDs, THE GUT BARRIER, AND INCREASED INTESTINAL PERMEABILITY

The intestinal epithelial barrier regulates the absorption of nutrients and water but prevents the translocation of pathogens and bacteria-derived endotoxins to the bloodstream. The gut barrier is composed of structural proteins (zona occludens-1, desmosomes, and occludin), forming tight and gap junctions. Fukui et al[59] reported that ASA treatment, by inducing the production of reactive oxygen species, modified the expression of zona occludens-1 protein and increased cell permeability, resulting in small intestinal mucosal injury. Lambert et al[60] documented a significant increase in intestinal permeability after the administration of a single dose (975 mg) of ASA. Similarly, Sequeira et al[61] detected an increase in intestinal permeability resulting from a single (600 mg) oral dose of ASA in healthy woman. In contrast, this damage to the intestinal mucosa could be reversed or prevented by antibiotic administration,[61] indicating an important etiopathogenic influence of the gut microbiota. Treatment with NSAIDs has been associated with shifts toward an abundance of gram-negative bacteria in the small intestine.[13,62] Enteric gram-negative bacteria secrete lipopolysaccharides and interact with bile in the intestine. As a consequence of bacterial enzymatic activity, secondary bile acids with the potential to aggravate intestinal damage are formed. These processes are, at least in part, dependent on β-glucuronidase enzymatic activity in the gut. Of importance, half of the human microbiome contains the coding sequence for this enzyme, with the greatest activity in the distal part of the small intestine where NSAID-related mucosal lesions are most frequently seen.

An altered intestinal microbiota contributes to low-grade, but chronic, inflammation. Initially silent, persistent host-microbe interplay leads, in time, to clinically overt disease.[63-65] Amar et al[64] analyzed data from an Epidemiological Study on the Insulin Resistance Syndrome and measured the bacterial 16S ribosomal DNA concentration in the blood of patients with metabolic syndrome. The authors delivered the evidence that the presence of bacterial 16S ribosomal DNA in the blood was an independent marker of the risk of diabetes mellitus.[64] These pathological yet subtle changes, due to a long and clinically silent course, are most often not taken into consideration by clinicians in their daily practice.

PPIs EXACERBATE NSAID-INDUCED MUCOSAL LESIONS IN THE SMALL INTESTINE

In the past 2 decades, the coadministration of NSAIDs and PPIs led to a decrease in the prevalence of upper GI tract adverse events but has been associated with an increased frequency of lower GI tract events. We envisage that enteropathy induced by the combination of an NSAID and a PPI is common but often clinically silent, yet lesions induced by these drugs

in the small intestine could be of considerable clinical importance.[66-70]

In accordance with current recommendations of gastroenterology and cardiology societies, the use of concomitant PPIs and NSAIDs is considered appropriate to reduce the risk of bleeding in individuals 65 years and older, those with a history of peptic ulcer disease or GI bleeding, those using more than 1 antiplatelet drug, or in combination with anticoagulants, oral biphosphonates, serotonin reuptake inhibitors, or systemic corticosteroids.[8-10] Capsule endoscopy studies have revealed that adding PPIs to NSAIDs results in a higher frequency of mucosal lesions in the small intestine in comparison to that seen in patients taking NSAIDs only.[71-73] Of note, some investigators report that all patients taking both NSAIDs and PPIs have ulcerations in the small intestine.[71] Most of the patients (80%-100%) taking low-dose NSAID and PPI therapy have active mucosal lesions in the small bowel after 2 weeks of therapy.[72] Moreover, the concentration of fecal calprotectin (a sensitive marker for intestinal inflammation) in the stool was significantly higher among patients taking diclofenac and omeprazole.[72] The PPIs and H2 blockers were also identified as independent risk factors for the development of severe mucosal lesions in the small intestine among patients with rheumatoid arthritis taking NSAIDs chronically.[42] In a recent study, Endo et al[74] evaluated the risk factors for the development of small-bowel mucosal breaks in chronic low-dose aspirin users, defined as 75 to 325 mg of ASA daily for a minimum of 3 months. These authors, in their prospective CE study, found that enteric-coated ASA and PPI were the 2 most important risk factors for the development of mucosal breaks in the small intestine. In addition, patients with identified mucosal injury were more frequently diagnosed with anemia.[74] The augmentation of NSAID small-bowel mucosal toxicity by antisecretory drugs could be explained by their potential to alter microbiota.[13] On the basis of a series of elegantly performed experiments in animal models, Wallace et al[13] demonstrated how antisecretory drugs influence the number of bacteria in the GI tract. In their experiments, rats treated with omeprazole had higher numbers of aerobes and enterobacteria in their intestines than did control animals. Moreover, omeprazole-treated animals had a significant reduction in actinobacteria and markedly diminished numbers of bifidobacteria in the jejunum.[13] These investigators further demonstrated that the administration of a PPI augmented the toxicity of NSAIDs in the small intestine of treated animals. Moreover, these animals developed clinically significant anemia.[13] Of relevance, repopulation of the GI tract with bifidobacteria restored the capability of the intestinal mucosa to heal after the administration of NSAIDs. These results indicate that the gut microbiota plays a crucial role in mucosal protection against NSAIDs. Fujimori et al[75] presented a case series of 6 patients evaluated by CE of whom 2 developed numerous mucosal breaks after 2 weeks of therapy with only 20 mg of omeprazole. The changes in microbiota induced by NSAIDs and PPIs seem to be of importance in the pathogenesis of mucosal injury in the small intestine. However, validation of microbiota alterations in everyday clinical practice is difficult and poses significant challenges. One change in the microbiota that has been associated with the use of PPIs is small intestinal bacterial overgrowth (SIBO).

