

Pathogenesis of nonsteroidal anti-inflammatory drug gastropathy: Clues to preventative therapy

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SMA Bastaki, JL Wallace. Pathogenesis of nonsteroidal anti-inflammatory drug gastropathy: Clues to preventative therapy. *Can J Gastroenterol* 1999;13(2):123-127. Gastric ulceration and bleeding are major impediments to the chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs). The development of effective therapies for prevention of these adverse effects requires better understanding of their pathogenesis. Several features of NSAIDs contribute to the development of damage in the stomach, including the topical irritant effects of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury. The presence of acid in the lumen of the stomach also contributes to the pathogenesis of NSAID-induced ulcers and bleeding in a number of ways. Acid impairs the restitution process, interferes with hemostasis and can inactivate several growth factors that are important in mucosal integrity and repair. Profound suppression of gastric acid secretion has been shown to be effective in preventing NSAID-induced ulceration. There is a strong possibility that new NSAIDs entering the market will have greatly reduced toxicity in the gastrointestinal tract.

Key Words: Acid secretion, H_2 receptor antagonists, Nonsteroidal anti-inflammatory drugs, Proton pump inhibitors, Ulcer

La pathogenèse de la gastropathie liée aux AINS : Conseils pratiques pour un traitement préventif

RÉSUMÉ : L'hémorragie et l'ulcère gastriques sont d'importants obstacles à l'emploi prolongé des anti-inflammatoires non stéroïdiens (AINS). La mise au point de traitements efficaces pour la prévention de ces effets indésirables requiert une compréhension plus approfondie de leur pathogenèse. Plusieurs caractéristiques des AINS contribuent à l'installation d'une atteinte à l'estomac; mentionnons leurs effets irritants topiques sur l'épithélium, l'atteinte des propriétés de la muqueuse en tant que barrière, la suppression de la synthèse des prostaglandines gastriques, la réduction du débit sanguin dans la muqueuse gastrique et l'interférence avec la réparation des lésions superficielles. La présence d'acide dans la lumière stomacale contribue également à la pathogenèse des ulcères et des hémorragies liés aux AINS et ce, de plusieurs façons. L'acide nuit au processus de rétablissement, interfère avec l'hémostase et peut inactiver plusieurs facteurs de croissance qui sont importants pour l'intégrité et la réparation de la muqueuse. Une suppression profonde de la suppression de l'acide gastrique s'est révélée efficace à prévenir l'ulcération provoquée par les AINS. On suppose aussi fortement que les nouveaux AINS qui feront leur apparition sur le marché s'accompagneront d'une toxicité considérablement moindre pour le tractus digestif.

To develop better strategies for preventing the gastric ulcers and episodes of bleeding that occur in patients who are chronically ingesting nonsteroidal anti-inflammatory drugs (NSAIDs), it is necessary to understand the mechanisms through which these drugs produce damage to the stomach. There are two major components to the ulcerogenic effects of NSAIDs in the stomach: topical irritant effects on the epithelium and suppression of gastric prostaglan-

din synthesis. Effects of NSAIDs on the hydrophobic nature of the gastric mucosa and on gastric acid secretion may also contribute to their ulcerogenic effects.

TOPICAL IRRITATION OF THE MUCOSA

Topical irritant properties are predominantly associated with acidic NSAIDs, such as those with a carboxylic acid residue. Acetylsalicylic acid is the best characterized NSAID

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in terms of topical irritant effects on the gastric epithelium. Epithelial damage caused by NSAIDs is likely related in part to the accumulation of these drugs inside these cells ('ion trapping'). The un-ionized forms of these drugs can enter the epithelial cells, but, once in the neutral intracellular environment, they are converted to an ionized state and cannot diffuse out. Osmotic forces then pull water into the cell, resulting in swelling, sometimes to the point of lysis (1,2).

Topical irritant properties have also been attributed to the ability of NSAIDs to decrease the hydrophobicity of the mucous gel layer in the stomach. Lichtenberger (3) and Goddard et al (4) have proposed that this layer is a primary barrier to acid-induced damage in the stomach. They have demonstrated that a hydrophobic layer is present on the surface of the stomach and that it can be altered by various pharmacological agents. For example, they demonstrated that NSAIDs associate with the surface active phospholipids within the mucous gel layer, thereby reducing its hydrophobic properties (4-6). Indeed, they showed that the mucous gel layer in the stomachs of rats and mice given NSAIDs was converted from a nonwetable to a wettable state. This was not just an acute effect because they observed that the reduced hydrophobicity of the mucous gel layer persisted for several weeks to months after cessation of NSAID administration (3,5).

It has been repeatedly suggested that another mechanism through which NSAIDs may damage the stomach is via uncoupling of oxidative phosphorylation in epithelial cells (2,7). This theory has been challenged, however, based on the observation of gastric and duodenal ulcers following parenteral or rectal administration of NSAIDs (8,9). Erosions and ulcers can also be produced in experimental circumstances in which NSAIDs are administered parenterally (10). It is difficult to comprehend how uncoupling of oxidative phosphorylation would occur in gastrointestinal epithelial cells but not in the numerous other cells that an NSAID would have contact with after its absorption.

