New insight into the mechanisms of gastroduodenal injury induced by nonsteroidal anti-inflammatory drugs: practical implications

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs), especially acetylsalicylic acid (ASA), are commonly used in the therapy of various diseases. However, the serious side effects of these drugs, such as bleedings, acute lesions, gastric ulcers, and even intestinal perforations, are widely recognized. NSAIDs inhibit cyclooxygenase (COX) activity resulting in the suppression of mucosal generation of gastroprotective prostaglandins (PGs) derived from a constitutive isoform, COX-1, as well as an inducible isoform, COX-2. COX-1-derived PGs are responsible for gastroprotection, while PGs generated via COX-2 activity also play an important role in gastroprotection and ulcer healing. Recently, a new class of NSAIDs has been developed by adding NO moiety to conventional NSAIDs. In contrast to native NSAIDs, their NO-releasing derivatives such as NO-ASA were found to exhibit lower gastric toxicity despite inhibiting both COX-1 and COX-2 activity in the gastric mucosa. Similar limited gastrointestinal toxicity and protective actions were observed with a new class of hydrogen sulfide (H2S)-releasing NSAIDs, such as H2S-releasing naproxen (ATB-346). Dual antiplatelet therapy with ASA and clopidogrel increases the risk of gastrointestinal bleeding in patients with acute coronary syndrome in whom concomitant treatment with a proton-pump inhibitor (PPI) was less effective owing to the interaction of clopidogrel and PPI with the same hepatic cytochrome P-450. In conclusion, new derivatives of NSAIDs releasing vasoactive gaseous mediators NO or H2S are associated with fewer gastrointestinal adverse effects, suggesting that, in the future, they may be used as a safer alternative in everyday clinical practice and antithrombotic therapy.
An inhibition of proinflammatory COX-2 activity, may also induce adverse effects such as GI bleedings and epithelial damage mainly due to COX-1 inhibition. On the other hand, COX-2 may have also beneficial effects important for the physiological function of the gastric mucosal barrier because COX-2 inhibition by selective COX-2 inhibitors increased the susceptibility of gastric mucosa to damage, similarly as conventional NSAIDs and selective COX-1 inhibitors (Fig. 2). Moreover, the selective inhibitors of COX-1 (SC-560) and COX-2 (rofeccoxib, celecoxib), when administered together, not only spontaneously cause gastric lesions but also dramatically delay the healing of acute gastric lesions and prolonged the healing of chronic gastric ulcers.

Previous studies have confirmed that the administration of nonselective COX inhibitors (eg, ASA), except the therapeutic effect resulting from an inhibition of proinflammatory COX-2 activity, may also induce adverse effects such as GI bleedings and epithelial damage mainly due to COX-1 inhibition. On the other hand, COX-2 may have also beneficial effects important for the physiological function of the gastric mucosal barrier because COX-2 inhibition by selective COX-2 inhibitors increased the susceptibility of gastric mucosa to damage, similarly as conventional NSAIDs and selective COX-1 inhibitors (Fig. 2). Moreover, the selective inhibitors of COX-1 (SC-560) and COX-2 (rofeccoxib, celecoxib), when administered together, not only spontaneously cause gastric lesions but also dramatically delay the healing of acute gastric lesions and prolonged the healing of chronic gastric ulcers.

Therefore, a number of studies have suggested that COX-1 and COX-2 are involved in the regulation of various physiological processes, including gastric integrity and gastroprotection. The balance between COX-1 and COX-2 is crucial for maintaining the health of the gastric mucosa. However, the selective inhibition of COX-2 by nonselective NSAIDs can lead to adverse effects, mainly due to COX-1 inhibition. This highlights the importance of understanding the role of both COX isoforms in the physiological function of the gastric mucosa.
There is a general agreement that NO released in the luminal mucosa from these NSAIDs could limit GI side effects caused by conventional NSAIDs due to their beneficial effect on the gastric mucosa resulting from NO-induced hyperemia, activation of protective mucus and bicarbonate secretion, and inhibition of motility.