SMALL INTESTINAL BACTERIAL OVERGROWTH

The topic of SIBO is controversial in the literature because a direct relationship between PPIs and SIBO has not been proven.[76] Several authors reported that the use of PPIs has been associated with the generation of SIBO, but others failed to confirm their observations.[77] In the most recent meta-analysis[78] summarizing 11 trials with 3134 patients, the authors observed an increased risk of SIBO development (odds ratio, 2.282; 95% CI 1.238-4.205). Limitations to the data were stressed: heterogeneity of trials (I^2=83.7) and publication bias. Most of the trials, save one with a relatively higher number of patients, found no positive correlation between the use of PPIs and SIBO. Also, the method used for the assessment of SIBO was reported to be of importance. A causative relationship between the use of PPIs and SIBO was found only in those studies in which duodenal and intestinal fluid aspirates were obtained and analyzed. Studies utilizing the easy-to-perform breath tests failed to find correlations. When evaluating divergent reports on the association between the use of PPIs and SIBO, the following should be taken into account: (1) the duration of PPI

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treatment, (2) diet, and (3) geographical location (European trials are often positive and others negative).[79] These factors could also be responsible for the lack of consistency regarding the association between the use of PPI and the risk of SIBO, IBS, and *Clostridium difficile* infection.

CONSIDERING THE ABOVE FACTORS, IMPORTANT QUESTIONS ARISE FOR CLINICIANS: IS COMBINING NSAIDs AND PPIs ALWAYS SAFE? WHAT PRECAUTIONS SHOULD BE TAKEN WHEN PRESCRIBING THESE 2 DRUGS SIMULTANEOUSLY?

PPI treatment increases the stomach pH above 4, which is associated with higher survival of swallowed bacteria in the upper GI tract[80] and disturbances in the GI microbiota,[73] which leads to an increased risk of *C difficile* infection[81] and pathological flora overgrowth. Other consequences of PPI treatment are (1) inhibition of gut peristalsis[82]; (2) slowing of gastric emptying[83]; (3) changes in the mucus composition of the stomach[84]; (4) increased bacterial translocation; and (5) impairment of neutrophil chemotaxis, adhesion, and phagocytosis.[85-88] These factors additionally influence the survival of pathogens in the gut.

Moreover, PPIs may contribute to *Campylobacter jejuni*, *Salmonella enteriditis*, and *C difficile* infection.[88]

PREVENTION AND THERAPY OF SMALL-BOWEL MUCOSAL INJURY INDUCED BY NSAIDs/PPIs

The unfulfilled dream of doctors and pharmacologists has been to develop NSAIDs with a full safety profile throughout the GI tract. So far the safety of NSAID therapy is still only a dream. Attempts to develop nitric oxide—releasing NSAIDs, despite early promising results in in vitro studies, were unsuccessful in in vivo trials.[89] The idea to develop NSAIDs that release hydrogen sulfide is being evaluated in in vitro and animal models.[90] Other attempts to develop efficacious mucosa-protective drugs, despite promising results in early[91] and more recent trials,[92,93] still await clinical confirmation. Recently, the mucus and prostaglandin-stimulating drug rebamipide with anti-inflammatory properties has been tested with the expectation to prevent NSAID-related intestinal injury. Initial clinical reports are promising because the healing potential of intestinal mucosa has been observed in patients who were simultaneously administered rebamipide and NSAIDs.[94] The idea to modulate the gut barrier by means of dietary interventions is interesting but far from ready for implementation in daily practice. Other mechanisms underlying food-drug interactions with the intestinal barrier are being actively pursued.[95] However, recent experimental data concerning the role of the microbiota in the generation of mucosal lesions during the course of NSAID and PPI therapy suggests that modulation of the gut microbiota seems to be a very promising therapeutic as well as preventive modality. Several laboratory and clinical observations already indicate that this strategy could be useful.

SHARP FOCUS ON GUT MICROBIOTA MODULATION

Germ-free mice are resistant to mucosal injury after high-dose indomethacin administration.[96] The administration of broad-spectrum antibiotics to laboratory animals diminished or even reversed NSAID-induced enteropathy.[97] Watanabe et al[55] reported that reducing the number of gram-negative but not gram-positive bacteria correlates with the degree of mucosal injury in the small intestine during the course of antiplatelet therapy. Administration of rifaximin to patients for 14 days results in the resolution of abdominal pain, induced by long-term PPI treatment.[98] Even though antibiotics have been useful in the treatment of symptoms induced by NSAID/PPI therapy, their long-term or repeated use might result in the generation of multistrain microbial resistance and numerous unwanted adverse effects.[99] Other regimens capable of modulating the gut microbiota are therefore needed.[100] Based on pilot experimental and clinical results, prebiotics and probiotics might prove efficacious to protect the intestinal mucosa in patients continuing NSAID and PPI therapy.