Attempts have been made to produce NSAIDs with reduced topical irritant effects. These include formulation of slow release or enteric-coated tablets, or preparation of the drug as a prodrug that requires hepatic metabolism in order to be active (eg, sulindac and nabumetone). However, the incidence of gastroduodenal ulceration with these prodrugs is comparable with that seen with standard NSAIDs (11-13). This is evidence that the topical irritant properties of NSAIDs are not paramount in their ability to induce frank ulceration in the stomach. However, this possibility cannot be completely excluded. Most NSAIDs are excreted in bile. Therefore, even with parenteral administration of NSAIDs, reflux of duodenal contents into the stomach would result in topical exposure of the gastric mucosa to these drugs.

INHIBITION OF PROSTAGLANDIN SYNTHESIS

There is substantial evidence that the ability of an NSAID to cause gastric damage correlates well with its ability to suppress gastric prostaglandin synthesis (14-16). There is also a good correlation between the time- and dose-dependency of suppression of gastric prostaglandin synthesis by NSAIDs

and their ulcerogenic activity (14,15,17). Why does suppression of gastric prostaglandin synthesis lead to mucosal injury? Several components of gastric mucosal defence are mediated by prostaglandins, including the secretion of mucus and bicarbonate by the gastric and duodenal epithelium, mucosal blood flow, epithelial cell proliferation, epithelial restitution and mucosal immunocyte function (18). Inhibition of prostaglandin synthesis, alone, may not result in the formation of gastric erosions or ulcers. However, suppression of mucosal prostaglandin synthesis leads to a reduction in the ability of the gastric mucosa to defend itself against luminal irritants. This has been demonstrated in experimental animals. Doses of NSAIDs that did not cause gastric injury were able to greatly increase the susceptibility of the gastric mucosa to damage induced by irritants (eg, bile salts) (19).

EFFECTS ON THE MICROCIRCULATION

The ability of NSAIDs to reduce gastric mucosal blood flow has been recognized for several decades (20-22). More recently, it has become clear that damage to the vascular endothelium is an early event following administration of NSAIDs to experimental animals (23,24). Studies performed in our laboratory and others showed that NSAID administration to rats resulted in a significant increase in the number of neutrophils adhering to the vascular endothelium in both the mesenteric and gastric microcirculation (16,25-27). This was observed within 30 mins of NSAID administration, which is consistent with the period of time required for significant inhibition of prostaglandin synthesis by these drugs (28). The contribution of neutrophils to the gastric injury associated with NSAIDs was demonstrated by the observation that the severity of damage was substantially reduced in neutropenic rats (ie, rats pretreated with antineutrophil serum or methotrexate) (24,29). Depletion of neutrophils also resulted in prevention of NSAID-induced vascular endothelial damage (24). Further evidence for a role of neutrophils in the pathogenesis of NSAID-induced gastric injury came from studies in which monoclonal antibodies against neutrophil or endothelial adhesion molecules were employed to prevent neutrophil adherence; these antibodies also markedly reduced the severity of gastric damage caused by NSAIDs (27,30).

There are two likely pathways through which neutrophil adherence may contribute to the pathogenesis of NSAID-induced gastric mucosal injury (31). First, the adherence of neutrophils to the vascular endothelium is likely accompanied by activation of these cells, leading to the release of proteases (eg, elastase and collagenase) and oxygen-derived free radicals (eg, superoxide anion). These substances may mediate much of the endothelial and epithelial injury caused by NSAIDs. Indeed, several compounds that scavenge for oxygen-derived free radicals were shown to reduce significantly the severity of NSAID-induced gastric mucosal injury in rats (32,33). The second pathway through which neutrophil adherence to the vascular endothelium may contribute to mucosal injury is by producing an obstruction of capillaries, thereby reducing gastric mucosal blood flow. Interest-

ingly, the well characterized ability of NSAIDs to reduce gastric blood flow (20-22) was shown to occur after the appearance of 'white thrombi' in the gastric microcirculation (21).

INTERFERENCE WITH REPAIR OF MUCOSAL INJURY

When the epithelium of the stomach is damaged, it can be repaired within minutes through rapid migration of healthy cells from the gastric pits (34). These cells move along the denuded basement membrane, which is the template necessary for the process of 'restitution' (34-37). The factors that trigger the movement of cells over the denuded basement membrane are not clear. Damage to the basement membrane can occur when it is exposed to acid (28,38,39). This does not occur during normal circumstances because of the formation of a microenvironment in which the pH is maintained at near 7 over sites of injury, even in the presence of a significant acid load in the lumen (28,38). A 'cap' of mucus, cellular debris and plasma proteins forms within seconds of gastric epithelial injury, trapping the plasma that leaks from the underlying microcirculation (38). This plasma accounts for the near neutral pH within the protective 'mucoïd cap'. Even a very brief cessation of mucosal blood flow results in a rapid decrease in the pH within the mucoïd cap, leading to the formation of hemorrhagic erosions (28).

