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NSAID-gastroenteropathy: new aspects of pathogenesis and prevention

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Nonsteroidal anti-inflammatory drugs (NSAIDs) remain among the most commonly used medications because of their effectiveness in reducing pain and inflammation. Inhibitors of gastric acid secretion can substantially reduce the damaging effects of NSAIDs in the stomach and duodenum. However, there are no proven effective preventative or curative treatments for NSAID-induced enteropathy. In recent years, substantial progress has been made in better understanding the pathogenesis of NSAID-enteropathy, and in particular the interplay of enteric bacteria, bile and the enterohepatic recirculation of the NSAIDs. Moreover, it is becoming clear that suppression of gastric acid secretion significantly worsens NSAID-enteropathy.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a mainstay for treatment of numerous inflammatory diseases, including osteoarthritis, despite significant untoward effects on the gastrointestinal (GI) tract. The damage caused by these drugs in the stomach and duodenum can be greatly reduced by co-administration of inhibitors of gastric acid secretion, such as proton pump inhibitors (PPIs) and histamine H_2 receptor antagonists (H_2RAs). As discussed in the article, these drugs are not without adverse effects, so there continues to be a search for improved approaches for preventing NSAID-gastroduodenopathy.

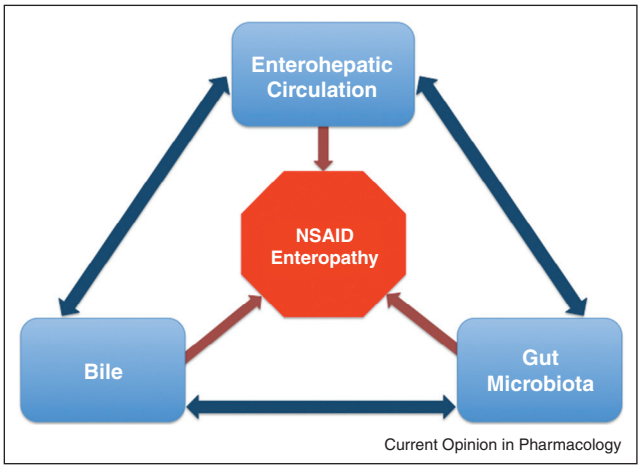
Much recent research has been focused on the damage caused by NSAIDs in the lower intestine. NSAID-enteropathy has a distinct pathogenesis from the damage produced in the upper GI tract [1]. Suppression of cyclooxygenase activity contributes to NSAID-enteropathy, but the roles of bile and bacteria appear to be much more significant (Figure 1). There is a growing interest in NSAID-enteropathy largely because of improved methods for detecting the damage, through video capsule endoscopy and double-balloon enteroscopy. Moreover, emerging evidence that the use of agents that suppress gastric acid secretion is causing a significant worsening of the small intestinal damage caused by NSAIDs [2–4,5•] is stimulating further research into the pathogenesis of this condition.

Gastroduodenal protection

Secretion of bicarbonate by gastric and duodenal epithelial cells is an important component of mucosal defence. Hydrogen sulfide (H_2S) has been shown to markedly reduce the severity of gastric damage induced by NSAIDs [6] or by ischemia–reperfusion [7]. Maintenance of gastric blood flow [8] and inhibition of leukocyte–endothelial adhesion [9] contribute to the protective effects of H_2S, but stimulation of bicarbonate secretion may be another important mechanism. Takeuchi *et al.* [10••] demonstrated a key role of endogenous H_2S in the secretion of bicarbonate in the rat duodenum that is stimulated by mucosal acidification. Duodenal bicarbonate secretion was increased following the administration of an H_2S donor, and reduced by an inhibitor of endogenous H_2S synthesis. The latter also led to enhanced acid-induced duodenal damage. Acid-induced duodenal bicarbonate secretion was also shown to be mediated by two other gaseous mediators, nitric oxide and carbon monoxide [10••].

