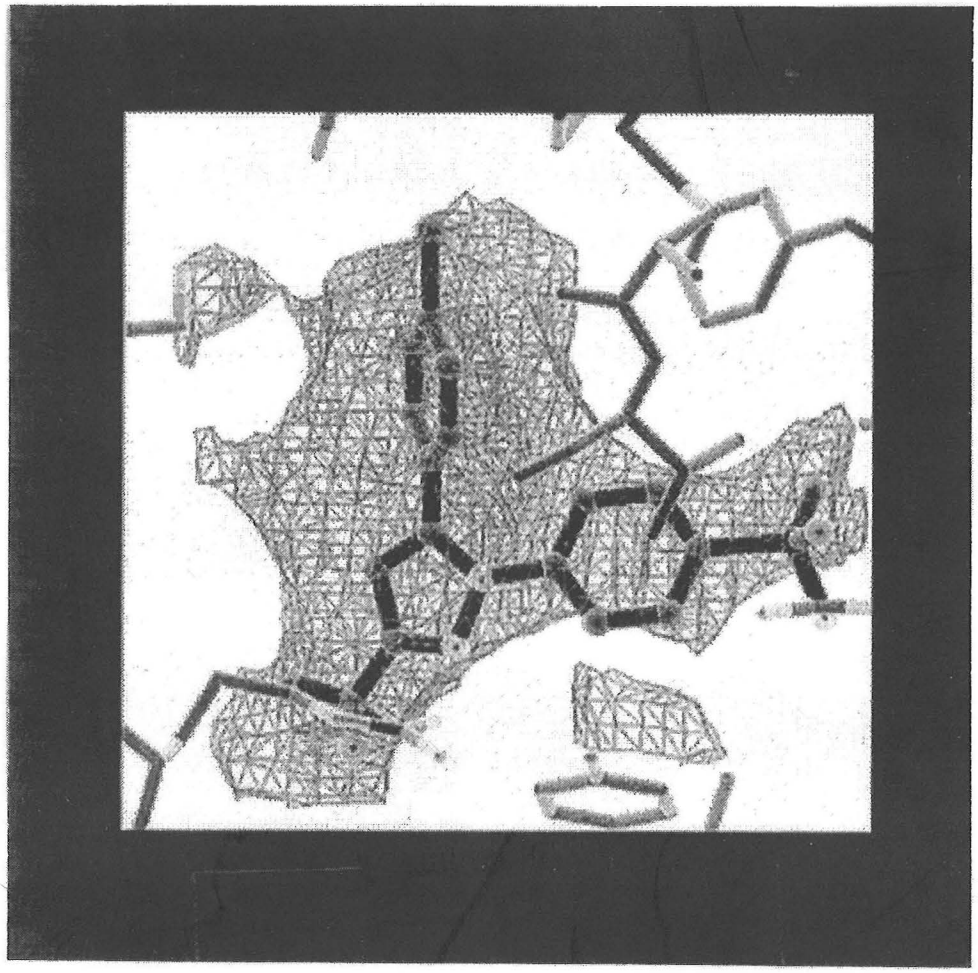
INTERNAL MEDICINE GRAND ROUNDS

August 19, 1999

Update on the Gastrointestinal Effects of the Non-Steroidal Anti-Inflammatory Drugs



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This is to acknowledge that Byron Cryer, M.D. has disclosed financial interests or other relationship with commercial concerns related directly or indirectly to this program.

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Front Cover:

X-ray crystallograph of active site of cyclooxygenase-2. The specific COX-2 NSAID, celecoxib, is shown in association with the COX-2 active site. (Kurumbail et al. *Nature* 1996;384:644-648)

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications in the world. The success of the NSAID market is attributable, in part, to the effectiveness of these drugs as anti-inflammatory and analgesic agents. Furthermore, the diseases for which NSAIDs are prescribed are quite common (**Figure 1**).

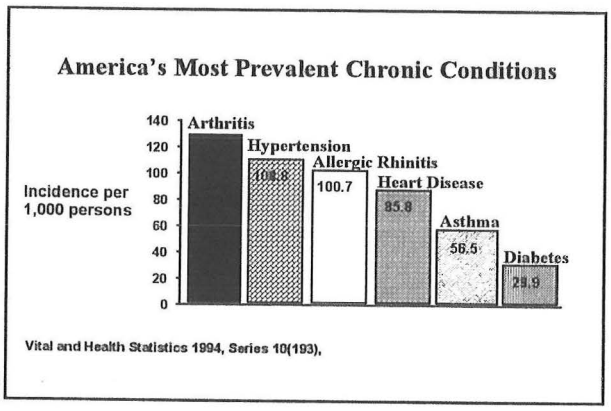


Figure 1.

While overall, NSAIDs are safe drugs and only a small percentage of patients experience adverse gastrointestinal (GI) events that result in serious complications, the GI complications are their major side-effects and limit their universal applicability. The incidence of significant GI complications has been estimated to be 1 to 4 % per year [1-4], numbers that seem relatively low at first glance. However, because NSAID use is so widespread, approximately 100 million people world wide, these small percentages of complications translate into significant morbidity and mortality annually, making NSAID-induced gastrointestinal complications a significant health hazard.

It is now clear that most NSAIDs can damage the gastrointestinal tract at multiple levels, namely, at the esophagus, stomach, small and large intestines. Additionally they can impair platelet function systemically, with a consequent increase in bleeding from a variety of gastrointestinal and non-gastrointestinal lesions. Since the major toxic effects of NSAIDs are within the gastrointestinal tract, the majority of the discussion that follows will concentrate primarily on the gastrointestinal consequences of NSAID use and strategies that may be possibly employed to reduce their gastrointestinal toxicity.

ADVERSE GASTROINTESTINAL EFFECTS OF NSAIDs

Adverse gastrointestinal effects of NSAIDs can be characterized in a number of ways ranging from mild dyspepsia and heartburn to severe life threatening complications. Much of the difficulty in attempting to precisely quantify adverse events attributable to NSAIDs is a consequence of the number of ways in which a NSAID-induced adverse outcome is defined. Symptoms, endoscopic mucosal lesions, and most importantly, serious GI complications have all been ways in which the magnitude of NSAIDs' effects have been assessed. The extent of the problem will vary depending on the outcome being assessed.

Symptoms

By far, the most common adverse effect of NSAIDs is dyspepsia and/or heartburn that may occur any where from 5 to 50% of patients taking NSAIDs [5,6]. The range in variability in reported rates of dyspepsia attributable to NSAIDs is largely due to

differences in study design, patient populations and study criteria used to define dyspepsia. However, contrary to popular perceptions, the specific symptom of dyspepsia alone, does not appear to be extremely common. On average, about 10 to 12% of patients will experience dyspeptic symptoms while taking a NSAID [7,8]. Moreover, only 5 to 15% of rheumatoid arthritis patients will discontinue their NSAID within the first six months because of dyspepsia [6].

