NSAID gastroenteropathy: Past, present and future

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs in North America (about 10 million prescriptions per year in Canada), as well as being used extensively as over-the-counter preparations. While their major use is as anti-inflammatory and analgesic agents, they are also widely used for antipyretic effects, and in the case of acetylsalicylic acid (ASA), for antithrombotic indications. However, long term use of NSAIDs is associated with a high risk of gastrointestinal injury. While the gastrointestinal adverse effects of NSAIDs are usually associated with the use of relatively high doses for relief of the pain and inflammation associated with rheumatoid arthritis, even very low doses of ASA for prophylaxis of myocardial infarction and stroke are associated with a significant increase in the risk of gastrointestinal bleeding.

Numerous strategies have been employed over the past 30 or 40 years to develop NSAIDs that spare the gastrointestinal tract. Until recently, none of these strategies markedly affected the incidence of clinically significant adverse reactions to NSAIDs. However, data from recent studies suggest that current strategies for the development of gastrointestinal-safe NSAIDs may be at least partially successful. In this review, the strategies that have been employed in the past and those currently being used are reviewed, as are some of the strategies that are being employed to achieve this goal in the future.

MECHANISM OF BENEFICIAL ACTIONS OF NSAIDs

Since the discovery by Vane (1) in 1971 that ASA and a number of different NSAIDs blocked the production of prostaglandins, it has become firmly established that this is the major reason for the anti-inflammatory, analgesic, antipyretic and antithrombotic actions of these drugs. The three-
dimensional structure of the enzyme cyclo-oxygenase (prostaglandin synthase) has been demonstrated, and the channel in the enzyme into which arachidonic acid binds has been identified (2). NSAIDs block the access of arachidonic acid to this binding site, thereby preventing the conversion of arachidonic acid to prostaglandins and thromboxane. ASA, on the other hand, modifies the shape of the binding channel for arachidonic acid by acetylating a serine residue on cyclo-oxygenase.

There is some debate regarding the mechanism responsible for the anti-inflammatory effects of ASA (3). This controversy has focused largely on the fact that ASA has an extremely short half-life in the plasma (less than 15 mins) and is converted to salicylate, which is a very weak inhibitor of cyclo-oxygenase. Therefore, how can ASA exert anti-inflammatory and antipyretic effects for several hours after ingestion and why does salicylate exert anti-inflammatory activity? It is becoming clear that in addition to suppressing cyclo-oxygenase enzyme activity, ASA and salicylate can inhibit induction of cyclo-oxygenase at sites of inflammation (4). This is discussed in more detail below.

HOW BIG IS THE PROBLEM?

Estimates of the incidence of NSAID-induced gastropathy vary greatly. Lanza (5) estimates the incidence to be between 15% and 20% of chronic NSAID users, while others have suggested that the incidence of symptomatic ulcers and potentially life-threatening consequences is 2% to 4% in patients taking NSAIDs for a year (6). The large differences in these estimates depend mainly on how ‘ulcer’ is defined in each study. For example, in a study by Graham et al (7) of the protective effects of misoprostol against NSAID-induced gastric injury, an ulcer was defined as a break in the mucosa of greater than 3 mm in diameter. Others might define such damage as an erosion rather than an ulcer. Some studies focus on the ‘clinical significant adverse effects’ of NSAIDs, such as perforation, bleeding requiring hospitalization or gastric outlet obstruction. In a recent study involving over 4000 patients taking NSAIDs over six months, 0.9% exhibited these clinically significant adverse effects (8).

Another problem regarding the incidence of NSAID gastropathy is that the majority of patients with endoscopically detectable NSAID-induced gastric damage are completely asymptomatic (7). It is possible that this phenomenon is attributable to the analgesic properties of NSAIDs masking any pain associated with the injury, but this has not been firmly established.

The incidence of NSAID-induced small bowel damage is even more difficult to define accurately. Intestinal bleeding has been suggested to occur in up to 65% of patients chronically taking NSAIDs (9), and significant permeability changes have been reported to be common and to persist for as long as 16 months after cessation of NSAID therapy (10). On the other hand, adverse events, such as the development of NSAID-induced intestinal strictures, are very rare (11). NSAIDs can exacerbate pre-existing colitis and cause a relapse of quiescent inflammatory bowel disease (12) but there are no data available on how frequently this occurs.

