

Mechanisms of nonsteroidal anti-inflammatory drug-induced gastrointestinal injury and repair: A window of opportunity for cyclooxygenase-inhibiting nitric oxide donors

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Nonsteroidal anti-inflammatory drugs (NSAIDs) cause damage in the upper gastrointestinal (GI) tract by impairing the ability of the mucosa to resist and respond to injury. Many of these effects of NSAIDs can be attributed to their ability to suppress mucosal prostaglandin synthesis. Selective inhibitors of cyclooxygenase (COX)-2 are less likely to disrupt mucosal defence and do not interfere with platelet aggregation. Thus, their use is associated with a reduced incidence of serious GI adverse events; however, a significant risk of such events still persists. At least in animal models, selective COX-2 inhibitors interfere with ulcer healing to the same extent as conventional NSAIDs. In contrast, COX-inhibiting nitric oxide donors (CINODs) produce anti-inflammatory and analgesic effects comparable or superior to those of NSAIDs, but with greatly reduced GI toxicity. Unlike NSAIDs and selective COX-2 inhibitors, CINODs do not interfere with ulcer healing. Moreover, because CINODs suppress the activity of both COX-1 and COX-2, they do not share with selective COX-2 inhibitors the lack of cardioprotection afforded by significant suppression of platelet aggregation. Because of their safety profile, CINODs may be particularly useful for long term prevention applications, such as for colon cancer, cardiovascular disease and Alzheimer's disease.

Key Words: Bleeding; COX; cyclooxygenase; Inflammation; Prostaglandin; Ulcer

Les mécanismes des lésions gastro-intestinales causées par des anti-inflammatoires non stéroïdiens et de leur réparation : Un créneau pour les donneurs de monoxyde d'azote inhibant la cyclo-oxygénase

Les anti-inflammatoires non stéroïdiens (AINS) endommagent le tractus gastro-intestinal (GI) supérieur en altérant la capacité de la muqueuse à résister et à réagir aux lésions. Bien des effets des AINS à cet égard peuvent être attribués à leur capacité de supprimer la synthèse de la prostaglandine muqueuse. Les inhibiteurs sélectifs de la cyclo-oxygénase 2 (COX-2) sont moins susceptibles de perturber la défense muqueuse, et ils ne nuisent pas à l'agrégation plaquettaire. Par conséquent, leur usage s'associe à une diminution de l'incidence de graves effets GI secondaires, mais le risque de tels effets demeure marqué. Du moins chez les modèles animaux, les inhibiteurs sélectifs de la COX-2 nuisent à la cicatrisation des ulcères tout autant que les AINS conventionnels. Par contre, les donneurs de monoxyde d'azote inhibant la COX (DMAIC) produisent des effets anti-inflammatoires et analgésiques comparables ou supérieurs à ceux des AINS, mais leur toxicité GI est beaucoup plus faible. Contrairement aux AINS et aux inhibiteurs sélectifs de la COX-2, les DMAIC n'entravent pas la cicatrisation des ulcères. De plus, tandis qu'ils suppriment l'activité tant de la COX-1 que de la COX-2, les DMAIC ne partagent pas avec les inhibiteurs de la COX-2 cette absence de cardioprotection découlant de la suppression marquée de l'agrégation plaquettaire. En raison de leur profil d'innocuité, les DMAIC pourraient être particulièrement utiles dans des applications de prévention à long terme, dans des cas de cancer du côlon, de maladie cardiovasculaire ou de maladie d'Alzheimer, par exemple.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, inflammation and fever. However, their use is associated with a relatively high incidence of adverse reactions in the gastrointestinal (GI) tract (1,2). Such damage can take the form of mucosal erosions or ulcers and can occur anywhere from the esophagus to the colon. In the small intestine, strictures can sometimes be found in chronic NSAID users. Of greatest concern from a clinical standpoint is the progression of ulcers to the point of perforation and the risk of severe bleeding from ulcers (1).