NO-releasing ASA as well as flurbiprofen, diclofenac, ketoprofen, or those of NSAIDs linked to an NO-releasing moiety retained their anti-inflammatory and antithrombotic properties comparable to those of parent NSAIDs while markedly reducing gastropathy. This has been confirmed by a lower incidence of ulcerogenic activity in the gastric mucosa observed with CINODs compared with conventional NSAIDs.

In contrast to native NSAIDs, their NO-releasing derivatives such as NO-ASA were found to cause fewer gastric injuries and less esophageal toxicity in rats with reflux esophagitis despite inhibiting both COX-1 and COX-2 activity in the gastric mucosa. Other classes of drugs, such as mesalamine, acetaminophen, and that COX-2 may play an important role in the maintenance of gastric mucosal integrity, gastroprotection, and ulcer healing, questioning as to whether the administration of specific COX-2 inhibitors is clinically safe.

Recently, a new class of NSAIDs, which are safer for the GI tract, has been developed by adding a nitric oxide (NO) moiety to native NSAIDs. This group is called COX-inhibiting nitric oxide donors (CINODs). NO released from CINODs has been shown to enhance GI mucosal defense and to prevent pathogenic events resulting from NSAID-induced suppression of prostanoid synthesis leading to a reduction in mucosal microcirculation, platelet activation, and enhancement in leukocyte-endothelial adherence (FIGURE 3).

These new NSAID adducts have been recently extensively tested in experimental and clinical studies because of their very promising gastroprotective efficacy in the animal models of GI injury and potential anticarcinogenic actions similar to those observed with their parent drugs. There is a general agreement that NO released in the luminal mucosa from these NSAIDs could limit GI side effects caused by conventional NSAIDs due to their beneficial effect on the gastric mucosa resulting from NO-induced hyperemia, activation of protective mucus and bicarbonate secretion, and inhibition of motility. NO-releasing ASA as well as flurbiprofen, diclofenac, ketoprofen, or those of NSAIDs linked to an NO-releasing moiety retained their anti-inflammatory and antithrombotic properties comparable to those of parent NSAIDs while markedly reducing gastropathy. This has been confirmed by a lower incidence of ulcerogenic activity in the gastric mucosa observed with CINODs compared with conventional NSAIDs. In contrast to native NSAIDs, their NO-releasing derivatives such as NO-ASA were found to cause fewer gastric injuries and less esophageal toxicity in rats with reflux esophagitis despite inhibiting both COX-1 and COX-2 activity in the gastric mucosa.
body, endogenous H$_2$S plays an important role as a gaseous transmitter involved in the control of physiological processes including the regulation of blood pressure.\textsuperscript{27,28} Studies published so far have shown that H$_2$S increases synaptic long-term potentiation in the central nervous system and exerts inflammatory and anti-inflammatory effects on the vascular endothelium.\textsuperscript{29,30} These effects clearly depend on the concentration of this gaseous molecule.\textsuperscript{30} H$_2$S shows a vasodilatory effect in the cardiovascular system similar to that exhibited by NO\textsuperscript{30} or carbon monoxide.\textsuperscript{31} There is convincing evidence that H$_2$S may play a potential role in the cardiovascular system including the mechanism of blood pressure regulation as well as the beneficial effects on gastroprotection and gastric ulcer healing in the upper GI tract but possibly also a protective effect in the lower parts of the digestive system against compromised factors such as intestinal microbiota (FIGURE 4).\textsuperscript{32,33}

Naproxen belongs to the most commonly used NSAIDs associated with fewer cardiovascular adverse effects than selective COX-2 inhibitors (coxibs) such as rofecoxib and other NSAIDs, but their use is limited owing to serious GI complications such as bleedings and mucosal ulcerations.\textsuperscript{28} The novel H$_2$S-releasing derivative of naproxen, prednisolone, have been linked with the NO moiety in a similar manner, and those agents were also found to exhibit enhanced anti-inflammatory activity in the experimental model.\textsuperscript{18,20,21} Corroborative with the beneficial role of NO in the protection of the gastric mucosa was the evidence that the NO synthase (NOS) inhibitor, asymmetric dimethylarginine, was shown to interact with gastric oxidative metabolism and to exaggerate gastric damage induced by various ulcerogens.\textsuperscript{24} Recent evidence has indicated that ASA can acetylate the COX-2 isomeric leading to an excessive formation of lipoxin A$_3$ (LXA$_3$), so called “aspirin-triggered lipoxin”, known to exhibit a potent gastroprotective action via an interaction with NOS–NO-dependent pathway.\textsuperscript{20,21,25} Both NO-ASA and LXA$_3$ have been shown to inhibit leukocyte migration and adherence to various tissues including the vascular bed of the GI mucosa in NO-dependent manner.\textsuperscript{21,26}