An alternative to attempting to define the prevalence or incidence of NSAID-induced gastropathy is to consider the financial costs of these adverse effects. The cost of NSAID gastropathy in the United States’ arthritic population alone has been estimated to be US$4 billion annually (13), and the cost of renal complications of NSAID use – while occurring less frequently – is likely to exceed this amount.

PATHOGENESIS

It is highly likely that the ulcerogenic effects of NSAIDs are directly related to their ability to suppress prostaglandin synthesis in the stomach. Prostaglandins play an important role in the gastrointestinal tract: they mediate several components of mucosal defence (bloodflow, mucus and bicarbonate secretion, and mucosal immunocyte function) (14). There is a good correlation between the ability of an NSAID to suppress gastric prostaglandin synthesis and its ulcerogenic actions (15). There is also a dose dependency of both suppression of prostaglandin synthesis in the stomach and ulcerogenic activity (15). Some NSAIDs, including ASA, also have topical irritant properties that may contribute to their ability to damage the gastric mucosa. This topical irritancy is predominantly seen in acidic NSAIDs, and may be related in part to the observation that these compounds can accumulate in gastrointestinal epithelial cells due to the phenomenon of ‘ion trapping’ (16,17) and/or their ability to uncouple oxidative phosphorylation in epithelial cells (17). However, topical irritant properties of NSAIDs do not appear to make a major contribution to the ability of these agents to produce clinically significant gastric ulceration, since similar adverse effects are observed following parenteral or rectal administration of NSAIDs (18,19). A further feature of NSAIDs that likely contributes to the bleeding that is sometimes observed in patients chronically ingesting these drugs is their inhibitory effects on platelet aggregation through the suppression of thromboxane synthesis (20,21).

In experimental NSAID gastropathy there is convincing evidence that neutrophils have a role in producing mucosal injury (Figure 1). Work in the author’s laboratory and that of others suggests that administration of NSAIDs results in an increase in the number of neutrophils adhering to the vascular endothelium in the gastric and mesenteric microcirculation (22-26). Experimental NSAID gastropathy was markedly reduced in neutropenic rats (27,28), and treatment with monoclonal antibodies, which prevent neutrophil adherence to the vascular endothelium, markedly attenuated the severity of NSAID gastropathy in rats and rabbits (22, 29). Furthermore, cytoprotective prostaglandins prevented NSAID-induced leukocyte adherence (24,25).

NSAID-induced leukocyte adherence could contribute to gastric mucosal injury in two major ways (30). First, adherence of neutrophils to the vascular endothelium would likely be accompanied by activation of these cells, leading to the liberation of oxygen-derived free radicals and proteases. These substances could mediate much of the endothelial and
epithelial injury caused by NSAIDs. Second, neutrophil adherence to the vascular endothelium could lead to capillary obstruction, resulting in a reduction in gastric mucosal bloodflow and thereby predisposing the mucosa to injury. A reduction in gastric bloodflow following NSAID administration has been reported by many groups (31-33) and has been shown to occur after the appearance of ‘white thrombi’ in the gastric microcirculation (31). Whether neutrophils contribute to NSAID-induced gastric mucosal injury in humans has yet to be investigated.

The pathogenesis of small intestinal damage induced by NSAIDs is less well understood than the pathogenesis of gastric injury (Figure 2). There is reasonable evidence that the injury to the small intestine is produced through completely different mechanisms. The suppression of prostaglandin synthesis by NSAIDs does not appear to be a major contributor to the production of mucosal injury in the small intestine (34). There is evidence that bile contributes to NSAID enteropathy (35) and that enteric bacteria has a role (36). With respect to the latter, various antibiotics have been shown to reduce the severity of experimental NSAID enteropathy (35) and, in one clinical study, to decrease the epithelial permeability changes induced by an NSAID (37). Furthermore, the severity of NSAID enteropathy is markedly reduced in rats raised in germ-free conditions (38). It has been suggested that NSAIDs, which are acidic, are more likely to cause damage in the small intestine, similar to the topical irritant properties in the stomach. Whether an NSAID undergoes enterohepatic recirculation also appears to be a primary determinant of its potential to cause small bowel injury (39).

PROPHYLACTIC THERAPY

Before reviewing various strategies for developing NSAIDs that don’t cause gastrointestinal damage, it is worthwhile considering the question of whether the injury caused by existing NSAIDs can be prevented through prophylaxis with another agent. Essentially two approaches to prophylaxis have been taken. First, based on the belief that acid plays a role in the pathogenesis of NSAID gastropathy, it has long been suggested that suppression of acid secretion prevents the development of ulcers during NSAID therapy. However, while numerous studies have convincingly shown a beneficial effect of prophylaxis against duodenal ulcer formation, a significant protective effect against gastric ulcer formation has not been demonstrated (40,41). Similarly, omeprazole has been shown to reduce the incidence of NSAID-induced gastric erosions (42), but efficacy in preventing gastric ulcers has not yet been demonstrated.