There is also no clear correlation between NSAID-induced gastrointestinal symptoms and objectively definable gastrointestinal outcomes such as ulcers or complications. For example, in a group of NSAID-taking patients with GI ulcers on endoscopy, only 45% experienced dyspeptic symptoms [9]. In a more recent evaluation of a large data base of arthritis patients taking NSAIDs who presented with NSAID-induced complications such as bleeds or perforations, only 20% had gastrointestinal symptoms prior to presentation [10]. Thus, the absence of symptoms in a NSAID user is not equivalent to a reduced risk for NSAID-induced complications. In contrast, the presence of symptoms in NSAID users is also not a good predictor of NSAID complications. Many patients with mild dyspepsia while taking NSAIDs will have normal endoscopic exams. However, the presence moderate to severe dyspepsia in a NSAID user, strongly predicts endoscopic ulcers or multiple erosions. For example, NSAID-taking arthritis patients who have dyspepsia have a higher frequency of GI complications than NSAID-taking arthritis patients without dyspepsia [8]. In another study, NSAID-using patients who had continued dyspepsia despite use of cimetidine had a 31-fold increased probability of ulcer [11]. Patients with persistent symptoms at the end of the first month of NSAID use also appear to have increased risk of gastric ulceration [11]. One can conclude that management of NSAID-induced symptoms and management of the risks associated with NSAIDs are conceptually two different therapeutic strategies as the presence or absence of symptoms while on NSAIDs does not predict risk. Other characteristics (discussed later) should be used to identify individuals at high risk for NSAID complications.

Mucosal Lesions

The spectrum of NSAID-induced GI mucosal injury ranges from a combination of minor gastroduodenal lesions such as hemorrhages and erosions to more significant consequences such a bleeding and perforation and death.

NSAID Gastropathy. A very common initial event occurring soon after ingestion of a NSAID is acute topical damage in the gastrointestinal surface epithelium which results in numerous endoscopically-detectable hemorrhages and erosions[5]. This process occurs over several minutes to hours. This combination of acute hemorrhages and erosions is classified as "NSAID gastropathy" and is mostly asymptomatic. NSAID gastropathy is an acute phenomeon which can be endoscopically seen in 80% of NSAID users. It has a tendency to improve with persistent NSAID exposure and, most importantly, does not closely correlate with the development of mucosal ulceration [3,12,13], or of greater concern, the risk of serious NSAID complications[5,14].

Endoscopic Ulceration. Numerous prospective studies have identified an average prevalence of 15 to 25% for NSAID-induced

gastric ulcers and 5 to 8% for NSAID-induced duodenal ulcers after 2 to 6 months of NSAID therapy **(Table 1)** [5,9,15,16].

Incidence of Endoscopic NSAID-Induced Ulceration

	Mean	Range
Gastric Ulcer	15 %	10 to 30%
Duodenal Ulcer	5 %	4 to 10 %
Clinically Significant Ulcers	2%	1 to 4%

Table 1.

However, as stated earlier, the development of ulcers can not be predicted by the presence of abdominal pain as the majority of NSAID-induced ulcers are asymptomatic.

Gastrointestinal Complications

Since about 10 to 20% of NSAID users will have endoscopic ulceration, but only 1 to 2% of chronic NSAID users have significant complications **(Table 1)**, it can be reasonably estimated that approximately 1 of 10 endoscopic ulcers will progress to complication such as a bleed or a perforation. On average, a NSAID user has approximately a four to eight fold greater likelihood of developing a gastrointestinal complication than a non-NSAID user. However, the magnitude of this increased risk is not uniform. It varies with the specific NSAID, medication dose, and with patient risk factors.

Risk Factors for Gastrointestinal Complications

Certain groups of NSAID-taking patients appear to be at greater risk for development of NSAID-ulcer complications. These high-risk groups have been consistently identified through, prospective randomized studies, multiple case-control population and data base studies **(Table 2).** [3,8,12,17]. Because of this high risk for NSAID-induced ulcers be given greater consideration for strategies to prevent or to reduce ulceration **Table 2.**

Risk Factors for NSAID Induced-Ulcers

Definite Risk Factors
- Prior ulcer disease
- Prior gastrointestinal complication
- Advanced age
- Concomitant use of corticosteroids
- Concomitant use of anticoagulants
- High doses or multiple doses of NSAIDs
- Co-morbid diseases

Possible Risk Factors
- Ethanol use
- Smoking
- Gender
- H_2-receptor antagonists
- *Helicobacter pylori*

Table 2.

Prior Ulcer Disease. The most significant risk factor for a NSAID-induced complication is a history of prior peptic ulcer disease or a prior ulcer complication, factors that increase the risk of NSAID-induced GI events by two to three fold [4,8,18]. A single prospective study of almost 9,000 patients taking NSAIDs showed that those with a history of prior peptic disease were 2.3 times more likely to have a significant complication [4]. It should also be noted that a history of prior

peptic disease increases the risk of an ulcer in those patients not taking NSAIDs [8,12,17]. Prior peptic disease and NSAID therapy appear to be independent risk factors for gastrointestinal bleeding [17].

Age. There are also epidemiologic data suggesting that advancing age is an independent risk factor for an NSAID complication. Although there does not appear to be a threshold age where risk dramatically increases, the risk increases linearly with advancing age [7,17,19], at a rate of approximately 4% increase in risk per year [8]. For example, a case-control study indicated that for patients taking NSAIDs, the risk of a GI complication was increased 1.6 fold, 3.1 fold and 5.6 fold for patients ages 50-59 years, 60-69 years, and 70-80 years, respectively [20] **(Figure 2)**.

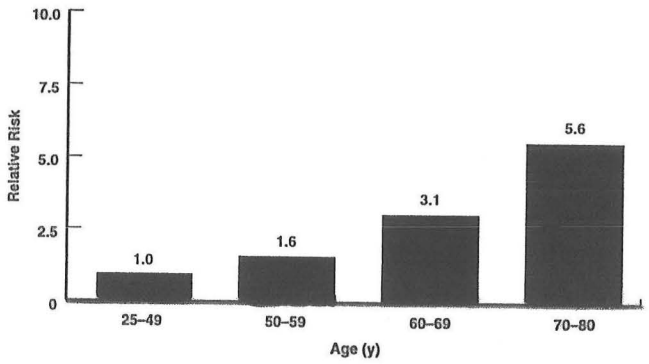


Figure 2. Relative risk by age for developing GI bleeding or perforation in NSAID users. Data from Lancet [17].

Corticosteroids. The use of corticosteroids alone does not independently cause ulcer disease [21]. The use of these drugs in combination with NSAIDs, however, increases the risk of a gastrointestinal complication approximately two fold [8,17,21].

Anticoagulants. Concomitant anticoagulant use also increases the risk of NSAID-induced ulcer bleeding [17,22]. This increase in risk ranges from 2-fold to 12-fold, depending on the patient population.

NSAID Dose. It has been clearly shown in epidemiologic studies that as the dose of a NSAID increases, the risk of ulcer complications also increases in a parallel manner [12]. This dose-response relationship is seen across all classes of NSAIDs. Similarly, concomitant therapy with more than one NSAID approximately doubles the risk of a gastrointestinal complication [17].

Comorbid Illnesses. Many studies have suggested that the presence of comorbid illnesses increase risk of NSAID-induced ulceration [4,8]. A 6-month evaluation of patients taking NSAIDs indicated that a history of heart disease increases the risk of a complication by 80%. Furthermore, recent data suggest that the type of arthritis may influence risk for NSAID complications. According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 1.3% of rheumatoid arthritis patients and 0.7% of osteoarthritis patients will have a serious gastrointestinal complication over one year of taking NSAIDs [23].

