REVIEW ARTICLE

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

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KEY WORDS

antithrombotic therapy, gastroprotection, hydrogen sulfide, nitric oxide, nonsteroidal anti-inflammatory drugs

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 (H_2S)-releasing NSAIDs, such as H_2S-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 H_2S 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.

Nonsteroidal anti-inflammatory drugs (NSAIDs), especially acetylsalicylic acid (ASA) are commonly used in the therapy of various diseases.[1] The side effects of these drugs, mainly affecting the stomach, such as bleedings, acute lesions, gastric ulcers, and even perforations, are widely recognized in clinical practice. It is crucial to elucidate the pathomechanism of gastric damage to explain severe clinical complications after NSAID administration.[2]

NSAIDs are effective in the treatment of numerous diseases owing to their potent anti-inflammatory, antithrombotic, and analgesic actions and are recommended for the prevention of cardiovascular disorders and stroke.[3,4] Previous studies revealed that ASA, the most common NSAID, directly damages the surface epithelium and also markedly impairs the potential lines of mucosal defense in the gastric mucosa. This is mainly due to the inhibition of cyclooxygenase (COX) activity, resulting in a reduction in the mucosal generation of major gastroprotective prostaglandins (PGs) derived from arachidonate metabolism (such as those of series E [PGE_2] and prostacyclin [PGI_2]), activation of white blood cells and proinflammatory cytokines, cessation of gastric microcirculation, as well as an increase in lipid peroxidation and gastrointestinal (GI) motility[1-5] (FIGURE 1). ASA has also been proposed as an effective drug in chemoprevention against GI cancers.[6] PGs inhibit the gastric acid secretory activity, produce an increase in gastric blood flow, stimulate mucus and bicarbonate (HCO_3^-) secretion, and enhance the mucosal sulfhydryl content,

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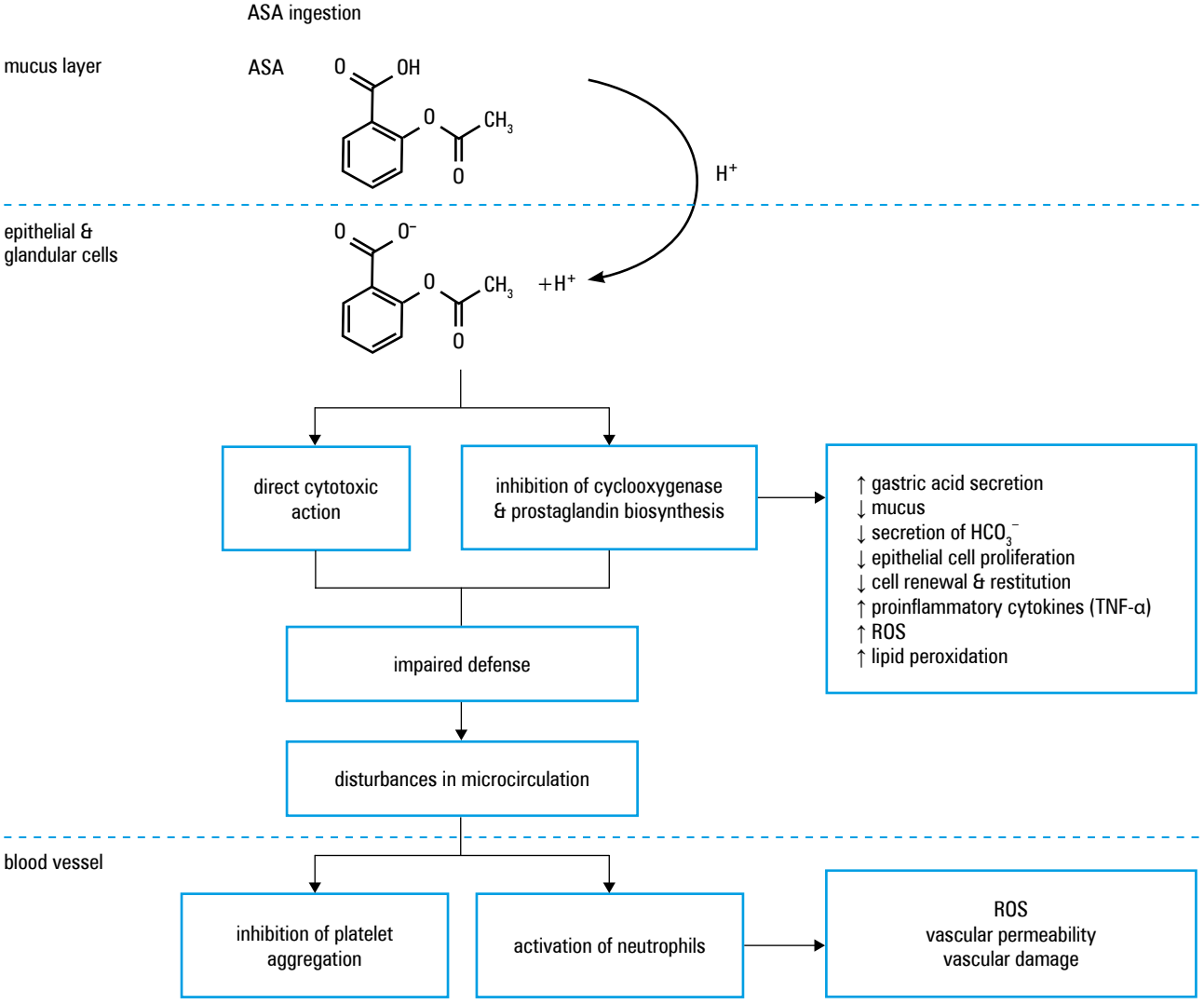