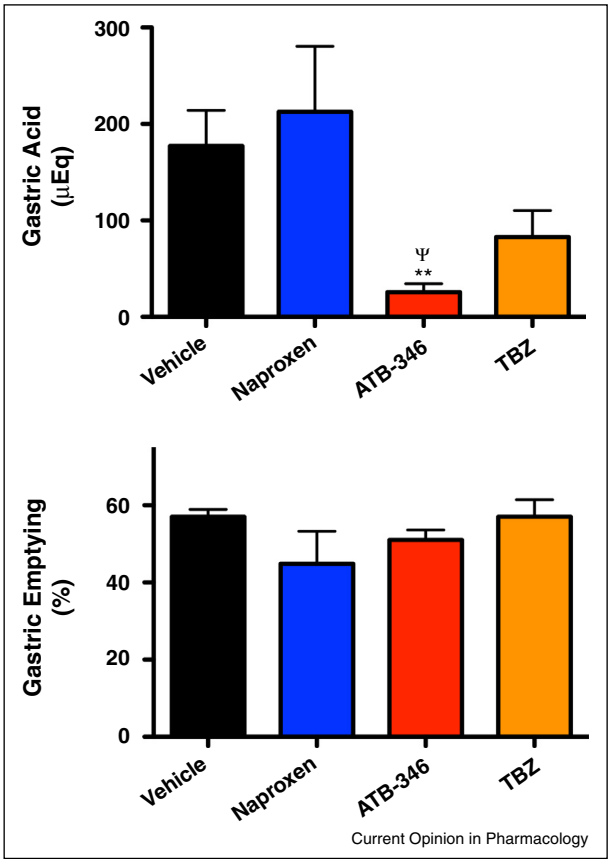
Regulation of bicarbonate secretion by H_2S also extends to the stomach and may contribute significantly to the gastroprotective effects of this mediator [11]. As shown in Figure 2, administration of an H_2S-releasing derivative of naproxen (ATB-346) resulted in a marked (~50%) decrease in gastric acidity, with an increase in mean pH of gastric juice from 1.48 to 2.11, and a ~82% decrease in the volume of secretion. These changes are most likely

Figure 1



Interactions among bile, intestinal microbes and enterohepatic circulation of NSAIDs contribute significantly to NSAID-induced intestinal damage. The cytotoxicity of bile is increased following NSAID administration, and also by conversion from primary to secondary bile acids (catalyzed by bacterial enzymes). Bacteria also contribute to enterohepatic recirculation of NSAIDs, as bacterial β-glucuronidase is necessary for NSAID reuptake in the ileum. Suppression of gastric acid secretion leads to significant changes to the intestinal microbiota and increases the cytotoxicity of bile, but the temporal relationship of these effects remains unclear.

Figure 2



ATB-346, a hydrogen sulfide-releasing derivative of naproxen, significantly reduced gastric acidity (upper panel), but did not affect gastric emptying rates (lower panel). In contrast, naproxen itself did not affect gastric acidity, and the effect of the H_2S-releasing moiety of ATB-346 (4-hydroxy-thiobenzamide; TBZ) did not reach statistical significance. Naproxen was administered at 20 mg/kg, and the other drugs were administered at equimolar doses to that of naproxen. $^{**}P < 0.01$ versus the vehicle-treated group; $^{\Psi}P < 0.05$ versus the TBZ-treated group. Data are shown as the mean ± standard error of the mean of at least 5 rats per group. The data were analyzed by a one-way analysis of variance followed by Dunnett's multiple comparison test.

attributable to a combination of increased gastric bicarbonate secretion and decreased gastric acid secretion. Mard *et al.* [12] recently reported that H_2S could inhibit gastric acid secretion, but it is possible that at least some of the decrease in titratable acidity that they observed was actually due to stimulation of bicarbonate secretion. ATB-346, naproxen and TBZ did not affect gastric emptying rates (Figure 2).

NSAID-enteropathy

Exacerbation by acid suppressing drugs

A number of studies have confirmed the ability of NSAIDs, including low-dose aspirin, to cause significant ulceration and bleeding in the small intestine [13–15]. Indeed, co-use of an NSAID with low-dose aspirin and inhibitors of gastric acid secretion is now commonplace, but can result in a synergistic increase in intestinal injury and bleeding [16••,17], which has been described as '*the perfect intestinal storm*' [5•]. As is the case in humans, the most severe ulceration caused by NSAIDs is found in the ileum [15]. Recent human data are consistent with what has been reported in animal studies [2–4,5•,16••]. Thus, using video capsule endoscopy, Watanabe *et al.* [18••] examined the small intestine of rheumatoid arthritis patients taking NSAIDs. Using multivariate regression analysis, they identified risk factors associated with severe intestinal damage and significantly decreased hemoglobin levels [18••]. The three statistically significant relative risk factors (RR) were the use of a PPI (RR: 5.22), age over 65 years (RR: 4.16), and the use of a H_2RA (RR: 3.95).