Gastric erosions are common (35% to 60% of patients) and observed within a few hours of consumption of an NSAID. These lesions heal quite quickly and are generally regarded as being clinically insignificant. Ulcers are rare with fewer than six weeks of treatment with an NSAID, but their frequency increases linearly thereafter to 20% in six months (3,4). It is possible that the true incidence and prevalence rates for ulcers are higher because the lesions are often asymptomatic (5). Of particular concern is the progression of NSAID-induced ulcers to the point where perforation or severe bleeding occurs, which is the case for 2% to 4% of chronic NSAID users (1).

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The incidence of intestinal lesions is more difficult to establish because these lesions often occur beyond the reach of an endoscope. However, it has been suggested that significant increases in intestinal permeability, significant bleeding and intestinal leukocyte accumulation occur in up to 70% of patients receiving long term NSAID therapy (6).

Whether there are different risks of ulceration with different NSAIDs has been a controversial subject, at least until recently (7,8). With the introduction of a number of new NSAIDs in recent years (eg, meloxicam, nimesulide, etodolac, celecoxib, rofecoxib, valdecoxib), it has become clear that different NSAIDs do exhibit different risks for ulcer development. It has been suggested that these differences are related to the relative potency of these agents for inhibition of cyclooxygenase (COX)-1 (9). By sparing COX-1, these agents produce less suppression of mucosal prostaglandin (PG) synthesis, which, as described in more detail below, should result in less impairment of mucosal defence (10). Selective COX-2 inhibitors, such as rofecoxib and celecoxib, have been promoted as being as effective as conventional NSAIDs in terms of anti-inflammatory and analgesic activities, while causing less GI injury. There is emerging evidence that challenges both aspects of these claims; that is, there is evidence that COX-1-derived PGs contribute to the generation of pain and inflammation (11-14), that COX-2-derived PGs contribute to the resolution of inflammation (11,15) and that COX-2-derived PGs contribute to mucosal defence (16-21). Selective COX-2 inhibitors also elicit additional adverse effects not seen with conventional NSAIDs, such as a propensity to increase the risk of myocardial infarction (22-24).

Improved GI safety profiles have also been reported for nitric oxide (NO)-releasing anti-inflammatory drugs, such as those in the new COX-inhibiting NO donor (CINOD) class (25-27). These agents are at least as effective as traditional NSAIDs (showing increased potency in some animal studies of analgesia) (28,29) and have cardiovascular effects distinct from those of the selective COX-2 inhibitors (30-32). These cardiovascular effects are due to the fact that CINODs suppress COX-1 activity, thereby inhibiting platelet aggregation, and release NO, which itself can inhibit platelet aggregation, inhibit leukocyte adherence to the vascular endothelium and attenuate vascular injury in many settings. Indeed, NO-releasing NSAIDs have been shown to have beneficial effects in animal models of hypertension, myocardial dysfunction and restenosis, in contrast to the behaviour of selective COX-2 inhibitors in these models (29-36).

The safety and efficacy of NO-releasing NSAIDs have recently been demonstrated in a number of phase I and phase II clinical trials. The results of several of these trials have yet to be published. However, two recent papers did report on the GI safety of NCX-4016, an NO-releasing derivative of aspirin (37,38). Figure 1 shows some of the key data from one of those trials. Administration of acetylsalicylic acid (ASA) twice daily for eight days resulted in significant endoscopic damage to the stomach and duodenum (37). However, administration of NCX-4016, at equimolar doses, did not produce significant damage (ie, scores of the patients in the endoscopic group were not different from scores of those in the placebo group). Nevertheless, NCX-4016 produced suppression of platelet aggregation comparable to that seen with ASA. The observations that selective COX-2 inhibitors appear to increase the risk of myocardial infarction (22-24) led to the suggestion by