Risk According to Type of NSAID. In the past it was stated that the risk of ulceration was equivalent for all types of NSAIDs. However, more recent epidemiologic data have stratified various types of NSAIDs by risk of NSAID-induced ulcer bleeding or perforation [3,18,24,25]. Across studies ibuprofen consistently has been associated with the lowest risk of GI events.

Shown in **Table 3** are the results of a recent meta-analysis that assessed the effect of different types of NSAIDs on serious gastrointestinal complications, using ibuprofen as the reference standard [24].

Risks of Serious GI Events With NSAIDs

Comparator	No. Studies	Pooled Relative Risk
Ibuprofen	---	1.0*
Fenoprofen	2	1.6
Aspirin	6	1.6
Diclofenac	8	1.8
Sulindac	5	2.1
Diflunisal	2	2.2
Naproxen	10	2.2
Indomethacin	11	2.4
Tolmetin	2	3.0
Piroxicam	10	3.8
Ketoprofen	7	4.2
Azapropazone	2	9.2

*Reference category for calculating relative risk

Table 3. Results of a meta-analysis of 12 studies assessing the association of different NSAIDs with serious gastrointestinal complications. Data from Br. Med. J.[24]

These data indicate a non-statistically significant trend for ibuprofen being less likely to cause serious gastrointestinal complications than all other NSAIDs. However, ibuprofen's ranking should be interpreted with caution as it is frequently taken as an over-the-counter preparation and at doses that have lower therapeutic equivalences than other NSAIDs. Thus this apparent low ranking of ibuprofen may be a reflection of dose of NSAID rather than type of NSAID. Although not evaluated in the meta-analysis shown in **Table 3**, other NSAIDs that might be considered as low risk include the nonacetylated salicylates, nabumetone, etodolac, and the recently introduced COX-2 inhibitors (see later discussion).

Low-Dose Aspirin. Low daily doses of aspirin, usually 325 mg/day or less, are very commonly prescribed for prevention of cardiovascular and cerebrovascular diseases. In placebo-controlled studies, low-dosage aspirin therapy increases risks of GI bleeding[26] and increases likelihood of hospitalization for ulcers [27]. Moreover, aspirin doses as low as 75 mg/day have been associated with increased risk of GI bleeding [28]. Although it was suggested in many of these trials that low-dose aspirin may be associated with an increased risk of GI toxicity, there are few data as to the degree of risk. One placebo-controlled study of low-dose aspirin for prevention of cerebrovascular events reported increased rates of GI bleeding with aspirin in comparison to placebo [29]. Over the course of four years, more that 3400 patients were randomized to placebo, aspirin (300 mg/day) or to aspirin (1200 mg/day). With these doses, there was a significant dose-response relationship between aspirin dose and GI bleeding **(Figure 3)**.

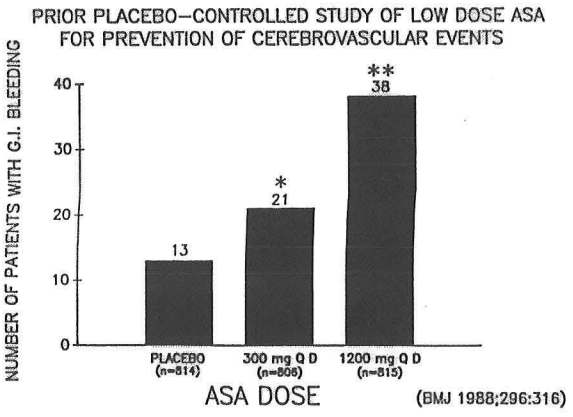
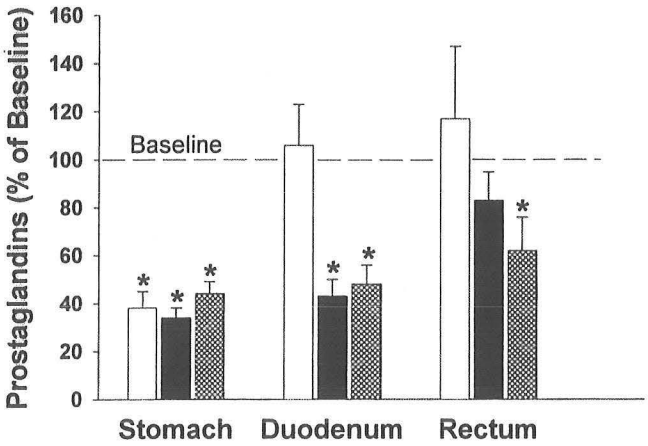


Figure 3.

Furthermore, these data suggest that aspirin, at a dose of 300 mg/day, is significantly associated with significant GI events.

These findings have led to investigations of the effects of lower aspirin doses in search of an effective aspirin dose that might be without GI ulceration [30,31]. We recently evaluated the GI effects on the GI tract of aspirin daily doses of 10, 81 and 325 mg in healthy subjects who were administered aspirin over 3 months [31]. As seen in **Figure 4,** all aspirin doses significantly inhibited gastric mucosal prostaglandin concentrations. Furthermore, gastric ulceration was endoscopically observed with aspirin 10 mg/day. With regard to clinically relevant gastrointestinal outcomes, aspirin has been associated with perforations and bleeds of both the upper and lower GI tracts [32,33].



Effects of aspirin treatment at 10 (□; n = 8), 81 (■; n = 11), or 325 (▨; n = 10) mg/day on mucosal PG concentrations in the stomach (gastric body and antrum combined), duodenum (bulb and postbulbar duodenum combined), and rectum expressed as a percentage (±SEM) of the baseline value. *Dashed line* represents baseline mucosal PG concentrations before exposure to aspirin (see text). Data at 1.5 and 3 months and data in the various mucosal regions have been averaged. In the rectum, n = 7 for each aspirin-dosage group, and no biopsy specimens were taken at 1.5 months. *$P < 0.05$ vs. baseline by the Wilcoxon signed-rank test.

Figure 4.

Other Potential Risk Factors. There are several other risk factors for NSAID-induced GI complications that have been proposed but remain unproven. Alcohol consumption increase the risk of a NSAID-induce GI complication in some studies, but not in others. Two case control studies suggested increased complications in patients with cirrhosis [34] or those who consume more than five alcoholic beverages per day [35]. While cigarette smoking has been suggested as a risk factor for NSAID-induced ulcer complications, the available data do not support this [4,34]. In spite of earlier reports there does not appear to be a greater risk for females taking NSAIDs to have a GI complication [34,36]. The data on the contribution of *Helicobacter pylori* towards NSAID risk are conflicting. The majority of the data suggest that *H. pylori* infection contributes no additional risk. The interaction between these two is discussed in more detail later.

It is not uniformly agreed on whether the presence or the lack of GI symptoms increase the risk of NSAID-associated ulcer complications. On the one hand, the data are fairly consistent in the observation that 60 to 80% of patients on NSAIDs who present with a gastrointestinal complication have no prior symptoms [23,37]. On the other hand, patients with arthritis who are taking NSAIDs and have dyspepsia have a higher frequency of GI complications than patients without dyspepsia [8]. To further complicate this issue, data form a large data base of arthritis patients indicate that patients taking H_2-receptor antagonists and antacids with NSAIDs have a 2-fold greater risk of a GI complication than those not taking these medications [6,8]. H_2-receptor antagonists are effective for treating NSAID-induced dyspepsia, but they do not decrease the risk of NSAID ulcer complications. Thus,

dyspeptic NSAID-taking patients who also take H_2-receptor antagonists continue to be at risk for NSAID ulcers but are rendered asymptomatic. Without the H_2-receptor antagonists these patients might have presented for early evaluations of their symptoms.