Intestinal protection through inhibition of NSAID reabsorption

Enterohepatic circulation of NSAIDs is a key component of the mechanism of damage these drugs produce in the small intestine (Figure 1). After absorption, NSAIDs can undergo glucuronidation in the liver and are then secreted into bile. Bacterial β-D-glucuronidase can deconjugate the NSAID-glucuronides, facilitating reabsorption of the NSAID in the ileum. Inhibition of this enzyme with

a novel inhibitor has been shown to prevent enterohepatic circulation of NSAIDs, and to reduce the intestinal injury caused by these drugs [19]. Saitta *et al.* reported that pretreatment of rats with an inhibitor of β-D-glucuronidase markedly protected against diclofenac-induced damage in the small intestine [20•]. A similar effect was observed when indomethacin or ketoprofen was the NSAID used to induce intestinal damage. Delaying administration of the β-D-glucuronidase inhibitor until three hours after NSAID administration resulted in a diminished protective effect, which was consistent with pharmacokinetic data suggesting a short half-life of the inhibitor [20•].

H_2S prevents NSAID-enteropathy

An H_2S-releasing derivative of naproxen (ATB-346) was previously shown not to produce gastric damage, even at exceptionally high doses [21]. Administration of the drug to rats with compromised gastric mucosal defence also did not result in significant damage, while the comparator drug, naproxen (and sometimes celecoxib), caused extensive hemorrhagic damage [21]. This drug also did not produce intestinal damage when administered twice-daily over several days [16••]. Blackler *et al.* [16••] examined the effects of this drug in several models of clinical conditions in which susceptibility to NSAID-induced GI damage is markedly increased, for example, arthritis, obesity, and hypertension. In each case, ATB-346 did not cause significant GI damage. Moreover, when administered together with low-dose aspirin and a PPI (over several days), ATB-346 did not cause detectable small intestinal damage, whereas naproxen and celecoxib at comparable anti-inflammatory doses caused severe intestinal ulceration and bleeding [16••].