FIGURE 1 Mechanism of gastric damage induced by acetylsalicylic acid (ASA), the most widely used nonsteroidal anti-inflammatory drug (NSAID). Ingested ASA passes through the mucus layer to reach epithelial cells where it becomes ionized in acidic milieu of the stomach. In this ionized form, ASA exerts direct cytotoxic action on epithelial cells mainly due to the inhibition of cyclooxygenase (COX) activity. Deficiency of prostaglandind affects the blood vessels and weakens epithelial cell barrier. In blood vessels, disturbances of microcirculation, impaired platelet activation, activation of neutrophils, and subsequent increase in the production of reactive oxygen species (ROS), vascular permeability, and vascular damage are observed. The ASA-induced gastric epithelial damage results from a decrease in the major lines of mucosal defense caused by this NSAID, including a decrease in mucus and HCO_3^- secretion, the retardation of epithelial cell proliferation, as well as an increase in gastric acid secretion, proinflammatory cytokine production, especially of tumor necrosis factor α (TNF-α), and the enhancement of ROS generation with subsequent lipid peroxidation.

thus preventing damage to deeper structures of the gastric mucosa induced by various irritants and necrotizing substances.[1,2,5]

Two isoforms of COX, namely a constitutive isoform, COX-1, as well as an inducible isoform, COX-2, have been proposed.[7] Based on the experimental evidence, it has been established that COX-1-derived PGs contribute to the maintenance of gastric integrity and gastroprotection, while high levels of PGs produced by an increase in the expression and activity of COX-2 produce deleterious local and systemic effects such as an increase in vascular constriction and permeability, pain, and fever associated with inflammation.[7-10]

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.[11,12] 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[8-12] (FIGURE 2). Moreover, the selective inhibitors of COX-1 (SC-560) and COX-2 (rofecoxib, celecoxib), when administered together, not only spontaneously cause gastric lesions but also dramatically delaye the healing of acute gastric lesions and prolonged the healing of chronic gastric ulcers.[13-16] Therefore, a number of studies have suggested