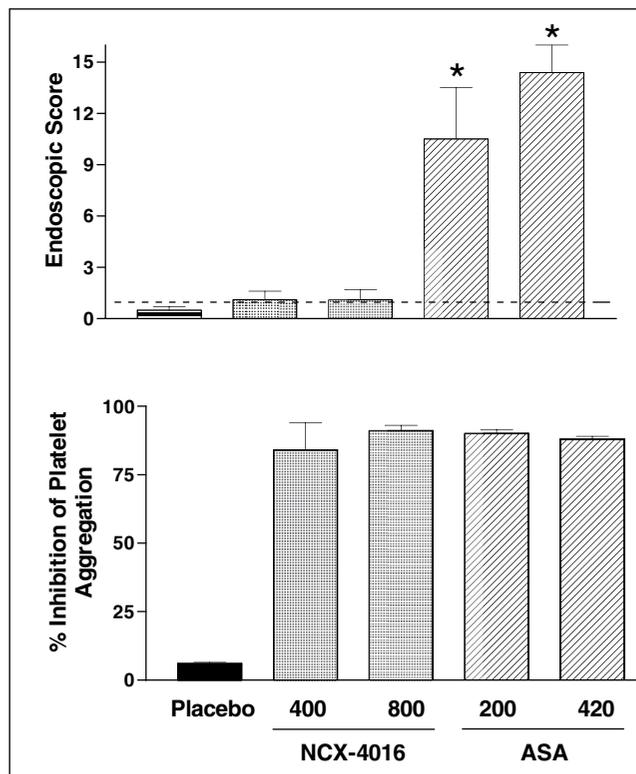


Figure 1 Top Endoscopic scoring of gastroduodenal damage in human volunteers taking placebo, acetylsalicylic acid (ASA) (200 mg or 420 mg bid) or NCX-4016 (400 mg or 800 mg twice daily) for 14 days. * $P < 0.05$ versus the placebo group. The dotted line indicates two standard deviations above the mean for the placebo group. Bottom Percentage inhibition of arachidonate-induced platelet aggregation. Samples of platelets were prepared from blood taken from each of the volunteers on the final day of the study. Data from reference 37

some that these drugs should be taken together with low dose ASA in patients at risk of serious cardiovascular disease. However, a concern with this approach is that taking these two types of drugs together may cause significant gastric damage. Indeed, this is precisely what was observed in animal studies (39,40). This prompted us to examine, in healthy volunteers, whether co-administration of low dose ASA and a selective COX-2 inhibitor would cause significant GI damage, and if the same degree of damage would be observed when NCX-4016 was substituted for ASA. As shown in Figure 2, celecoxib administration resulted in a significant increase in the extent of endoscopically detected gastroduodenal damage as compared with that induced by ASA alone (38). However, NCX-4016 did not produce significant damage when given alone or together with celecoxib.

MECHANISMS OF NSAID-INDUCED INJURY

The mechanisms responsible for NSAID-induced ulcerative lesions of the GI tract are not completely understood, particularly with respect to the lesions in the small intestine (2,41,42). A number of possible etiological factors has been proposed, including direct toxic effects of these drugs on the epithelium, alterations in the mucosal microcirculation and impairment of normal repair processes.

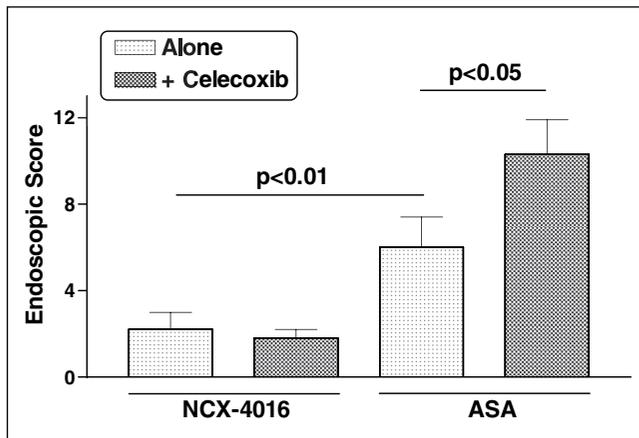


Figure 2) Endoscopic scores of gastroduodenal damage in human volunteers taking acetylsalicylic acid (ASA) (100 mg daily) or NCX-4016 (800 mg twice daily) alone or together with celecoxib (200 mg twice daily). Celecoxib significantly exacerbated gastroduodenal damage caused by ASA, but with NCX-4016 the level of damage remained minimal. Data from reference 38