THE EMERGING ROLE OF PROBIOTICS IN THE PREVENTION OF DRUG-INDUCED ENTEROPATHY

Several bacterial strains have been tested in humans to try to prevent or reverse NSAID-related enteropathy. Despite negative results of initial trials demonstrating lack of efficacy of *Lactobacillus rhamnosus GG* in the prevention

of indomethacin-related intestinal injury in healthy volunteers,[101] other studies that followed later reported optimistic results. Montalto et al[102] have documented the protective effect of the VSL#3 multispecies probiotic mixture against indomethacin-induced intestinal injury. Endo et al[14] selected a group of patients with severe microcytic anemia of unknown origin. All these patients had been treated with low-dose aspirin (100 mg/d) and omeprazole (10 mg/d). Initial CE examinations revealed small intestinal mucosal lesions in all patients enrolled. The authors then divided the patients into 2 study groups: (1) controls continuing therapy with NSAIDs and PPIs only and (2) the study group with probiotic added to standard treatment. After 3 months of continuing therapy, CE examinations were repeated. The study group continuing standard therapy with probiotics showed almost complete mucosal healing in the small intestine and improvement in the full blood cell count parameters. No such observations were made in the group continuing NSAIDS and PPI standard therapy only.[14] These results are consistent with other observations that probiotic preparations are able to prevent NSAID-induced mucosal damage in the small intestine.[13,102-104] Wallace et al[13] in an animal model of disease showed that food enriched with bifidobacteria species protected the small intestine against mucosal damage induced by NSAIDs and PPIs. Based on available data, the question of full safety of both drugs (NSAIDs and PPIs) administered together is still incomplete. Future clinical trials and more basic research in this field will help to answer this question.[105] Similarly, as has been very recently shown in experimental animal models of cancer, the modulation of microbiota might critically regulate the response to and outcome of chemotherapy.[33] Based on current research, it would be interesting to know whether and how concomitant NSAID/PPI treatment influences the response to chemotherapy in cancer patients.

Also of interest are interventional studies investigating the effects of probiotics on inflammatory markers outside the GI tract. Groeger et al[106] studied the effect of 6 to 8 weeks of administration of *Bifidobacterium infantis 35624* on inflammatory biomarker and plasma cytokine levels in 3 different randomized, double-blind, placebo-controlled interventions in patients with ulcerative colitis, chronic fatigue syndrome, and psoriasis in comparison to healthy subjects. The authors demonstrated the efficacy of *B infantis 35624* in decreasing the proinflammatory response in both GI and non—GI-related conditions and concluded that immunomodulatory effects of the microbiota have the potential to reach beyond the intestinal mucosa and have an impact on the systemic immunological response. Extrapolating these results to NSAID/PPI-related mucosal injury and its systemic consequence suggests that it would be worth designing novel trials. The similar extrapolation can be made in case of potential beneficial effect of probiotics in patients with IBS.[107-110] Especially tempting would be studying the potential of prebiotics and probiotics to modulate microbiota and prevent mucosal injury in patients chronically exposed to NSAIDs and PPIs.

It is also worth remembering that the effects of prebiotics and probiotics in contrast to most drugs are modest. The efficacy of a probiotic is strain dependent, and its choice should be based on evidence for the efficacy in the given clinical condition. If the evidence is scarce or not available, probiotic use should be guided by such factors as quality and stability control as well as the safety profile of a given probiotic.[111]

CONCLUSION

1. Prescriptions for PPIs should be supported by evidence-based medicine.
2. Medical practitioners should be advised to use the lowest effective dose for the shortest possible duration of PPI therapy in accordance with a given clinical condition.
3. Extra care should be paid to high-risk patients treated with PPIs: (1) older people, (2) hospitalized patients, (3) patients requiring repeated *Helicobacter pylori* eradication, (4) patients chronically treated with NSAIDs and/or ASA, and (5) patients with immunodeficiency.
4. Modulation of the gut microbiota with probiotics should be considered as adjuvant therapy to PPI treatment because the administration of probiotics during combined NSAID/PPI therapy lowers the risk of intestinal mucosal injury and generation of IBS symptoms.

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Abbreviations and Acronyms: **ASA** = acetylsalicylic acid; **CE** = capsule endoscopy; **GI** = gastrointestinal; **IBD** = inflammatory bowel disease; **IBS** = irritable bowel syndrome; **NAFLD** = nonalcoholic fatty liver disease; **NSAID** = nonsteroidal anti-inflammatory drug; **PPI** = proton pump inhibitor; **SIBO** = small intestinal bacterial overgrowth

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