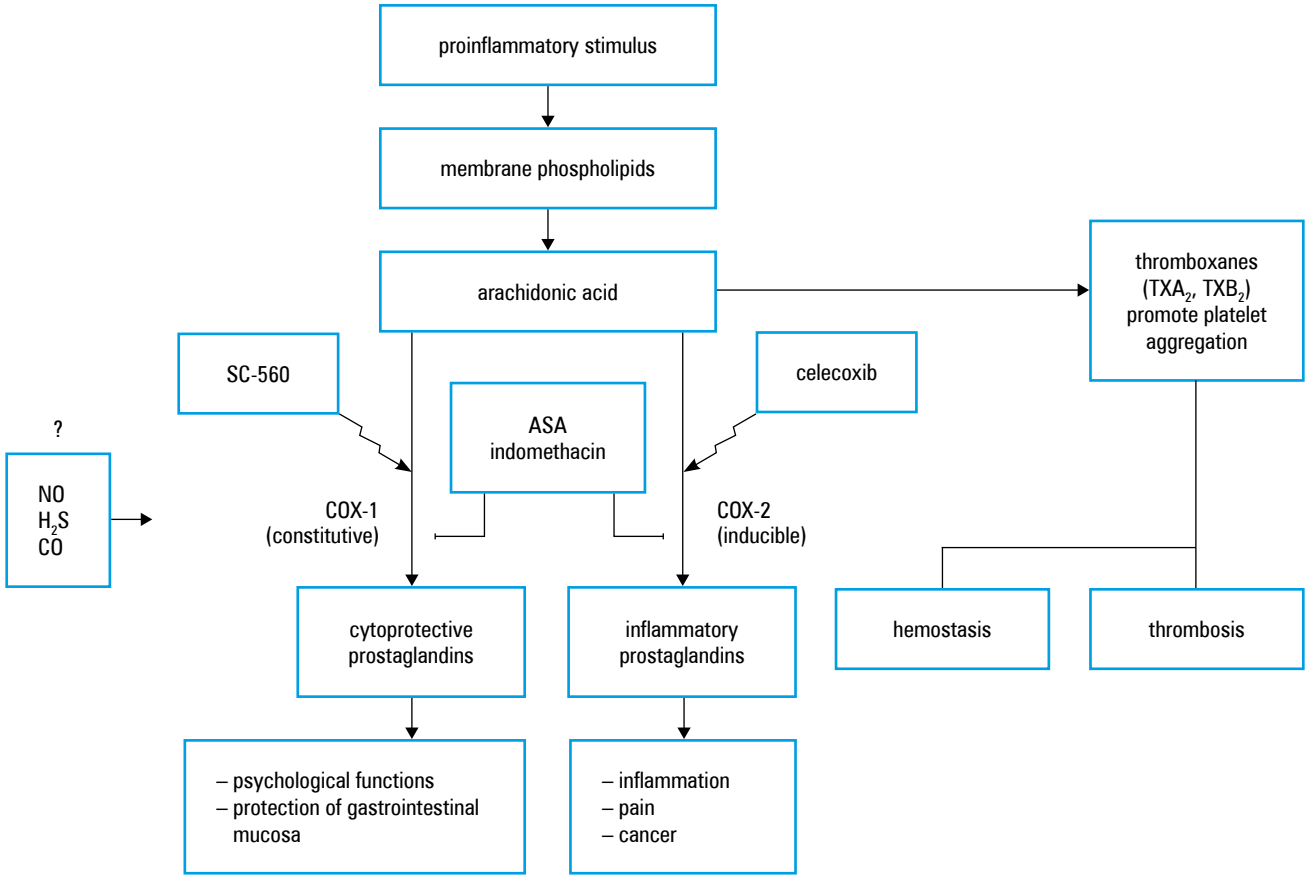

FIGURE 2 Cyclooxygenase (COX)-1 and COX-2 enzymatic pathways and their products, prostaglandins (PGs) and thromboxane (TX) in the mechanism of gastrointestinal protection. Proinflammatory stimulus releases the arachidonic acid from membrane phospholipids. Arachidonic acid undergoes metabolic transformation via a constitutive isoform of COX-1 or inducible isoform COX-2. Physiological PG produced by COX-1 maintains gastric mucosal integrity and exerts beneficial effects on gastroprotection and ulcer healing. On the other hand, COX-2-derived PG associated with inflammation has been proposed to exert deleterious effects on the gastric mucosa and to contribute to adverse reactions such as pain, fever, and even cancer development. Besides PG, TX (mainly TXA_2 and TXB_2), which promotes platelet aggregation, is formed from arachidonic acid. The activities of COX-1 and COX-2 may be selectively blocked by SC-560 and coxibs such as celecoxib, respectively, or by nonselective NSAIDs such as indomethacin or ASA. There is increasing preclinical evidence from experimental studies that gaseous mediators, nitric oxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO) can interact with arachidonic acid metabolites to afford protection of the gastrointestinal tract; however, this requires confirmation in clinical trials.