Topical irritant properties

Some NSAIDs, particularly those that are weak acids, produce epithelial damage at sites of contact with the GI mucosa (43). In locations where the mucosa is in contact with acid, the drugs behave in accordance with the pH partition hypothesis. In the presence of hydrogen ions, the drug becomes an uncharged, lipid-soluble compound capable of nonionic diffusion into the mucosal cells (44,45). In the near neutral intracellular environment, re-ionization of the drug occurs, which can lead to osmotic swelling and lysis of the cells. These drugs may also uncouple mitochondrial respiration, leading to cell death (42). A higher prevalence of esophageal ulcers and strictures has been reported for patients taking NSAIDs (46,47), which includes over-the-counter NSAIDs and low dose ASA (48). Topical injury seems to be related to the time of contact of the drug with the esophageal mucosa because most of the lesions are at the level of the aortic arch and above the lower esophageal sphincter, where the capsule's transit tends to be delayed. However, in an experimental model of acid- and pepsin-induced esophagitis in rabbits, both the topical exposure to acidified ASA and intravenous administration of ASA increased mucosal injury and mucosal barrier dysfunction compared with controls (49). This damage was significantly reduced by the administration of PGE₂ before exposure to the acidified ASA (49). In the stomach, the topical irritant properties of NSAIDs may also be related to the ability of NSAIDs to decrease the hydrophobicity of the mucus gel layer in the stomach, which has been suggested to be a primary barrier to damage induced by acid (50). It is important to note that gastric mucosal injury can occur after parenteral or rectal administration of NSAIDs, or after their administration in a prodrug or enteric-coated form, suggesting that systemic, rather than topical, effects may be of more importance in the pathogenesis of NSAID-induced ulceration (51-56).

Topical irritant effects of NSAIDs appear to play a clearer role in the pathogenesis of small intestine damage, where the enterohepatic recirculation of NSAIDs increases the exposure of the intestinal epithelium to these drugs. Ligation of the bile duct prevents much of the damage that is normally observed

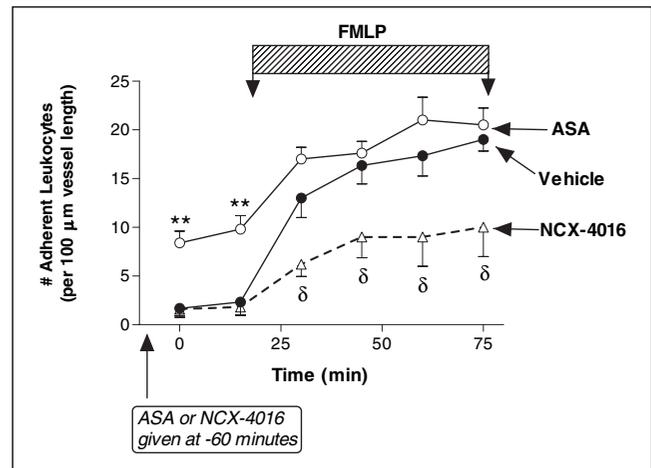


Figure 3) Leukocyte adherence to the vascular endothelium of rat mesenteric venules is stimulated by oral administration of acetylsalicylic acid (ASA), but not by nitric oxide (NO)-releasing ASA. Superfusion of the blood vessel (64) with a chemotactic peptide (fMLP; 5 μ M) led to an increase in leukocyte adherence in vehicle-treated rats, and a further increase in leukocyte adherence in rats treated with ASA. In contrast, in rats treated 1 h before the experiment with a cyclooxygenase-inhibiting NO-donating drug, NCX-4016 (83 mg/kg by mouth), there was no effect on basal levels of leukocyte adherence (in contrast to results using an equimolar dose of ASA; 50 mg/kg by mouth), and the fMLP-induced leukocyte adherence was significantly reduced. NCX-4016 is an NO-releasing derivative of ASA (32). Each point represents the mean \pm SEM of at least five experiments. ** $P < 0.05$ versus the control and NCX-4016 groups; $\delta P < 0.05$ versus the ASA- and vehicle-treated groups

after NSAID administration in rats (41,57). Chemical modification of diclofenac, such that it underwent significantly less enterohepatic recirculation, resulted in a marked attenuation of its ability to cause small intestinal damage (41). Moreover, such damage is not observed after administration of NSAIDs that do not undergo enterohepatic recirculation (41).