Acid suppression and enteropathy

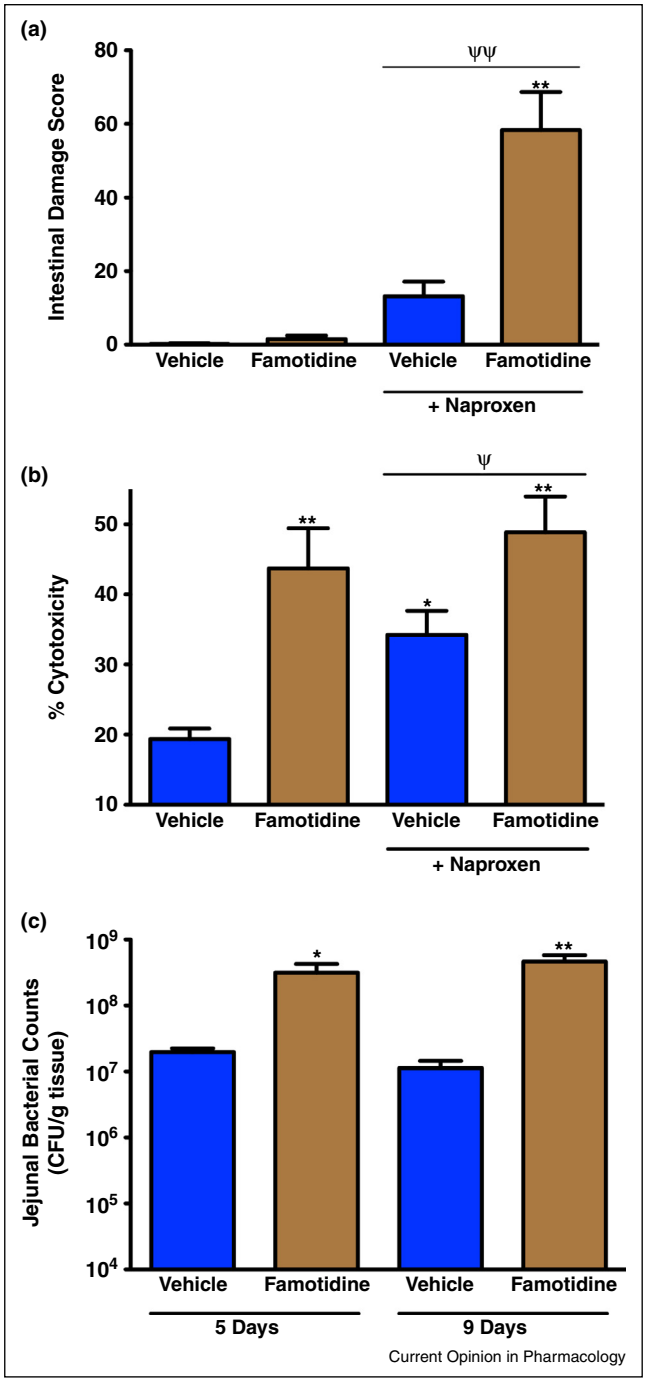
The most commonly used agents for preventing or treating NSAID-induced damage in the stomach and duodenum are antisecretory drugs, such as H_2RAs antagonists and PPIs. However, it has been clear for many years that these drugs offer no protection to the lower small intestine, and in recent years it has been reported that they exacerbate NSAID-induced small intestinal lesions in rats [2,3,5•]. There are no proven effective preventative or therapeutic regiments for NSAID-enteropathy [1]. Satoh *et al.* [22•] examined the effects of three agents with proven protective effects in the upper GI tract (misoprostol, irsogladine, and rebamipide) on diclofenac-induced intestinal lesions, as well as on the exacerbation of those lesions by ranitidine or omeprazole. Pretreatment with misoprostol, irsogladine, or rebamipide inhibited the formation of intestinal lesions caused by a high dose of diclofenac alone. These agents also prevented the exacerbation of diclofenac-induced lesions that was caused by ranitidine and omeprazole. These studies involved only acute administration of diclofenac, so it remains to be seen if these potential protective agents are effective in a model where the NSAID is administered repeatedly over several days [22•].

Bile, bacteria and enterohepatic circulation in NSAID-enteropathy

Several studies have demonstrated critical roles for the bile, enteric bacteria and the enterohepatic circulation of the NSAIDs in the pathogenesis of NSAID-induced enteropathy [23–27] (Figure 1). A critical role for bacteria was recently reinforced by a study demonstrating that the exacerbation of NSAID-enteropathy in rats by treatment with a PPI was attributable to the dysbiosis that occurred following PPI administration [2]. Specifically, there was a marked loss of *Bifidobacter* following PPI treatment. The increased susceptibility to NSAID-enteropathy caused by the PPI could be reversed if intestinal levels of *Bifidobacter* were replenished [2]. It remains unclear *why* the PPI-induced dysbiosis resulted in greater NSAID-induced intestinal damage and bleeding, but it is possible that this triggered changes in bile that contributed to intestinal injury.

Numerous clinical reports and animal studies have associated the chronic use of PPIs or H_2RAs with alterations in the GI tract. Among the reported changes are small intestinal bacterial overgrowth (SIBO) and bile acid dysmetabolism [28–31]. The development of SIBO is a direct consequence of suppression of gastric acid secretion. The ensuing bile acid dysmetabolism in patients with SIBO is likely the result of the disproportionate increase in numbers of microbes capable of deconjugating bile acids and/or of converting primary bile acids to secondary bile acids [28,29,32]. The deconjugation of bile acids by bacterial enzymes increases bile acid hydrophobicity, thereby increasing the ability of the bile acid to disrupt the cellular membranes of enterocytes [33]. Bacterial enzymatic conversion of primary bile acids to secondary bile acids may also contribute to ulceration, because secondary bile acids are particularly damaging to intestinal epithelial cells [17,34]. Therefore, we hypothesized that bile acid dysmetabolism as a consequence of treatment with an inhibitor of gastric acid secretion would exacerbate NSAID-enteropathy. Using a rat model, we modeled the common clinical scenario of co-use of an NSAID and an inhibitor of gastric acid secretion, and we explored how this would affect the cytotoxic properties of bile. The results are summarized in Figure 3. Rats treated twice-daily with famotidine (an H_2RA) for nine days did not develop significant small intestinal damage (Figure 3a), but the bile collected from these rats was significantly more cytotoxic when added to cultured intestinal epithelial cells (IEC-6) than the bile collected from vehicle-treated rats (Figure 3b). Co-treatment of rats with both famotidine (9 days) and an NSAID (naproxen, for the final 4.5 days) resulted in extensive ulceration and bleeding in the small intestine (Figure 3a), and bile from rats receiving these treatments was significantly more cytotoxic *in*