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.[8,9,11,12]

Recently, a new class of NSAIDs, which are safer for the GI tract, has been developed by adding a nitirc oxide (NO) moiety to native NSAIDs. This group is called COX-inhibiting nitric oxide donators (CINODs).[17-19] 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).[17-19]

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.[20]

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.[18-20] 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.[21,22] 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.[23] Other classes of drugs, such as mesalamine, acetaminophen, and

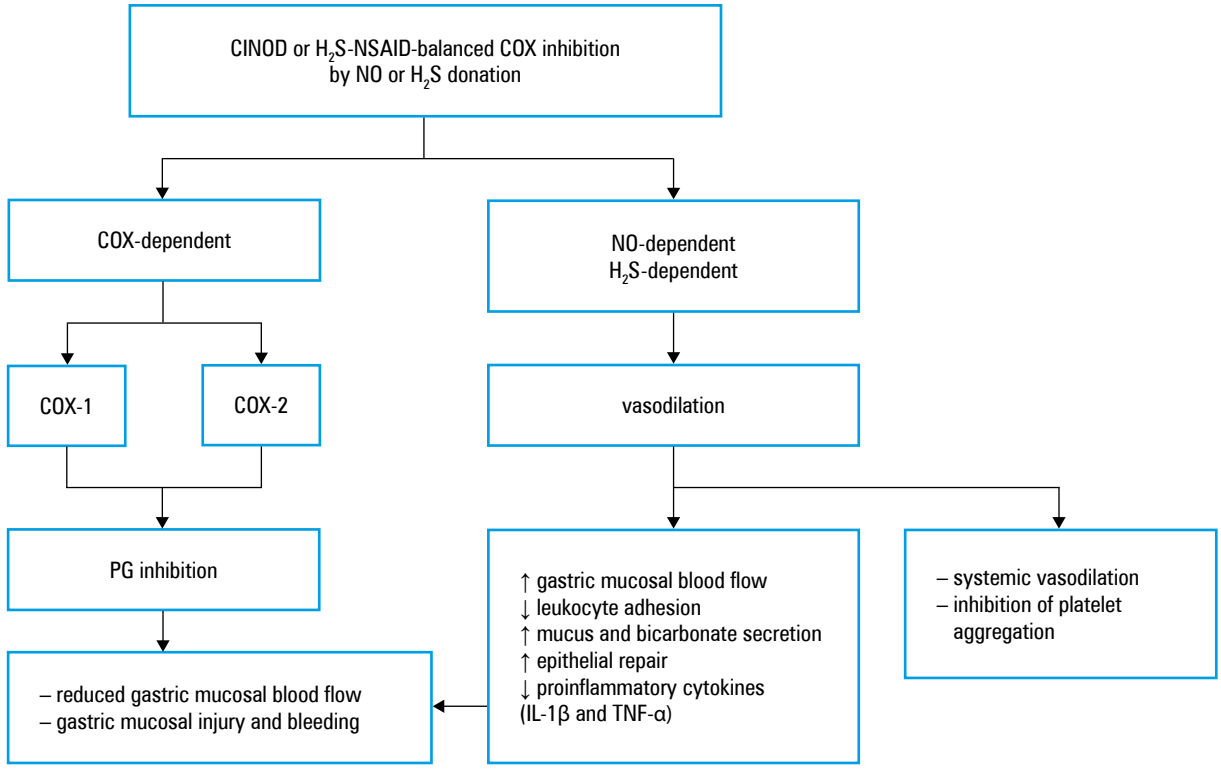

FIGURE 3 Mechanisms of protection of the gastrointestinal mucosa by a new class of gastric-sparing nonsteroidal anti-inflammatory drugs (NSAIDs), namely nitric oxide (NO)-releasing NSAIDs (NO-NSAID) and hydrogen sulfide-releasing NSAIDs (H_2S-NSAID) against gastrointestinal lesions induced by conventional NSAIDs. Despite affecting cyclooxygenase (COX)-1 and COX-2 activities and inhibition of prostaglandins (PGs), the COX inhibiting NO donators or H_2S-NSAID have been shown to release NO and H_2S. These vasodilatory gaseous mediators can counteract the side effects resulting from COX-1 and COX-2 inhibition and PG depletion by NSAIDs, such as the reduction of gastric mucosal blood flow being a major cause of gastric bleeding and mucosal damage. The release of both NO and H_2S from NO-NSAIDs or H_2S-NSAIDs, respectively, does not affect the inhibitory effect of NSAIDs on platelet aggregation but inhibits leukocyte adhesion and their tissue infiltration and causes vasodilatation while increasing gastric mucosal blood flow, mucus, and bicarbonate secretion, thus contributing to epithelial repair.