One way that NSAIDs can promote gastric injury is by interfering with the process of restitution. Following systemic administration of an NSAID, the pH within the mucoïd cap over sites of epithelial damage begins to decline in parallel with the inhibition of prostaglandin synthesis (28). This in turn leads to the formation of hemorrhagic erosions (28). This effect could be prevented through luminal delivery of exogenous prostaglandins (28). It is possible that this effect of NSAIDs is related to their ability to reduce gastric blood flow, but this has not yet been established. Interestingly, however, the decrease in pH within the mucoïd cap could be prevented by topical application of exogenous prostaglandins; this treatment would also prevent the formation of hemorrhagic erosions (28).

ROLE OF ACID

The observation that NSAID-induced ulcers can occur in achlorhydric individuals (40,41) has contributed to a widely held belief that these lesions occur independently of the presence of acid in the stomach. This was reinforced by several reports that demonstrated that treatment with histamine H₂ receptor antagonists did not reduce the incidence of NSAID-induced ulceration (42-44). This interpretation of the latter findings has been quite controversial, however, mainly because of inconsistencies from one study to another in the discrimination between gastric erosions and true ulcers. Many studies have demonstrated that H₂ receptor antagonists and proton pump inhibitors can prevent NSAID-induced gastric lesions, but prevention of the formation of the clinically more significant ulcers, as well as ulcer complications, was not clearly established. Taha et al (45) recently

reported that a high dose of famotidine (40 mg bid) was effective in preventing NSAID-induced 'ulcers'. It should be noted that the dose required to induce this effect was double the dose approved for the healing of ulcers. Moreover, the study of Taha et al (45) has been criticized on the basis of the definition of ulcer used (break in the mucosa of more than 3 mm). Graham (46) suggested that if Taha and colleagues were to reassess their data using a more robust definition for ulcer, they might find that famotidine was ineffective in preventing ulceration, as had been reported in an earlier study (44). On the other hand, the recent demonstration that omeprazole can significantly reduce the incidence of NSAID-induced ulcers (47) adds support to the claim of Taha et al (45) that profound suppression of acid secretion, as is produced by omeprazole or a high dose of famotidine, was necessary to have a significant impact on the incidence of NSAID-induced ulcers.

There are several mechanisms through which acid may contribute to ulcer formation in NSAID users. First, it is clear that acid can exacerbate damage to the gastric mucosa induced by other agents. For example, acid can convert regions of ethanol-induced vascular congestion in the mucosa to actively bleeding erosions (34). A second mechanism through which acid can contribute to ulcer formation is by interfering with hemostasis. Platelet aggregation, for example, is inhibited at a pH of less than 4 (48). Third, acid can convert superficial injury to deeper mucosal necrosis interfering with the process of restitution. As described in more detail above, the basement membrane is crucial to the restitution process in that it acts as a template for epithelial cell migration. If the basement membrane is exposed to acid, it is rapidly degraded (39). A fourth mechanism through which acid contributes to ulcer formation is by inactivation of growth factors. Many growth factors that are important for maintenance of mucosal integrity and for repair of superficial injury are acid labile (49).

The effects of NSAIDs on gastric acid secretion are pertinent to the potential role of acid in the pathogenesis of NSAID-induced gastric ulceration. Prostaglandins exert inhibitory effects on parietal cells (50). By inhibiting prostaglandin production by the mucosa, NSAIDs can increase gastric acid secretion (51). Whether NSAID-induced increases in gastric acid secretion contribute to the development of gastric ulcers has not been directly examined.

FUTURE DIRECTIONS

A great deal has been learned about the pathogenesis of NSAID-induced gastric injury over the past two decades. As a result, a number of new NSAIDs that will have greatly reduced gastrointestinal toxicity relative to the current drugs are on the verge of being introduced into the marketplace. For example, selective inhibitors of cyclo-oxygenase-2, which will spare the major form of prostaglandin synthase in the gastrointestinal tract, will produce substantially less injury than the current NSAIDs that inhibit cyclo-oxygenase-1 and -2 (52). Whether these agents prove to be as effective for the treatment of the full range of inflamma-

tory conditions currently treated with NSAIDs remains to be seen, and some experimental studies suggest that this may not be the case (53). Nitric oxide-releasing NSAIDs provide another approach to reducing the adverse effects normally associated with NSAIDs (54).

Until the newer NSAIDs are introduced and fully accepted by patients with inflammatory diseases, a reduction of the incidence of gastric ulcers associated with the use of these drugs can be accomplished through profound suppression of acid secretion, either with proton pump inhibitors or with high doses of histamine H₂ receptor antagonists.

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