The question remains whether other important physiological gaseous mediators linked with NSAIDs can exhibit gastric-sparing effects comparable with those of NO-releasing ASA. For instance, among gaseous mediators, hydrogen sulfide (H$_2$S) is commonly recognized as a toxic gas with an unpleasant odor.\textsuperscript{26} However, in the human body, endogenous H$_2$S plays an important role as a gaseous transmitter involved in the control of physiological processes including the regulation of blood pressure.\textsuperscript{27,28} Studies published so far have shown that H$_2$S increases synaptic long-term potentiation in the central nervous system and exerts inflammatory and anti-inflammatory effects on the vascular endothelium.\textsuperscript{29,30} These effects clearly depend on the concentration of this gaseous molecule.\textsuperscript{30} H$_2$S shows a vasodilatory effect in the cardiovascular system similar to that exhibited by NO\textsuperscript{30} or carbon monoxide.\textsuperscript{31} There is convincing evidence that H$_2$S may play a potential role in the cardiovascular system including the mechanism of blood pressure regulation as well as the beneficial effects on gastroprotection and gastric ulcer healing in the upper GI tract but possibly also a protective effect in the lower parts of the digestive system against compromised factors such as intestinal microbiota (FIGURE 4).\textsuperscript{32,33}

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ATB-346, was shown to exhibit protective and chemopreventive activity owing to the inhibition not only of COX-1 but also COX-2 responsible for the generation of “inflammatory” PGs without causing mucosal damage and with limited toxicity to the upper and lower GI tract (Figure 3). This indicates that ATB-346 has an improved gastroduodenal safety profile compared with equimolar doses of naproxen. Thus, new derivatives of NSAIDs releasing H$_2$S similarly as NO-releasing NSAIDs (eg, NO-ASA) demonstrate less serious GI side effects than classic NSAIDs or coxibs (Figures 3 and 4). Therefore, these agents may be successfully investigated in future clinical trials.

ASA is known to exert antithrombotic and antiplatelet actions, which is particularly useful for antithrombotic therapy in cardiovascular disorders. Recently, dual therapy with ASA and clopidogrel has been implemented in patients with coronary heart disease complicated by coagulant disorders. Both ASA and clopidogrel affect platelet function because ASA inhibits thromboxane A$_2$ (TXA$_2$) production by irreversible acetlylation of platelet COX-1, while clopidogrel selectively and irreversibly blocks platelet receptor for adenosine diphosphate (ADP), thereby inhibiting ADP-induced platelet activation and aggregation. This dual therapy with ASA and clopidogrel is effective in preventing thrombosis but the benefits of this antithrombotic therapy are counterbalanced by serious adverse effects such as an increased risk of GI bleeding. Furthermore, recent evidence has indicated that dual antiplatelet therapy impairs gastric adaptation to ASA because of the downregulation of inducible antioxidant enzyme, heme oxygenase-1. Proton-pump inhibitors (PPIs) are recommended as the gold standard treatment for
NSAID-induced gastric complications and adverse reactions including an increased gastric secretory activity, hypermotility, and GI microbleedings; however, the administration of a NSAID in the presence of a PPI negatively interacts with the antipaleate activity of clopidogrel and considerably inhibits its antipalteate effect.\textsuperscript{53, 54} The mechanism of this phenomenon should be further studied but some PPIs such as omeprazole or esomeprazole may reduce the antipaleate activity of clopidogrel by inhibiting CYP2C19, a hepatic cytochrome P450 enzyme.\textsuperscript{55} In the CHARISMA trial (High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), in which clopidogrel was administered in all participants who received ASA, an increased bleeding with a long-term administration of clopidogrel was strongly associated with mortality.\textsuperscript{56} However, in other reports, the combination of ASA and a PPI was considered superior to clopidogrel alone in patients with prior ulcer bleeding.\textsuperscript{46, 47}