Other Gastrointestinal Consequences of NSAIDs

Gastroesophageal Reflux Disease. Clinically there is a pervasive belief that NSAID use increases gastroesophageal reflux disease (GERD) and the principal symptom of GERD, heartburn [38]. However, there is no documentation for this concept in the published literature. In one previous double-blind, placebo-controlled study of the effect of the NSAID naproxen on gastroesophageal reflux in normal volunteers, naproxen did not induce reflux in most healthy subjects [39]. While the only available data suggest that NSAIDs do not increase GERD in *healthy* subjects, we recently questioned whether NSAIDs might increase acid reflux in patients with established GERD.

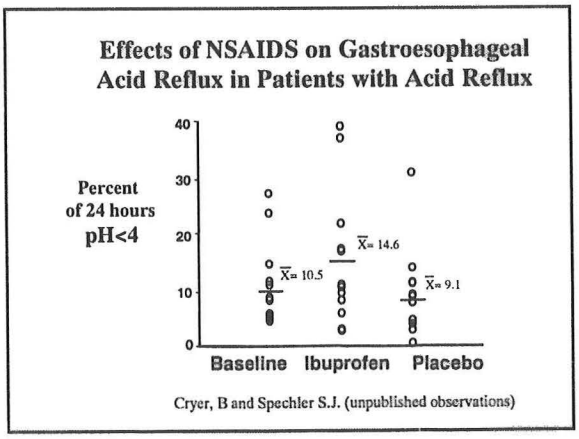


Figure 5.

As shown in **Figure 5,** in a group of patients with established GERD (esophageal pH<4 for greater than 5% of a 24-hour period) ibuprofen (800 mg t.i.d) increases acid reflux compared to baseline values and compared to placebo. The mechanism for increased esophageal acid reflux in GERD patients is unclear. Nevertheless, increased acid reflux with NSAIDs supports the clinical perception of this association.

NSAIDs' Other Gastrointestinal Manifestations. In addition to the GI consequences of NSAIDs mentioned previously, there are other NSAID-related complications that occur in other areas of the GI tract. Serious complications of NSAID use in these other area that are far less commonly recognized include pill esophagitis, small-bowel ulceration, small bowel strictures, diverticular disease and exacerbations of inflammatory bowel disease [40].

MECHANISMS OF TOXICITY OF NSAIDs

Irrespective of site of GI damage, the mechanisms through which NSAIDs cause injury are similar throughout the GI tract and can be grouped into two categories: 1) those dependent on inhibition of the enzyme, cyclooxygenase and, 2) those independent of cyclooxygenase inhibition. The later category is composed of local mucosal toxic processes.

Topical Effects

After NSAID exposure, the initial type of injury is a direct topical effect. Within a few minutes of NSAID ingestion, denudation of surface epithelial cells and increased mucosal permeability can be observed. NSAIDs are weak organic acids which at the usual acidic gastric pHs are

unionized, thus allowing them to be freely lipid soluble. Once lipid soluble, NSAIDs diffuse across gastric mucosal epithelial cell membranes into the intracellular cytoplasm with its pH of close to 7. Intracellular NSAIDs then ionize, become water-soluble and, are "trapped" within the cells. Because of intracellular trapping, NSAIDs accumulate intracellularly at very high concentrations causing local toxic effects. The topical effects of NSAID are likely the major mechanism responsible for the clinical phenomenon of NSAID gastropathy described earlier.

Cyclooxygenase inhibition

The beneficial effect of NSAIDs to decrease systemic inflammation and their deleterious effects in the gastrointestinal tract are both, in part, related inhibition of the enzyme, cyclooxygenase (COX). Within the GI tract, NSAID associated reduction in mucosal prostaglandin concentrations is the major contributor towards NSAID mucosal toxicity. COX converts arachidonic acid to prostaglandins and thromboxane (**Figure 6**).

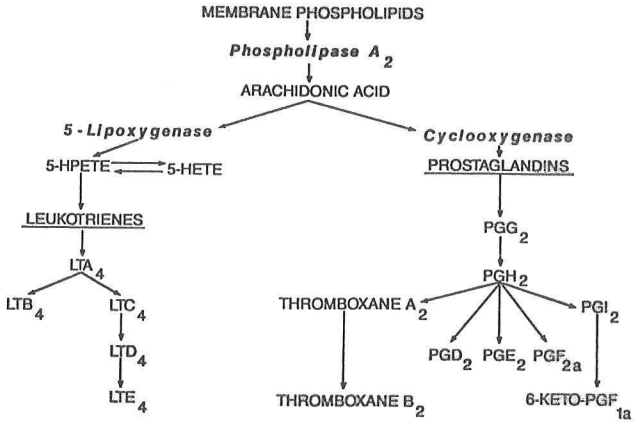


Figure 6.

Prostaglandins participate in a variety of activities, including mediation of inflammatory responses and regulation of renal blood flow. GI prostaglandins protect against injury by stimulating mucosal bicarbonate and mucus secretion, and by increasing mucosal blood flow [41]. Among these, reduction in blood flow is thought to be the mechanism most responsible for NSAID-induced GI injury. In response to NSAIDs, reduction in blood blow occurs as a result of adherence of neutrophils to vascular endothelium in the gastric and mesenteric microcirculations via increased expression of intercellular adhesion molecules (ICAMs)[42].

Nearly all NSAIDs inhibit COX and, therefore, prostaglandin concentrations. Aspirin, by acetylation of COX, inhibits this enzyme irreversibly, while all other NSAIDs inhibit COX in a reversible, concentration-dependent manner. With aspirin, when COX is irreversibly inhibited, the capacity for prostaglandin synthesis does not return to normal until new enzyme can be synthesized. This may explain, why aspirin, in comparison to the other NSAIDs remains one of the most potent inhibits of prostaglandin synthesis. A non-aspirin NSAID which does not suppress gastric prostaglandins is etodolac [43,44]. The non-acetylated salicylates such as salsalate also do not lower gastrointestinal prostaglandins and do not cause significant gastric injury [45].

Relationship of *Helicobacter pylori* to NSAID-Induced Ulcers

Many characteristics of NSAID-induced ulcers and *H. pylori*-related ulcers suggest that these two types of ulcers are separate pathophysiologic entities. First, NSAID-

induced ulcers occur in persons not infected with *H. pylori* [46]. Anatomic location, histologic findings, patterns of recurrence and symptoms also distinguish the two types of ulcers. **(Table 4)**. In patients in whom ulcers develop in association with NSAID use, gastric ulcers are about twice as common as duodenal, whereas *H. pylori*- related ulcers are more frequently duodenal. *H. pylori* nearly always is associated with a chronic active gastritis, whereas histologic gastritis is not an expected feature of NSAID-induced ulcer [47].

Differences Between NSAID-Induced and *H. pylori*-Induced Ulcers

	NSAID-Induced	*H. pylori*
Site of damage	Gastric twice as often as duodenal	Duodenal more often than gastric
Histology	Surrounding mucosa normal (does not have increase in gastritis)	Surrounding mucosa inflamed (chronic active gastritis)
Symptoms	More often asymptomatic	Usually pain and/or dyspepsia
Pattern of Recurrence	Does not recur if NSAID is stopped	Recurs if *H. pylori* is not eradicated

Table 4.