The second approach to prophylaxis is the administration of exogenous prostaglandins to replenish the mucosal ‘supply’ of this substance caused by the NSAID. Misoprostol, a prostaglandin E₁ analogue, markedly reduces the incidence of NSAID-induced gastric (7) and duodenal ulcers (43). The former study was criticized for two main reasons. First, the
Figure 3) The central principle underlying the strategy of developing a selective, inducible form of cyclo-oxygenase isozyme (COX-2) inhibitors. A constitutively expressed form, COX-1, is constitutively expressed in many tissues, including the gastrointestinal tract. This form of COX produces prostaglandins that mediate mucosal defence, and its inhibition leads to tissue injury. COX-2 is induced at sites of inflammation and produces prostaglandins that mediate edema formation and pain. Selective suppression of COX-2 should result in reduced inflammation and pain without causing gastrointestinal injury. NSAID Nonsteroidal anti-inflammatory drug.

Definition of 'ulcer' used (a break in the mucosa of more than 3 mm in diameter) is questionable because this definition does not clearly distinguish true ulcers from erosions. Second, many patients at greatest risk of NSAID-induced ulcer or gastric bleeding were excluded from the study. A large study was undertaken, partly to address these two criticisms, to determine whether misoprostol can reduce the incidence of serious adverse reactions to NSAIDs, namely upper gastrointestinal bleeding, perforation and gastric outlet obstruction (8). Almost 9000 patients were enrolled in this randomized, double-blind, controlled study. Patients ingested NSAIDs and misoprostol, or NSAIDs and placebo over six months. The incidence of serious adverse effects in the placebo group was 0.947% (42 of 4433 patients). Misoprostol treatment significantly reduced the incidence of serious adverse effects to 0.567% (25 of 4406). Thus, one interpretation of these data is that prophylactic treatment with misoprostol significantly reduces the incidence of serious adverse gastrointestinal events in NSAID users. Another interpretation is that misoprostol failed in 60% of the patients taking this medication. Because of these results and the cost and the relatively high incidence of adverse effects (incidence of diarrhea is approximately 11%) associated with misoprostol, its widespread use for prophylaxis of NSAID gastropathy is of questionable value.

**GASTROINTESTINAL-SAFE NSAIDS: THE PAST**

Over the past 30 years a number of strategies have been taken to reduce the gastrointestinal injury caused by NSAIDs. These include coating the NSAID to prevent absorption in the stomach, parenteral administration and formulation of pro-drugs that require hepatic metabolism for the cyclo-oxygenase activity to be unmasked. While in each case claims have been made of reduced gastrointestinal irritancy, these modifications have had little impact on the incidence of severe adverse reactions. For example, sulindac is an NSAID that must undergo hepatic metabolism before becoming active and therefore is expected to have reduced topical irritant properties. However, little protective advantage over other NSAIDs is conferred by this formulation (55,56). Enteric-coated ASA may cause less acute, superficial injury to the mucosa (57) but still causes significant ulceration and bleeding (58). Gastric ulcers are also observed when NSAIDs are administered parenterally or intrarectally (18,19). Indeed, there is evidence that with intrarectal administration of NSAIDs, the risk of a significant adverse reaction is increased over that observed with oral administration (19).

While many NSAIDs have been introduced over the past 15 years that have been claimed to have reduced ulcerogenic potential, the long term clinical experience with these compounds has been disappointing. In part this was due to the widespread use of human volunteer studies to substantiate safety. Use of healthy human volunteers doesn’t always predict what happens in patients. For example, doses of drugs shown not to cause damage in healthy volunteers are not necessarily innocuous in patients (56,59). Problems also arise when the doses of NSAIDs tested in such studies are lower than that found to be effective for relieving pain and inflammation in the arthritic patient.
GASTROINTESTINAL-SPARING NSAIDs: THE PRESENT