Inhibition of PG synthesis

The metabolism of arachidonic acid to PGs and leukotrienes is catalyzed by the COX and the 5-lipoxygenase enzyme pathways, respectively. In the gastric and duodenal mucosa, most arachidonic acid is converted into PGs of the E₂, F_{2 α} and I₂ subtypes. Perhaps the most important feature of NSAIDs that contributes to their ability to cause GI injury is the suppression of mucosal PG synthesis, by inhibiting the activity of COX (10,58). Of course, inhibition of PG synthesis is also the mechanistic basis for many of the beneficial actions of NSAIDs. By suppressing mucosal PG synthesis, NSAIDs impair many of the key components of mucosal defence, including mucus formation and secretion, bicarbonate secretion and the protective pH gradient adjacent to the GI mucosa (10). Inhibition of mucosal PG synthesis also results in important changes in the GI microcirculation that appear to play crucial roles in the pathogenesis of ulceration (2).

Decreased mucosal blood flow

A high rate of blood flow to the luminal surface of the stomach is essential for mucosal defence. Acid back-diffusion into the mucosa can be tolerated so long as there is sufficient blood flow

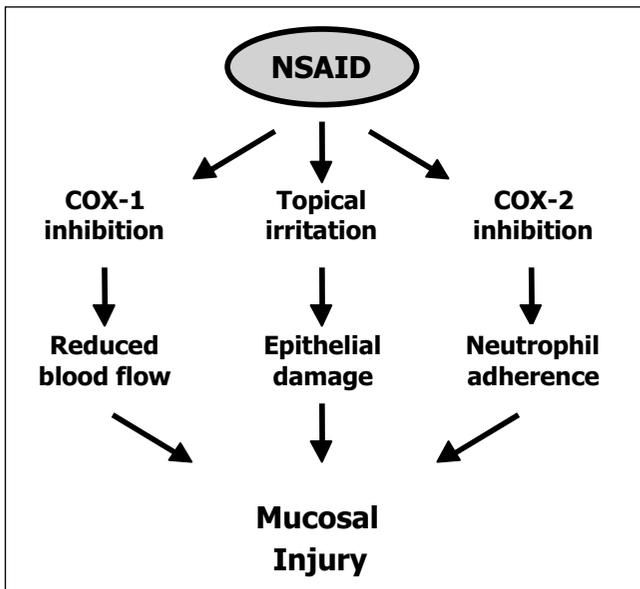


Figure 4) Nonsteroidal anti-inflammatory drug (NSAID)-induced mucosal injury occurs through at least three pathways. Suppression of cyclooxygenase (COX)-1 and COX-2 activity is essential for these lesions to form. In animal studies, suppression of COX-1 was shown to account for the reduction in gastric blood flow observed following NSAID administration (16). In contrast, suppression of COX-2 accounted for the induction of leukocyte adherence to the vascular endothelium observed following NSAID administration (16). Some NSAIDs, particularly those that are acidic, also have topical irritant properties that contribute to their ulcerogenicity (42)

to allow for buffering of the acid. When blood flow to the mucosa is decreased, the tissue becomes more susceptible to acid- and pepsin-induced damage. NSAIDs decrease mucosal blood flow to the stomach, but appear to do so in a 'patchy' manner. That is, blood flow is reduced at some foci in the stomach, but not at others. NSAID-induced lesions form predominantly at the sites of reduced mucosal blood flow (59). The reasons for this patchy distribution of blood are not clear. NSAID-induced inhibition of the synthesis of PGE₂ and PGI₂, which are vasodilators, is likely to be the underlying cause of the focal ischemia produced by these agents. Selective COX-2 inhibitors and CINODs do not reduce gastric mucosal blood flow (16,26).