Experimental administration of a NSAID does not cause a histologic gastritis [48]. Another notable difference between the two types of ulcers is that *H. pylori* ulcers, if the infection persists untreated, will recur. However, once NSAIDs are stopped the ulcers do not recur. Furthermore, NSAIDs decrease prostaglandin synthesis, and *H. pylori* increase the synthesis of prostaglandins [46]. Finally, data from multiple epidemiologic trials confirm that *H. pylori* infection is not a required co-factor for NSAID-associated ulcers[46,49].

Evidence that *H. pylori* eradication may reduce the incidence of NSAID-associated ulcers is relatively limited. In one controlled study of eradication of *H. pylori* infections prior to starting patients on naproxen, eradication of *H. pylori* was associated with a significant reduction if the occurrence of NSAID-induced endoscopic ulcers [50]. The previously mentioned study was one which evaluated patients who had never taken NSAIDs. However, *H. pylori* infection may play a different role in ulcer formation among chronic NSAID users. Among chronic NSAID users, the prevalence of *H. pylori* infection appears to be similar in those with or without ulcers. Furthermore, in chronic NSAID-taking patients eradication of *H. pylori* does not reduce the rate of subsequent bleeding ulcers when compared to those not eradicated of their *H. pylori* infections [51]. Finally, several large endoscopic studies suggest that *H. pylori* infection does not affect NSAID-ulcer healing rates or NSAID-ulcer recurrence rates [52,53].

THERAPY FOR NSAID-INDUCED ULCERS

Therapy for NSAID-induced ulcers needs to be tailored depending on whether one is attempting to heal an already established ulcer associated with NSAIDs or attempting to prevent a NSAID-induced from developing. Since therapeutic strategies differ, preventative strategies and healing strategies will be discussed separately.

Prevention of NSAID-Induced Ulcers

Earlier attempts to lower gastroduodenal toxic effects seen with aspirin and other NSAIDs was with prodrugs, drugs which, in their orally administered form, are inactive as antiinflammatory agents and COX inhibitors (e.g., sulindac). These types of drugs require hepatic metabolism to active products which

suppress inflammation and prostaglandins. Unfortunately, prodrugs disappointingly continue to be associated with ulceration as do, enteric-coated preparations, and suppositories. Consequently a major therapeutic focus has been to use other drugs that when co-administered with NSAIDs, will protect against mucosal ulceration. Since the majority of patients who chronically take NSAIDs will never develop clinically significant ulceration, the only candidates for co-therapy or therapy with a "safer NSAID" are those considered as high risk for NSAID-induced ulcers (Table 1). Possible therapeutic strategies are discussed in the following section.

H_2-Receptor Antagonists. A number of studies have evaluated whether a H_2-receptor antagonist, when co-administered with a NSAID, can prevent NSAID-induced ulcers [54-57]. These studies have consistently found that all four H_2-receptor antagonists, namely cimetidine, nizatidine, ranitidine and famotidine, when used as co-therapeutic agents at their usual doses, do not prevent NSAID-associated gastric ulcers. Since most NSAID-induced ulcers are gastric rather than duodenal, and since one can not predict which type of NSAID-induced ulcer will develop, H_2-receptor receptor antagonists are not ideal drugs for NSAID-ulcer prophylaxis. However, when one of the H_2-receptor antagonists, famotidine, is administered at a "high" dose (40 mg twice daily), NSAID induced duodenal and gastric ulcers are effectively reduced (**Figure 7**)[58].

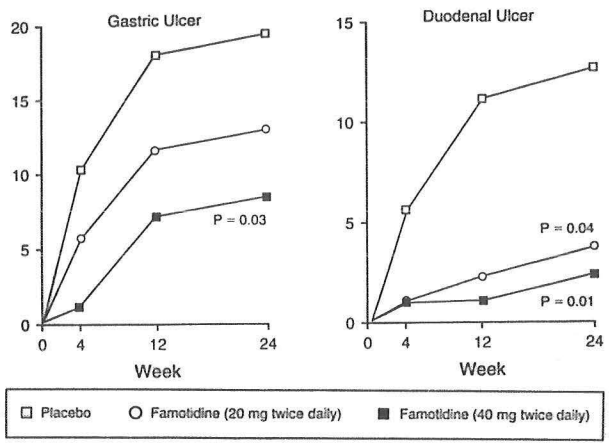


Figure 7.

Prostaglandins. A number of orally-administered synthetic prostaglandins (PGs) have been evaluated experimentally for their ability to prevent NSAID-mucosal damage. However, only one of these, misoprostol, the synthetic PGE_1 analogue, has been shown to effectively reduce NSAID-induced gastric and duodenal ulceration [15,59-62]. The first major trial which convincingly demonstrated that misoprostol was effective in the prevention of NSAID-induced gastric ulcers was a multicenter trial of 420 patients with osetoarthritis [60]. In this study, patients were randomized to receive either placebo, misoprostol (100 μg four times daily) or misoprostol (200 μg four times daily). At the end of three months, gastric ulcers had developed in 12.3% of the placebo-treated patients compared to only 4.2% and 0.7% of patients treated with the lower doses of misoprostol, respectively. The disadvantage to misoprostol is that it may cause dose-related diarrhea and is not effective in treating the dyspepsia associated with NSAIDs. Less frequent dosing of misoprostol, 200 μg administered twice daily, is effective for preventing NSAID-induced ulcers while being associated with a lower incidence of diarrhea [15]. In a recent direct comparison of

misoprostol and ranitidine within the same study, the two drugs were equal in efficacy for prevention of NSAID-induced duodenal ulcers while misoprostol was significantly more effective than ranitidine in prevention of endoscopically diagnosed gastric ulcers [61].

All of the previously mentioned trials of prophylactic co-therapies have all involved assessment of ulcers which were defined endoscopically, many of which were asymptomatic. The more clinically relevant question is whether prophylaxis against NSAID-ulcers with any drug will prevent ulcer bleeding or perforation. In a large multicenter trial enrolling almost 9000 NSAID-taking arthritis patients who were treated with either misoprostol or placebo, prophylaxis with misoprostol was associated with a 40% reduction in NSAID-related ulcer complications **(Figure 8)**[4].

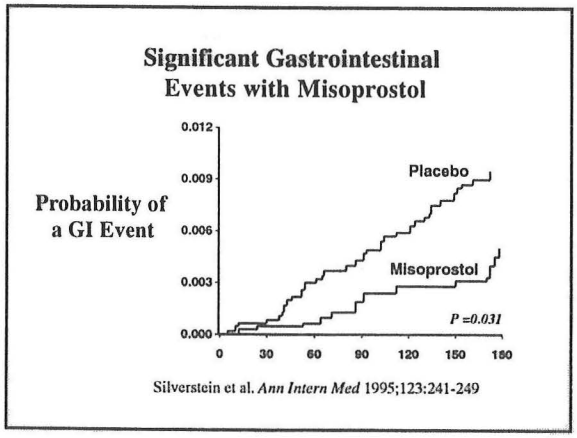


Figure 8.

Even though misoprostol will effectively reduce complications, a recent meta-analysis estimates that 264 chronic NSAID-taking patients of average risk would need to be treated with misoprostol for six months to prevent one GI complication [63]. However, in high-risk NSAID users the use of misoprostol is cost effective and therefore seems appropriate [64].