Figure 3



Treatment with an inhibitor of gastric acid secretion (famotidine) exacerbates NSAID-induced intestinal damage, increases bile toxicity, and alters the intestinal microbiome in rats. **(Panel a)** Twice-daily administration of famotidine (30 mg/kg, po) and naproxen (10 mg/kg, po) caused extensive small intestinal damage that was significantly more severe than that induced by naproxen alone ($^{\Psi\Psi}P < 0.01$) or famotidine alone ($^{**}P < 0.01$). Famotidine alone did not cause significant intestinal damage. Famotidine was administered for nine days, while naproxen was administered only on the final 4.5 days. **(Panel b)** *In vitro* exposure of rat intestinal epithelial (IEC-6) cells to bile (diluted 1:6 in buffer) that had been collected from rats treated with vehicle resulted in a low level of cytotoxicity as measured by lactate dehydrogenase release. However, when the bile was collected from rats treated with famotidine for nine days, there was a ~120% increase in cytotoxicity ($^{**}P < 0.01$ versus vehicle -treated). While treatment with naproxen for 4.5 days markedly increased the cytotoxicity of bile, it was significantly greater when the rats were treated with both famotidine and naproxen ($^{\Psi}P < 0.05$). **(Panel c)** Twice-daily treatment with famotidine for five or nine days significantly increased the number of total aerobes in the jejunum ($^{*}P < 0.05$, $^{**}P < 0.01$ versus the vehicle-treated group). For all panels, results are shown as mean ± SEM ($n = 6$ rats per group). The data were analyzed by a one-way analysis of variance followed by Dunnett's multiple comparison test.

vitro than that from rats treated only with naproxen (Figure 3b; $P < 0.05$). Therefore, these data suggest that a marked increase in the cytotoxicity of bile (seen with famotidine treatment) is not sufficient to produce overt intestinal damage, but is likely to be a contributing factor to the exacerbation of enteropathy when co-administered with an NSAID. Consistent with clinical reports of SIBO in patients treated with inhibitors of acid secretion [30,31], treatment of rats with famotidine resulted in significant increases (>16-fold) in the number of aerobes in the jejunum (Figure 3c).

Conclusions

Damage induced in the stomach and duodenum by NSAIDs can be reduced substantially by co-administration of a PPI, and to a lesser extent by co-administration of an H_2RA. However, these agents are ineffective in preventing NSAID-induced damage in the more distal small intestine, and there is growing evidence that by altering the intestinal microbiota, they worsen NSAID-enteropathy. H_2S is a particularly potent cytoprotective agent in the GI tract. H_2S-releasing NSAIDs produce negligible upper GI damage even at very high doses and in animal models where mucosal defence is significantly impaired. In the small intestine, H_2S-releasing NSAIDs produce negligible damage, even when co-administered with a PPI and low-dose aspirin.

Development of effective preventative or curative therapies for NSAID-enteropathy requires a better understanding of the complicated pathogenesis of this disorder. Three interrelated factors appear to be of paramount importance: the nature of bile, the enterohepatic circulation of the NSAID, and the nature of the intestinal microbiota. PPIs can alter these factors, leading to increased intestinal damage. Bacterial enzymes are important for deconjugation of NSAIDs in bile, allowing their reabsorption, as well as for conversion of primary bile acids to more cytotoxic secondary bile acids. These bacterial enzymes themselves may be targets for novel therapies for NSAID-enteropathy.

Conflict of interest statement

Dr John Wallace is a founder and director of Antibe Therapeutics Inc.

Disclosure

Dr Wallace is a founder and director of Antibe Therapeutics Inc.

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