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.[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 ulcerogenes.[24] Recent evidence has indicated that ASA can acetylate the COX-2 isoform leading to an excessive formation of lipoxin A_4 (LXA_4), so called "aspirin-triggered lipoxin", known to exhibit a potent gastroprotective action via an interaction with NOS–NO-dependent pathway.[20,21,25] Both NO-ASA and LXA_4 have been shown to inhibit leukocyte migration and adherence to various tissues including the vascular bed of the GI mucosa in NO-dependent manner.[21,25]

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_2S) is commonly recognized as a toxic gas with an unpleasant odor.[26] However, in the human body, endogenous H_2S plays an important role as a gaseous transmitter involved in the control of physiological processes including the regulation of blood pressure.[27,28] Studies published so far have shown that H_2S increases synaptic long-term potentiation in the central nervous system and exerts inflammatory and anti-inflammatory effects on the vascular endothelium.[29,30] These effects clearly depend on the concentration of this gaseous molecule.[30] H_2S shows a vasodilatory effect in the cardiovascular system similar to that exhibited by NO[30] or carbon monoxide.[31] There is convincing evidence that H_2S 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).[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.[28] The novel H_2S-releasing derivative of naproxen,

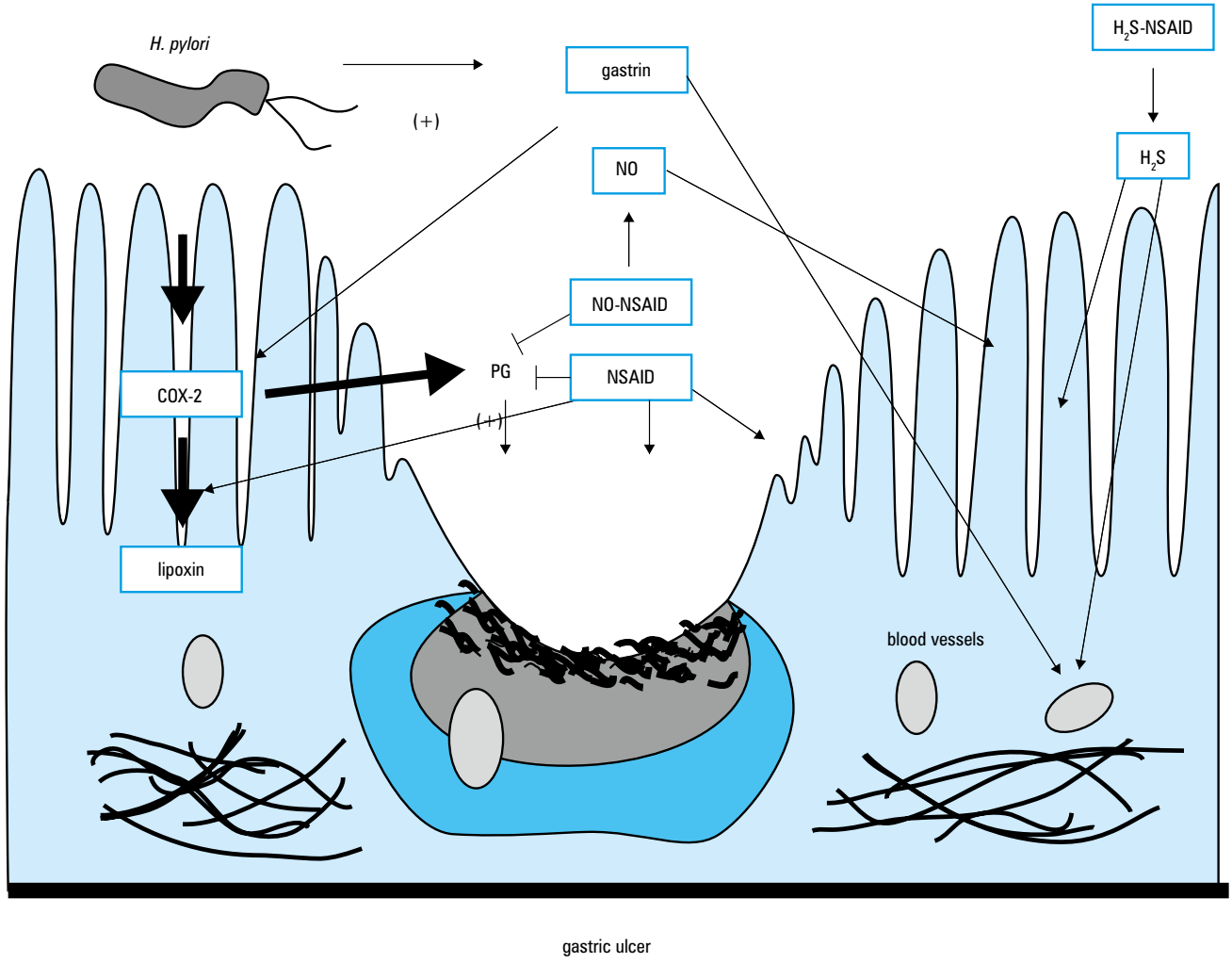

FIGURE 4 Interaction between two independent risk factors of peptic ulcer disease: nonsteroidal anti-inflammatory drugs (NSAIDs) and bacterial infection with *Helicobacter pylori* (*H. pylori*) in the pathogenesis of gastric ulcer formation with the major focus on the gastroprotective and ulcer healing promoting action of new derivatives of nitric oxide (NO)-releasing NSAIDs (NO-NSAID) and hydrogen sulfide-releasing NSAIDs (H_2S-NSAID). Classic NSAIDs, which can induce gastric microbleeding, epithelial erosions, and even gastric ulcers, have been shown to delay ulcer healing predominantly due to the inhibition of prostaglandin production. The damaging effect of NSAIDs is modified by a shift of cyclooxygenase-2 (COX-2) towards the production of cytoprotective lipoxins acting via NO-dependent pathway. *H. pylori* infection exerts cytotoxic effects on the gastrointestinal epithelium accompanied by an increase in plasma gastrin levels, which leads to an enhancement of gastric acid secretion predisposing the gastric mucosa to NSAID-induced gastric damage and the development of gastric ulcerations. In contrast to conventional NSAIDs, the new category of NSAID derivatives releasing either NO or H_2S have been shown to spare the gastric mucosa, exert gastroprotective properties, and accelerate ulcer healing.