Proton Pump Inhibitors. Use of proton-pump inhibitors (omeprazole and lansoprazole) for prophylaxis of NSAID ulcers has become an attractive strategy for many clinicians. Support for this practice comes from two recent studies demonstrating omeprazole to be more effective than ranitidine [65] or twice daily misoprostol [41] for the prevention of NSAID-induced endoscopic gastric and duodenal ulcers. In the first study of 432 patients with a past history of endoscopically confirmed ulcers (i.e., high-risk patients) were randomized to receive omeprazole 20 mg daily or ranitidine 150 mg twice daily along with their chronic NSAIDs[65]. After six months of treatment, gastric and duodenal ulcers recurred significantly less frequently in those treated with omeprazole compared to those treated with ranitidine **(Figure 9)** [65].

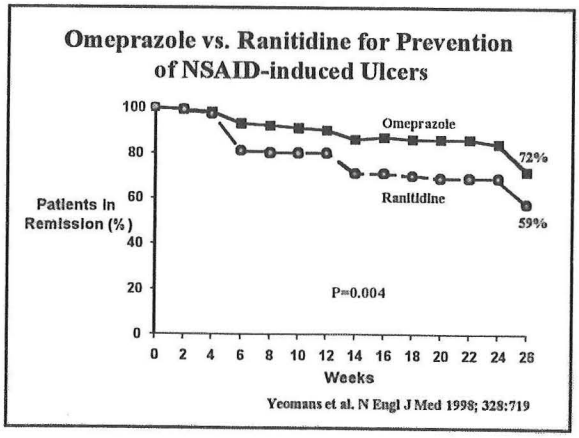


Figure 9.

One criticism of this study, however, is that the dose of ranitidine which was used for prophylaxis (150 mg b.i.d.) was shown in

earlier studies to not effectively prevent NSAID-induced gastric ulcers [56,66]. Thus, the study outcome was biased against ranitidine by virtue of study design.

In another recently reported study omeprazole was compared to misoprostol for reduction of NSAID-induced ulcers [41]. The investigators randomized 732 NSAID-taking patients with a past history of endoscopically confirmed ulcers to omeprazole 20 mg daily, misoprostol 200 μg twice daily or placebo. At the end of six months, NSAID-induced gastric ulcers occurred most commonly in 32% of the placebo group while incidence of recurrent gastric ulcers in the omeprazole and misoprostol groups were statistically similar, 13% and 10% respectively. Recurrent NSAID-induced duodenal ulcers were seen in significantly fewer of omeprazole-treated patients (3%) than in the misoprostol or placebo-treated patients (10% and 12%, respectively). The rates of recurrent duodenal ulcers in the misoprostol and placebo groups were not statistically different **(Figure 10)** [41].

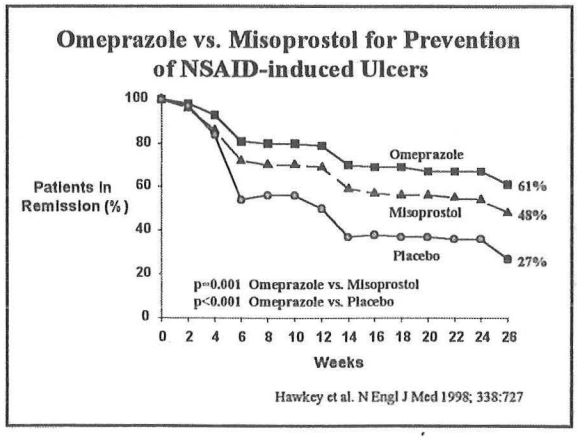


Figure 10.

A criticism of the previous study is that the efficacy of misoprostol to prevent NSAID-induced ulcers is dose-dependent [15]. The lowest effective dose of misoprostol (200 μg b.i.d.) was used as the comparator for omeprazole. Furthermore, end-points in the above studies were endoscopic ulcers which can not be extrapolated to expected outcomes with serious gastrointestinal complications. There are no studies evaluating whether proton pump inhibitors will reduce the frequency of serious upper gastrointestinal complications among NSAID users.

Prophylaxis of Patients Receiving Low-Dose Aspirin. As discussed earlier, low –dose aspirin causes gastric ulcers and gastrointestinal bleeding. This observations is compounded by the fact that many of the patients who take low daily doses of aspirin for cerebrovascular and cardiovascular prophylaxis also fall into one of the high-risk categories for NSAID-induced ulcer complications **(Table 2)**. Since the incidence of GI events with low-dose aspirin is comparatively low and since aspirin use is extremely common is, it is not cost-effective to recommend usual doses of prophylactic co-therapy to all users of low-dose aspirin. An alternative approach that might be more cost-effective might be to co-administer a low dose of a prophylactic therapy along with low-dose aspirin. In a recent placebo-controlled study from England, administration of low dose misoprostol (100 μg daily) to a group of healthy subjects taking 300 mg/day of aspirin was associated with a significant reduction in

erosive gastric injury (**Figure 11**)[28].

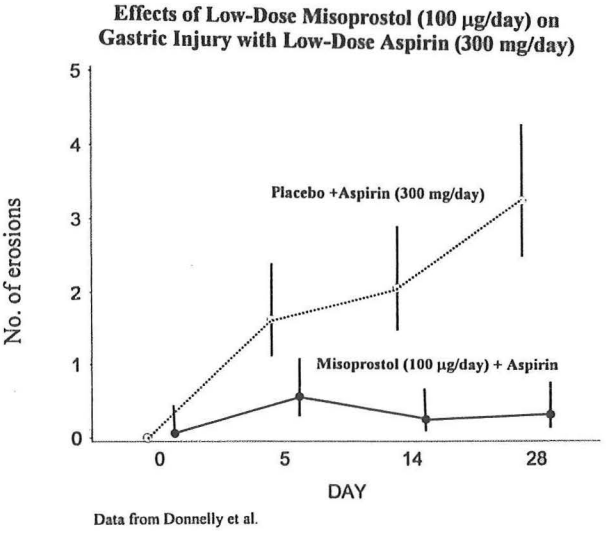


Figure 11.

In this small study of 32 healthy subjects, none developed ulcers (even in the aspirin/placebo group) and no misoprostol-treated subject developed diarrhea. The cost at the Dallas VAMC of a 100 µg tablet of misoprostol is $0.20 per tablet. Given the relatively low cost and lack of adverse effects of low-dose misoprostol, it is possible that using 100 µg per day of misoprostol might be a cost-effective approach to prevent complications in low-dose aspirin users who are at high risk for GI ulceration. However, this can only be speculated since such a study has not been conducted.

Treatment of NSAID-Induced Ulcers

Treatment of NSAID-induced ulcers is more straightforward than prophylaxis. When attempting to treat an ulcer that has formed during NSAID use, the first step is always to stop the NSAID. Once the NSAID is stopped, rapid ulcer healing can be achieved by treatment with standard doses of H_2-receptor antagonists [65,67]. In some patients, however, NSAIDs cannot be discontinued. In such patients use of a proton pump inhibitor will allow healing of both gastric and duodenal ulcers, even while NSAID use continues [67,68].

Development of Safer NSAIDs

Much work has been done to develop safer NSAIDs which might not be associated with as much GI toxicity as the traditional NSAIDs. Among the older NSAIDs, one that appears to not inhibit gastric COX is etodolac [43,44]. Interestingly, etodolac is also clinically associated with fewer GI ulcers and ulcer complications than other NSAIDs [43,69]. Nabumetone is another NSAID that has been available for a number of years which appears to be much safer than others in the class [70]. Possible explanations for nabumetone's improved safety profile may relate to it being administered as a non-acidic pro-drug that has much lower gastric solubility and has no enterohepatic recirculation as is seen with other more acidic NSAIDs [71].