Leukocyte activation

NSAIDs can stimulate leukocytes, particularly neutrophils, such that they adhere to the vascular endothelium within the GI microcirculation (60,61). A key role for neutrophils in the pathogenesis of NSAID-induced mucosal injury is supported by the observations that such damage is absent in neutropenic rats (62) and can be prevented by treatment of animals with neutralizing antibodies directed against leukocyte or endothelial adhesion molecules (63,64). A role for neutrophils in the pathogenesis of NSAID-induced gastropathy was further supported by the observation that administration of PGs at doses previously shown to prevent gastric injury also prevented NSAID-induced leukocyte adherence (60,61). Interestingly, in a human clinical trial of the use of famotidine for the prevention of NSAID-related gastroduodenal ulcers, the investigators reported that an increased peripheral white cell count correlated positively with the risk of ulcer development (65).

There are a number of mechanisms through which neutrophil adherence to the vascular endothelium could contribute to the pathogenesis of gastric mucosa injury. First, the factors that trigger the adherence of neutrophils to the vascular endothelium (such as leukotriene B₄ and tumour necrosis factor- α) also trigger the activation of these cells, leading to the liberation of oxygen-derived free radicals (eg, superoxide anion) and proteases (eg, elastase, collagenase). These substances may mediate much of the endothelial and epithelial injury caused by NSAIDs. Indeed, NSAID-induced mucosal injury can be markedly reduced by scavengers of oxygen-derived free radicals (66) and by inhibition of neutrophil-derived proteases (67). Second, neutrophil adherence to the vascular endothelium could lead to obstruction of capillaries, resulting in reduced gastric mucosal blood flow. This well-characterized ability of NSAIDs to reduce gastric blood flow has been shown to occur subsequent to the appearance of "white thrombi" in the gastric microcirculation (68).

Selective COX-2 inhibitors share the feature of conventional NSAIDs of causing leukocyte adherence to the vascular endothelium (16,31). In contrast, CINODs do not cause leukocyte adherence (25). Indeed, these agents have been shown to inhibit leukocyte adherence caused by inflammatory mediators (69) (Figure 3) which could contribute to their broader spectrum of anti-inflammatory and analgesic activity as compared with conventional NSAIDs (28,69).

COX isoforms

In connection with NSAID-induced GI mucosal damage, much research has recently been concentrated on the two known isoforms of COX. COX-1 is constitutively expressed throughout the GI tract (70). COX-2 is expressed at low levels in the GI tract, but can be rapidly induced in response to a number of factors. For example, COX-2 is rapidly induced in the stomach following administration of ASA (71). Recently a third isoform, COX-3, was described, and it was suggested that this isoform is susceptible to inhibition by acetaminophen (72). This enzyme is a splice variant of COX-1. Its role, if any, in GI mucosal defence has yet to be determined.

Therapeutic doses of conventional NSAIDs inhibit both COX-1 and COX-2 (9). There has been widespread speculation, including that by marketers of selective COX-2 inhibitors, that GI mucosal ulceration occurs predominantly because of inhibition of COX-1 (73). NSAIDs that selectively inhibit COX-2 (ie, that spare COX-1 at therapeutic doses) have been promoted on the basis that they cause less GI injury (73,74). However, large outcomes studies of celecoxib and rofecoxib have indicated that these agents still produce significant GI injury, and their use is associated with a reduction of about 50% of GI bleeds (22,74). Indeed, the incidence of serious GI adverse events with celecoxib did not differ significantly from that observed in patients taking one of two conventional NSAIDs (diclofenac and ibuprofen) (75). Concomitant use of low dose ASA appears to abrogate any benefit, in terms of GI injury, that is gained by taking a selective COX-2 inhibitor rather than a conventional NSAID (74). As outlined above, a recent study demonstrated, in healthy human volunteers, that administration of a selective COX-2 inhibitor significantly augmented the gastroduodenal injury caused by low dose ASA (38).

The relative contribution of inhibition of COX-1 versus COX-2 to NSAID-induced gastric mucosal injury was recently evaluated in the authors' laboratory (16) (Figure 4). The

reduction of gastric blood flow that one observes following NSAID administration is attributable to suppression of COX-1. On the other hand, it is the inhibition of COX-2 by NSAIDs that accounts for leukocyte adherence within the GI microcirculation. Selective inhibition of COX-1 or of COX-2 does not result in gastric damage in the rat. Rather, combined inhibition of both isoforms of COX is necessary for mucosal damage to be observed (16). This observation has now been confirmed by another laboratory and extended to NSAID-induced small intestinal injury (18,76).