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).[28,34,35] This indicates that ATB-346 has an improved gastroduodenal safety profile compared with equimolar doses of naproxen.[34,35] Thus, new derivatives of NSAIDs releasing H_2S 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.[7,12,36] Recently, dual therapy with ASA and clopidogrel has been implemented in patients with coronary heart disease complicated by coagulant disorders.[37,38] Both ASA and clopidogrel affect platelet function because ASA inhibits thromboxane A_2 (TXA_2) production by irreversible acetylation of platelet COX-1, while clopidogrel selectively and irreversibly blocks platelet receptor for adenosine diphosphate (ADP), thereby inhibiting ADP-induced platelet activation and aggregation.[37-39] 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.[40-42] Furthermore, recent evidence has indicated that dual antiplatelet therapy impairs gastric adaptation to ASA because of the downregulation of inducible antioxidizing enzyme, heme oxygenase-1.[41,42]

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 antiplatelet activity of clopidogrel and considerably inhibits its antiplatelet effect.[43,44] The mechanism of this phenomenon should be further studied but some PPIs such as omeprazole or esomeprazole may reduce the antiplatelet activity of clopidogrel by inhibiting CYP2C19, a hepatic cytochrome P450 enzyme.[45] 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.[44] However, in other reports, the combination of ASA and a PPI was considered superior to clopidogrel alone in patients with prior ulcer bleeding.[45,46]

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 with a high risk of GI bleeding.[47] In some studies, because of the proven interaction between a PPI, omeprazole, and an antithrombotic drug, clopidogrel, the concomitant therapy with an antagonist of histamine H_2-receptor has been recommended instead of omeprazole in patients receiving dual antiplatelet therapy.[41] Since the data on these GI effects of antisecretory therapy with PPI and/or histamine H_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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ARTYKUŁ POGLĄDOWY

Nowy wgląd w mechanizmy uszkodzeń żołądkowo-jelitowych wywołanych przez niesteroidowe leki przeciwzapalne: praktyczne implikacje

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SŁOWA KLUCZOWE

niesteroidowe leki przeciwzapalne, gastroprotekcja, tlenek azotu, terapia przeciwzakrzepowa, siarkowodór

STRESZCZENIE

Niesteroidowe 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 cyklooksygenazy (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 (H_2S), takich jak naproksen uwalniający H_2S (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 pompy 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 H_2S, 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.

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