Specific COX-2 Inhibitors. A previous, but now dispelled, concept was that NSAIDs equally inhibit COX at sites of inflammation and COX within the stomach. Based on this previous concept, if a NSAID were to be effective as an anti-inflammatory agent then this same NSAID would have to be an effective inhibitor of gastrointestinal COX and would therefore cause gastrointestinal injury. Inherent in this previous concept was that the efficacy and toxicity of a NSAID were

intertwined (**Figure 12**).

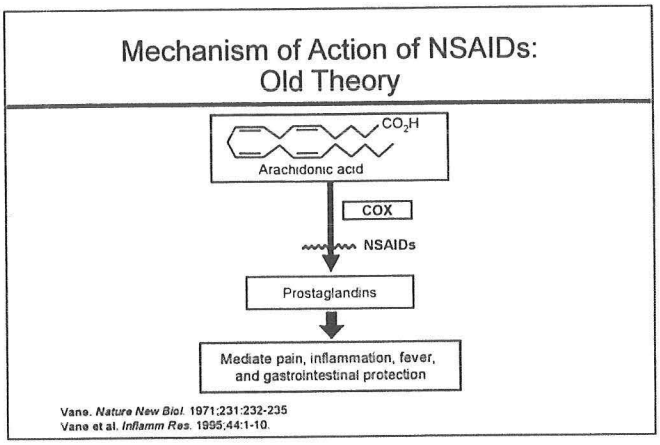


Figure 12.

In the early 1990s it was discovered that COX exists in two isoforms, COX-1 and COX-2 [72-75]. Although COX-1 and COX-2 are closely related, they are unique in several ways (**Table 5**).

Comparison of Cyclooxygenase (COX)-1 and COX-2

	COX-1	COX-2
Regulation	**Constitutive**	**Inducible**
Range of Expression	**2 to 4 fold**	**10 to 80 fold**
Tissue Expression		
	Most tissues	**Inflammatory Sites**
	Notably found in:	**Synoviocytes**
	Platelets	**Fibroblasts**
	Stomach	**Monocytes**

Table 5.

Two of the early observations that led to identification of two COX isoforms were that COX activity could be stimulated by bacterial endotoxin in human monocytes [76] and in mouse peritoneal macrophages [77]. The increases in prostaglandins in response to endotoxin were associated with synthesis of a new COX protein which could be inhibited by dexamethasone. These observations were soon followed by molecular identification of the mRNA transcripts of COX-1 and COX-2 , and identification of their unique proteins [72-74]. The two isoforms are encoded by genes located on separate chromosomes. COX-1 is located on human chromosome 9 [78], while COX-2 is located on human chromosome 1 [79,80]. Both isoenzymes are somewhat genetically similar, sharing 60% genetic homology with mRNA sizes of 2.8 kb and 4.5 kb for COX-1 and COX-2 [72-74,81-83]. Despite the genetic differences, both enzymes have a molecular weight of approximately 70kD, have highly conserved active sites and, differ by less than 10% of amino acids within the arachidonic acid binding domain [81]. Also, they both have approximately the same affinity for and capacity to convert arachidonic acid to prostaglandin H_2 [84]. Within the cell, both isoforms are located on the endoplasmic reticulum and the nuclear envelope [85,86]. However, the concentration of COX-2 within the nuclear envelope is approximately twice the concentration noted in the endoplasmic reticulum while COX-1 is found in equivalent concentrations in both intracellular locations [86].

With regard to potential therapeutic applications, the critical COX isoform distinctions are differences in their tissue distribution and differences in the regulation of their expression. COX-1 is present and is constitutively expressed in most cells and tissues. Under normal homeostatic conditions it produces prostaglandins that regulate essential physiologic functions such as gastric mucosal protection, maintenance of normal kidney function, and platelet aggregation. COX-1 expression can only be increased two to four fold under most circumstances. COX-2 can also be expressed constitutively, but only in a few tissues such as the kidney [87,88] and

brain [89], and human prostate and lung [90]. In most instances COX-2 is usually barely detectable during normal physiologic conditions. However, in response to several proinflammatory stimuli such as mitogens, cytokines and other growth factors, COX-2 can be rapidly induced to increase prostaglandin production 10 to 80 fold.

In summary of the above discussion, the most notable distinction is that COX-2 is felt to be the principal COX isoform that participates in inflammation. It is also thought that there is little COX-2 activity present in the stomach or platelet. In this revised hypothesis of COX inhibition, it is conceivable that if one developed a drug that was a specific inhibitor of COX-2, this drug would retain its anti-inflammatory properties while reducing or eliminating adverse gastrointestinal hemostatic side effects (**Figure 13**). This concept led to the development of COX-2 specific NSAIDs, thus allowing it to be possible to have NSAIDs that are effective while potentially less toxic in the GI tract.

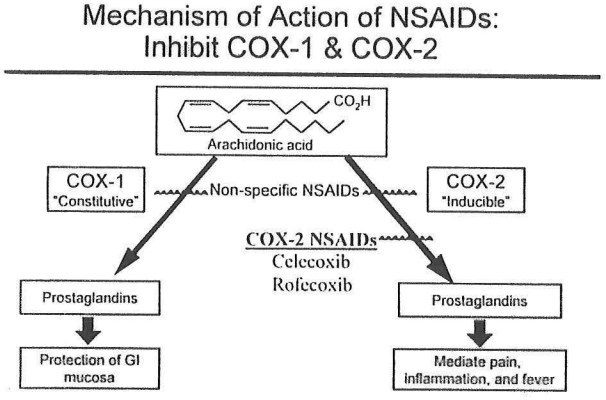


Figure 13.

In 1999, two specific inhibitors of COX-2 were introduced in the United States for clinical use, celecoxib (Celebrex™) and rofecoxib (Vioxx™) [91,92]. A third, meloxicam, will likely be available for clinical use in the United States in 2000. **(Table 6).**

COX-2 Inhibitors in Available or in Development in USA

COX-2 INHIBITOR	COMPANY	PHASE
Celecoxib (Celebrex™)	Searle	III/IV
Rofecoxib (Vioxx™)	Merck	III/IV
Meloxicam	Boehringer	III

Table 6.

Meloxicam, however, has a specificity for COX-2 which is considerably less than the
COX-2 specificity other two agents, possibly as much as an order of magnitude less specific for COX-2 than COX-1 [68] **(Table 7)**. Therefore, meloxicam should be considered as a *"preferential"* inhibitor of COX-2 rather than a "specific COX-2" inhibitor.