Data on the interaction between clopidogrel and ASA are conflicting but it seems likely that the treatment with clopidogrel alone or when given to patients on NSAIDs may not be safe in high-risk patients receiving NSAID therapy, and a concomitant prophylactic treatment with a PPI should be still considered. Moreover, the PPI cotherapy has been recommended instead of the administration of clopidogrel in ASA users with a high risk of GI bleeding.\textsuperscript{47} In some studies, because of the proven interaction between a PPI, omeprazole, and an antiplatelet drug, clopidogrel, the concomitant therapy with an antagonist of histamine H\textsubscript{2}-receptor has been recommended instead of omeprazole in patients receiving dual antiplatelet therapy.\textsuperscript{47} Since the data on these GI effects of antisecretory treatment with PPI and/or histamine H\textsubscript{2}-receptor antagonists and dual antiplatelet therapy are yet to be confirmed, the interaction between clopidogrel and NSAIDs such as the common ASA needs to be elucidated in the experimental models of gastroduodenal injury and protection and in randomized clinical trials.

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REFERENCES


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Streszczenie

Niesteroidalowe leki przeciwzapalne (NLPZ), w szczególności kwas acetylsalicylowy (acetylsalicylic acid – ASA), powszechnie wykorzystuje się w terapii różnych chorób. Szeroko znane są jednak poważne skutki uboczne stosowania NLPZ, takie jak krwawienia, ostre uszkodzenia, wrzody żołądka, a nawet perforacje jelitowe. NLPZ hamują aktywność cyklooksygenez na (COX), zmniejszając w ten sposób śluzówkową produkcję gastroprotekcyjnych prostaglandyn (PG), syntetyzowanych dzięki aktywności enzymatycznej konstytutywnej izoformy COX-1 oraz indukowalnej izoformy COX-2. PG tworzone z COX-1 odpowiadają za gastroprotekcję, podczas gdy PG generowane wskutek aktywności COX-2 również odgrywają ważną rolę w gastroprotekcji i gojeniu wrzodów. Niedawno utworzono nową klasę NLPZ poprzez dołączenie komponenty zawierającej tlenek azotu (nitric oxide – NO) do cząsteczki klasycznych postaci tych leków. W przeciwieństwie do klasycznych NLPZ, ich NO-pochodne, takie jak NO-ASA, wykazują mniejszą toksyczność dla przewodu pokarmowego, mimo że hamują zarówno aktywność COX-1, jak i COX-2 w błonie śluzowej żołądka. Podobne efekty ograniczenia toksycznego wpływu NLPZ na żołądek i jelita wraz z działaniem ochronnym zaobserwowano w przypadku podawania nowej klasy pochodnych NLPZ uwalniających siarkowodór (H₂S), takich jak naproksen uwalniający H₂S (ATB-346). Podwójna terapia przeciwpłytkowa obejmująca ASA i klopidogrel zwiększa ryzyko wystąpienia krwawień z przewodu pokarmowego wśród pacjentów z ostrym zespołem wieńcowym, u których stosowanie inhibitorów pompmy protonowej (IPP) jest mniej skuteczne, co wynika z interakcji klopidogrelu i IPP z tym samym wątrobowym cytochromem P-450. Podsumowując, nowe pochodne NLPZ, uwalniające naczyniowo-rozkurczowe gazowe mediatory NO lub H₂S, odznaczają się mniejszymi skutkami ubocznymi w przewodzie pokarmowym, co sugeruje, że w przyszłości leki te mogą znaleźć zastosowanie jako bezpieczniejsza alternatywa w codziennej praktyce klinicznej i w terapii przeciwzakrzepowej.