MECHANISMS OF MUCOSAL REPAIR

The processes involved in wound healing, and specifically in the healing of mucosal wounds and ulcers, are not completely understood. Damage to the GI tract likely occurs on a daily basis, but ulcers only rarely develop (77). This is because breaks in the epithelial lining are rapidly repaired through a process known as "restitution" (78). Restitution involves migration of healthy epithelial cells from the gastric pits over the area that has been denuded. This occurs very rapidly. In experimental models, a completely denuded gastric epithelium can be re-epithelialized within 15 min. The process occurs without need for cell division. Restitution requires there to be an undamaged basement membrane because this serves as the template along which the healthy epithelial cells migrate (79). In the presence of significant amounts of luminal acid, which can damage the basement membrane, restitution also requires the formation of a microenvironment over the site of damage in which the pH is relatively high (ie, close to neutral) (80). This "mucoic cap" is composed of mucus, fibrin and cellular debris. The maintenance of an appropriate pH within the mucoic cap is dependent upon uninterrupted blood flow to the mucosa.

When damage penetrates deeper into the mucosa, complete repair involves cell proliferation and re-establishment of the glandular architecture. If the damage does not penetrate the muscularis mucosae (which separates the mucosa from the submucosa), such repair can be achieved within one to three days. However, if the damage penetrates through the muscularis mucosa, a true "ulcer" is formed, and repair can take from weeks to months. Such repair involves the re-establishment of the vasculature, which involves new blood vessel growth (angiogenesis), re-establishment of glandular architecture and re-establishment of the mucosal immune system in the affected region. There is strong evidence for the involvement of a number of growth factors, including epidermal growth factor and vascular endothelial growth factor, in the process of ulcer repair (81,82). Moreover, there can be upregulation of the receptors for some of these growth factors at the ulcer site (83). Interesting, platelets seem to play an important role in ulcer healing outside of their contribution to hemostasis (84). Platelets contain a wide array of growth factors and can deliver those growth factors to a site of tissue injury. Drugs that affect the content of growth factors within the platelet may thereby affect rates of ulcer healing.

COX-2 is also expressed by cells at the margin of ulcers, which is a key site for epithelial cell proliferation (85). As discussed below, PGs derived from COX-2 play an important role in ulcer healing and in the process of angiogenesis (86,87).

INFLUENCE OF NSAIDS ON ULCER HEALING

NSAIDs can interfere with various aspects of mucosal repair. The rapid restitution that occurs through cell migration