There is a growing body of evidence supportive of the claims that two relatively new NSAIDs – etodolac and nabumetone – have markedly reduced capacities for causing gastric ulceration and bleeding compared with previous NSAIDs. Both nabumetone and etodolac have been reported to exert anti-inflammatory and analgesic properties comparable with the most widely prescribed NSAIDs (eg, naproxen, diclofenac). When tested in patients with rheumatoid arthritis or osteoarthritis, however, both compounds produce significantly less severe gastrointestinal complications, results that have been demonstrated in both endoscopic clinical trials and postmarketing surveillance studies. The latter, by virtue of the much larger sample size and typically longer period of drug ingestion, tends to provide more convincing results. For example, in a study in the United States, almost 11,000 patients taking nabumetone for up to one year for rheumatoid arthritis or osteoarthritis were studied (60). Only 11 serious events were reported during that period (0.1%), of which seven were gastrointestinal bleeding. In a German study, only two patients of 8865 treated with nabumetone for arthritis developed gastrointestinal bleeding (0.02%) (61), while in a study in the United States, ulcers were reported in only 13 of 1912 patients (0.7%) treated with nabumetone (62). In all these postmarketing surveillance studies, therefore, the incidence of serious gastrointestinal complications was well below the 2% to 4% range that has been documented for standard NSAIDs (6).

Similar studies with convincing results have been reported for etodolac. Many endoscopic studies have demonstrated reduced gastrointestinal damage compared with that seen with standard NSAIDs. Again, larger clinical trials and postmarketing surveillance studies provide more useful information because they tend to focus on serious adverse effects. In each of three postmarketing surveillance studies very low incidences of serious adverse effects were reported: six of 4947 patients (0.12%) treated with etodolac, of which three had ulcers (63); 11 of 3302 etodolac-treated patients (0.3%) (64); and fewer than 0.1% of patients receiving etodolac (63,64). Etodolac was also found to have other favourable properties compared with other NSAIDs, including the lack of interaction with plasma clearance of warfarin (65).

Why do etodolac and nabumetone produce less gastrointestinal injury while still being potent anti-inflammatory and analgesic agents? There are several possible answers. Because nabumetone is nonacidic it is expected to have reduced topical irritant properties. Nabumetone is also formulated as a pro-drug; the compound has very weak inhibitory activity on cyclooxygenase isofoms (COX), but is metabolized by the liver to 6-methoxy-2-naphthylacetic acid, which is a much more potent COX inhibitor. Unlike nabumetone, etodolac is an acidic compound and is not formulated as a pro-drug. As outlined above, enterohepatic recirculation of NSAIDs may be a key factor in the pathogenesis of NSAID enteropathy. Nabumetone and etodolac do not undergo en-

terohepatic recirculation. Another common feature of these two drugs that likely contributes to their good gastrointestinal tolerance is their weak inhibitory activity on gastrointestinal prostaglandin synthesis, despite being able to suppress prostaglandin synthesis potently at sites of inflammation (66-68). The reason for this discrepancy in effects on prostaglandin synthesis in different tissues is most likely related to differential potencies on the two known forms of COX. These drugs can be described as being 'COX-2 selective', although they do not exhibit the high degree of selectivity for this enzyme as shown with a number of recently developed compounds (outlined in more detail below). Etodolac is approximately 10 times more potent as an inhibitor of COX-2 than of COX-1 (69). For the active metabolite of nabumetone, the ratio is approximately 7:1 (70). It should be noted that these drugs were not specifically designed to be COX-2 selective inhibitors. Indeed, both compounds were developed before the existence of COX-2 was proven. However, it is possible that the marginal selectivity for COX-2 seen with these compounds may yield certain benefits over newer compounds that are more than 100-fold more selective for COX-2 than for COX-1.

GASTROINTESTINAL-SPARING NSAIDs: THE FUTURE

Highly selective COX-2 inhibitors: Considerable effort on the part of numerous pharmaceutical companies is being directed towards the development of highly selective inhibitors of COX-2. NSAIDs currently on the market show considerable variability in their potency as inhibitors of COX-2, but virtually all are far more potent inhibitors of COX-1 (53,54). As outlined above, the exceptions, nabumetone and etodolac, are somewhat more potent inhibitors of COX-2 and appear to have reduced gastrointestinal toxicity. However, it is possible that the retained ability of these drugs to suppress COX-1 contributes to some of their anti-inflammatory and analgesic properties. Some highly selective COX-2 inhibitors have been described, including L745,337 (70) and SC 58125 (71). In studies involving acute administration, these compounds did not cause as much damage as standard NSAIDs in the stomach of experimental animals (70,71). As discussed in more detail below, studies involving chronic administration of highly selective COX-2 inhibitors or, with the exception of a single study (72), involving administration to animals with pre-existing gut inflammation, have not been reported. Also, it is unclear whether these compounds will exhibit the same effectiveness in reducing pain and inflammation as existing NSAIDs. Appropriate clinical evaluation of highly selective COX-2 inhibitors is eagerly awaited.

The pursuit of a highly selective COX-2 inhibitor appears to be a sound approach to developing gastrointestinal-sparing anti-inflammatory drugs. Recently, numerous claims of new NSAIDs that spare the gastrointestinal tract have been made; because, for the most part, these drugs have not lived up to their advanced billing, a certain degree of scepticism is probably prudent until convincing clinical data are available. There are significant questions regarding the hypothesis that
highly selective COX-2 inhibitors will be effective analgesic and anti-inflammatory drugs but will spare the gastrointestinal tract of injury. These include the following.

- If COX-2 is primarily responsible for the production of prostanoids that mediate inflammation, pain and fever, it is unlikely that highly selective inhibitors of COX-2 will be more therapeutically effective than existing NSAIDs, since many of the existing NSAIDs are very effective inhibitors of COX-2 (53,54).

- It is possible that prostanoids produced via COX-1 contribute to inflammation, pain and fever. If this proves to be true, highly selective COX-2 inhibitors will be less effective anti-inflammatory, analgesic and antipyretic agents than existing NSAIDs, which block both forms of COX (eg, etodolac, nabumetone, diclofenac).

- COX-2 may produce prostanoids that carry out important physiological functions; therefore, highly selective COX-2 inhibitors may produce adverse reactions not seen with standard NSAIDs. For example, COX-2 has been shown to be expressed in human fetal membranes at term, and it has been suggested that it is the prostaglandins produced by this form of COX that are responsible for the initiation and maintenance of labour (73).

- Most gastrointestinal ulceration is associated with significant mucosal inflammation. In these circumstances it is likely that COX-2 is expressed.

Moreover, it is possible that the prostanoids derived from COX-2 in these circumstances are responsible for maintaining mucosal integrity and promoting healing. It is well known that NSAIDs retard the healing of ulcers (74). Matsuda and colleagues (75) recently reported that, in a mouse model of gastric ulcer, there was a profound increase in expression of mRNA for COX-2 during development of the ulcers, with a parallel rise in prostaglandin synthesis, but no changes in mRNA for COX-1 were detected. These observations suggest that COX-2 is an important source of prostaglandins when an ulcer is present. Similar results have been reported for human gastric tissue. COX-1 and COX-2 protein and mRNA were observed in both normal and ulcerated tissue, with COX-2 being more prominent than COX-1 in the mucosa of gastric ulcer patients (76).

- As outlined above, the damage produced by NSAIDs in the small intestine may occur through a mechanism different from that in the stomach; specifically, NSAID-induced enteropathy may not be related to suppression of prostaglandin synthesis. If this is the case, there is no reason to believe that a new NSAID that spares gastrointestinal prostaglandin synthesis will spare the small intestine of injury. The relatively selective COX-2 inhibitors currently on the market (etodolac, nabumetone) appear to spare the small intestine. However, this feature can be explained by other properties of these drugs, most notably that they do not undergo enterohepatic recirculation.

- Because platelets contain only COX-1, and it is this enzyme that is responsible for production of the pro-thrombotic substance thromboxane, a selective COX-2 inhibitor would not exert any antithrombotic activity. Thus, highly selective COX-2 inhibitors would not have the same use as ASA in the prophylaxis of stroke and myocardial infarction (77).

**Nitric oxide-releasing NSAID derivatives**: Nitric oxide is increasingly being recognized as a critical mediator of gastrointestinal mucosal defence. Interestingly, there is considerable overlap between the functions performed by prostaglandins and those performed by nitric oxide. For example, both modulate mucosal bloodflow, stimulate mucus release, facilitate repair of injury and inhibit activation of leukocytes. Like prostaglandins, nitric oxide or a nitric oxide donor can reduce the severity of experimental gastric damage (78). Based on evidence suggesting that reduced gastrointestinal bloodflow and activation of neutrophils play critical roles in the pathogenesis of NSAID-induced gastric injury, the present author proposed that the linking of a nitric oxide-releasing moiety to an NSAID may reduce its toxicity (Figure 4). If this derivation did not interfere with the ability of the NSAID to suppress cyclo-oxygenase activity, all the beneficial effects of the NSAID should ideally be retained. This hypothesis has now been proven in experimental models of