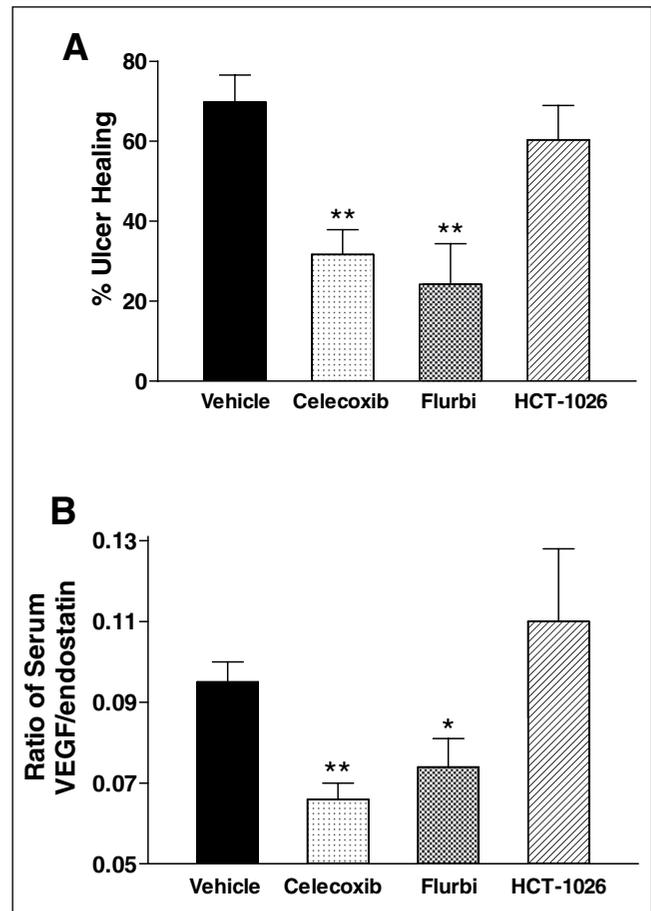


Figure 5) Effects of daily treatment with celecoxib, flurbiprofen (Flurbi) or a nitric oxide-releasing flurbiprofen derivative (HCT-1026) on gastric ulcer healing (A) and serum levels (B) of vascular endothelial growth factor (VEGF) and endostatin. The latter data are presented as a ratio of one to the other; VEGF is a potent pro-angiogenic factor, while endostatin is a potent anti-angiogenic factor. Celecoxib and flurbiprofen significantly impaired gastric ulcer healing and caused a significant shift in serum levels of VEGF versus endostatin. In contrast, HCT-1026 did not interfere with ulcer healing or cause a shift in the ratio of pro- to antiangiogenic factors. * $P < 0.05$, ** $P < 0.01$ versus the corresponding vehicle-treated group. Data from reference 90

following damage to the superficial epithelium of the stomach can be significantly impaired by NSAIDs. NSAIDs appear to rapidly dissipate the near neutral microenvironment within the mucoic cap over sites of damage. This is likely a consequence of inhibition of PG synthesis, which results in reduced mucosal blood flow (the pH within the mucoic cap is kept at near neutral by a continuous supply of plasma). NSAIDs can also reduce rates of epithelial turnover in the GI tract and interfere with angiogenesis (86). These actions likely contribute to the ability of NSAIDs to impair ulcer healing (88,89). This adverse effect of NSAIDs can be overcome by using powerful inhibitors of gastric acid secretion, such as proton pump inhibitors (88). As mentioned above, COX-2 is expressed by epithelial cells at the margins of ulcers (85). Perhaps not surprisingly, selective COX-2 inhibitors delay gastric ulcer healing (85,90). This action may be in part related to effects of these drugs on serum

levels of growth factors that regulate angiogenesis. Treatment of rats with a selective COX-2 inhibitor (celecoxib) was found to alter the balance of pro- and anti-angiogenic factors in serum, resulting in a shift in the 'angiogenic balance' towards inhibition of angiogenesis (90). A conventional NSAID, flurbiprofen, produced the same effect (Figure 5). Moreover, both celecoxib and flurbiprofen significantly inhibited ulcer repair in this model. In contrast, when a NO-releasing derivative of flurbiprofen was given in the same manner, the balance of angiogenic factors in serum was not altered and this compound did not interfere with ulcer healing. In another study, a NO-releasing derivative of diclofenac was found to accelerate ulcer healing relative to a group treated with vehicle (91).

Selective COX-2 inhibitors also interfere with healing in other parts of the GI tract, and have been reported to exacerbate experimental colitis (21) and human inflammatory bowel disease (92). In contrast, agents in the CINOD class, which offer a multifactorial mechanism of action involving NO

release and COX inhibition, do not interfere with ulcer healing and do not exacerbate colitis (91,93).

CONCLUSIONS

NSAIDs cause GI mucosal damage by disrupting protective factors and by interfering with the healing of mucosal ulcers. Selective inhibitors of COX-2 are less likely to disrupt mucosal defence, but appear to cause the same degree of inhibition of ulcer healing as is seen with conventional NSAIDs. In contrast, CINODs produce anti-inflammatory and analgesic effects comparable or superior to those of NSAIDs, but with greatly reduced GI toxicity. Unlike NSAIDs and selective COX-2 inhibitors, CINODs do not interfere with ulcer healing. Moreover, the inhibition of platelet aggregation and the many other beneficial effects of NO in the microcirculation make CINODs an attractive option for cardioprotective indications, or for use in patients where cardioprotection is warranted.

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