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**Figure 4** The principle underlying the development of nitric oxide-releasing nonsteroidal anti-inflammatory drug (NSAID) derivatives (NO-NSAIDs). By suppressing prostaglandin synthesis (cyclo-oxygenase activity), NSAIDs stimulate neutrophil adherence to the vascular endothelium, reduce mucosal bloodflow, and inhibit mucus and bicarbonate secretion, all of which contribute to ulcer development. Nitric oxide released from the NO-NSAID can counteract each of these effects of the NSAID moiety, thereby preventing mucosal injury. However, the nitric oxide moiety does not interfere with cyclo-oxygenase suppression, and therefore does not affect the ability of the compound to reduce inflammation, fever or pain, or to inhibit platelet aggregation.
NSAID-induced gastroenteropathy. Nitric oxide-releasing derivatives of flurbiprofen, ketoprofen and diclofenac (collectively referred to as ‘NO-NSAIDs’) have been shown to spare the gastrointestinal tract, even when given repeatedly over several weeks (79–81). Each of these compounds has anti-inflammatory activity comparable with that of the parent NSAID, and can suppress gastric prostaglandin synthesis as effectively. NO-NSAIDs also exhibit antiplatelet activity comparable with that of their parent compounds (82). These derivatives inhibit both COX-1 and COX-2, with similar selectivity as the parent NSAIDs, without being metabolized, indicating that these derivatives are not pro-drugs (83). Despite evidence that these agents generated nitric oxide in the rat in vivo, these compounds did not significantly affect systemic arterial blood pressure (79,80).

Concerns were noted above regarding the potential detrimental effects of selective COX-2 inhibitors in situations where the gastrointestinal mucosa is inflamed; there is the possibility that inhibition of COX-2 expression would lead to inhibition of the prostaglandins (which may perform important physiological functions) produced via this enzyme. Because NO-NSAIDs block COX-1 and COX-2 as effectively as the parent NSAIDs (83), the same concerns can be raised about this class of compounds. However, studies in animal models of chronic colitis (81) and gastric ulcer (72) have been performed in which NO-NSAIDs were administered daily for one week. In the case of colitis, the NO-NSAID did not cause an exacerbation of mucosal injury and inflammation, whereas standard NSAIDs did (81). In the case of gastric ulcer, daily treatment with an NO-NSAID accelerated healing in this rat model (72).

Unlike selective inhibitors of COX-2, NO-NSAIDs are capable of inhibiting platelet thromboxane synthesis and therefore platelet aggregation. The antithrombotic effects of a nitric oxide-releasing derivative of ASA were recently evaluated in the rat. This compound was found to have markedly enhanced antithrombotic effects without causing significant gastric damage or affecting systemic blood pressure (84). Thus, a nitric oxide-releasing ASA derivative may be suitable for long term prevention of myocardial infarction and stroke. ASA is increasingly used as the parent NSAIDs (83), the same concerns can be raised above this strategy still need to be addressed. An alternative approach, which involves the linking of a nitric oxide-releasing moiety to standard NSAIDs, has shown great promise in experimental models, but has not cleared the hurdle of demonstrated efficacy without toxicity in a clinical setting. When one considers the developments that have been made in the very recent past, and the promising developments being made at present, it is entirely possible that in the not-too-distant future, NSAID-induced gastroenteropathy will soon be a thing of the past.

REFERENCES

SUMMARY
While it has seemed unlikely that the ulcerogenic properties of NSAIDs could be separated from their beneficial effects because both are inextricably linked to suppression of prostaglandin synthesis, there are encouraging developments suggesting that gastrointestinal-sparing NSAIDs are attainable. Newly developed NSAIDs that show some selectivity for the inducible form of prostaglandin synthase (COX-2), such as etodolac and nabumetone, have greatly reduced gastrointestinal toxicity in treating rheumatoid and osteoarthritis. Development of highly selective COX-2 inhibitors may be a rational approach to developing potent anti-inflammatory agents that spare the gastrointestinal tract, although a number of concerns about this strategy still need to be addressed. An alternative approach, which involves the linking of a nitric oxide-releasing moiety to standard NSAIDs, has shown great promise in experimental models, but has not cleared the hurdle of demonstrated efficacy without toxicity in a clinical setting. When one considers the developments that have been made in the very recent past, and the promising developments being made at present, it is entirely possible that in the not-too-distant future, NSAID-induced gastroenteropathy will soon be a thing of the past.

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