COX Selectivity Using *in vitro* Human Whole Blood Assays

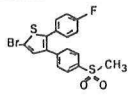
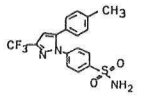
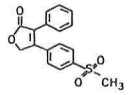
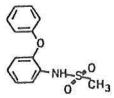
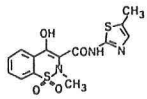
	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	RATIO (COX-1/COX-2)	
Flurbiprofen	0.4	4.2	10.5	COX-1
Ketoprofen	0.1	0.9	9.0	
Aspirin	4.5	13.9	3.1	
Oxaprosin	14.6	36.7	2.5	
Indomethacin	0.2	0.3	1.5	
Ibuprofen	5.9	9.9	1.69	
Naproxen	32.0	31.0	0.97	
Piroxicam	2.68	2.1	0.79	
Nabumetone	33.6	20.8	0.6	
Meloxicam[c]	1.4	0.5	0.36	
Etodolac	19.6	2.47	0.12	
Celecoxib[b]	31.4	3.4	0.11	
Diclofenac	0.26	0.013	0.05	
Rofecoxib[b]	28.6	1.3	0.045	
NS-398	21.9	0.92	0.042	
Nimesulide	10.5	0.18	0.017	
Dexamethasone	56.0	0.13	0.002	COX-2

Cryer & Feldman. Am J Med 1998;104:413-421
Cryer & Feldman. Unpublished data.

Table 7.

A comparison of structures of COX-2 inhibitors is shown in **Figure 14**. A common structural characteristic of COX-2 NSAIDs are side chains which possess a sulfa moiety. Meloxicam and nimesulide are currently clinically available in Europe. DuP 697 is a COX-2 inhibitor that is no longer a clinical candidate.

COX-2 INHIBITORS

DRUG	STRUCTURE	SELECTIVITY
DuP 697		-------
Celecoxib		Specific
Rofecoxib		Specific
Nimesulide		Preferential
Meloxicam		Preferential

Adapted from: Hawkey, C J. Lancet 1999;353:307-314.

Figure 14. Adapted from *Lancet* [93]

In placebo-controlled, prospective phase III trials with over one year of administration to arthritis patients, specific COX-2 inhibitors have been associated with rapid relief of pain, sustained anti-inflammatory effects, and have had efficacy comparable to non-selective NSAIDs, such as diclofenac, ibuprofen, and naproxen, NSAIDs which inhibit COX-1 and COX-2 [7,91-94]. The therapeutic dose required for the treatment of osteoarthritis with COX-2 NSAIDs, in general, is half the dose required for rheumatoid arthritis. In addition, rofecoxib also has efficacy as an analgesic and antipyretic [92,95].

The other component of the current COX isoform hypothesis is that the gastrointestinal tract is primarily comprised of COX-1 and of little COX-2. In studies of the human gastrointestinal tract, little to no COX-2 protein or activity has been demonstrated, while abundant COX-1 protein and COX-1 activity has been observed **(Figure 15)** [96].

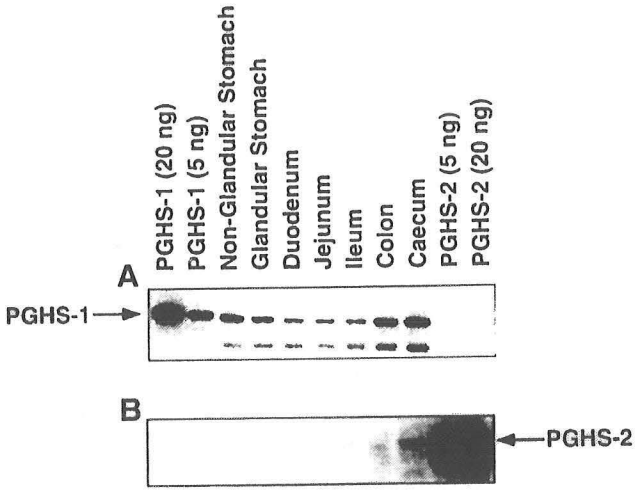


Figure 15. Western blot analysis of PGHS-1 (COX-1) and PGHS-2 (COX-2) proteins in various areas of the gastrointestinal tract. *Gastroenterology* [96].

In addition to confirming that there is quantitatively little COX-2 protein in the upper gastrointestinal tract, the complementary experiment is to document that functionally there is little COX-2 protein in the upper gastrointestinal tract. Working with this hypothesis, our laboratory group at Dallas VA Medical Center assessed gastric COX activity in healthy humans using the COX-2 specific inhibitor, rofecoxib [97]. Gastric

COX activity (as measured by its products, PGE_2 and $PGF_{2\alpha}$) was significantly inhibited by naproxen (inhibitor of COX-1 and COX-2) while no significant change in gastric COX activity was observed with rofecoxib (**Figure 16**). These results suggested that there is little functional COX-2 activity in the human stomach.

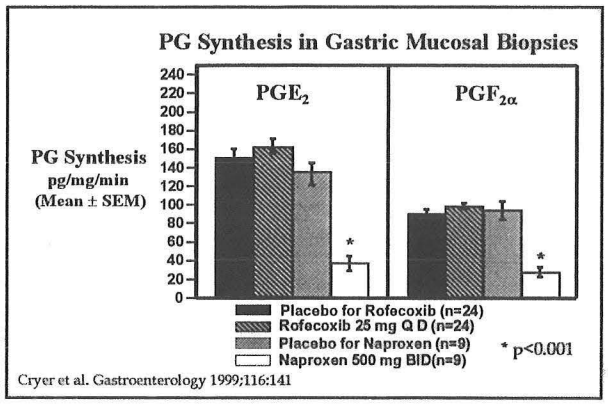


Figure 16. Data from *Gastroenterology* [97]

Short-term [98] and long-term [91,92] endoscopic studies of patients taking COX-2 inhibitors have demonstrated incidences of gastroduodenal endoscopic ulceration of approximately 3 to 5% while traditional NSAIDs, diclofenac, ibuprofen and naproxen caused a 20 to 25% incidence of endoscopic gastroduodenal ulcers (**Figure 17**).

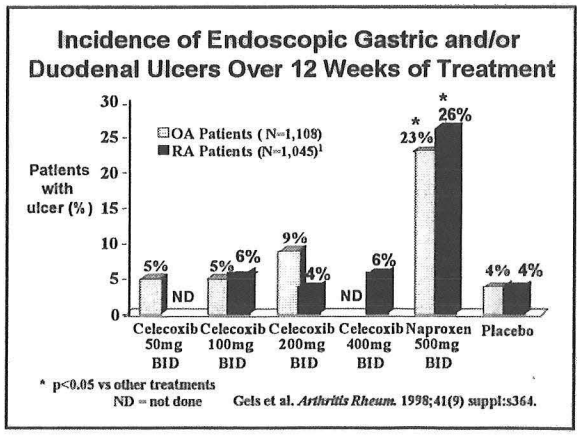


Figure 17. Data from *Arthritis Rheum* [99].

Many of the endoscopic studies of COX-2 inhibitors evaluated patients who would not be considered as high-risk for NSAID-induced ulceration. However, an ideal use for a COX-2 inhibitor would be in patients who are at high-risk. Therefore, it is probably not appropriate to use endoscopic results following COX-2 inhibitors in low-risk patients to reach conclusions regarding gastrointestinal risks in high-risk patient populations. A better understanding of the gastrointestinal risk in high-risk groups comes from a recently completed rofecoxib study in which approximately 15% of enrolled arthritis patients had a history of a previous gastrointestinal ulcer or gastrointestinal event (i.e., high-risk patients) [100]. Patients were randomized to ibuprofen (800 mg t.i.d), rofecoxib (25 mg daily), rofecoxib (50 mg daily), or placebo. As seen in **Figure 18,** at the end of twelve weeks patients with a previous history of gastrointestinal ulcers or events had a higher incidence of gastrointestinal ulcers in every treatment group.

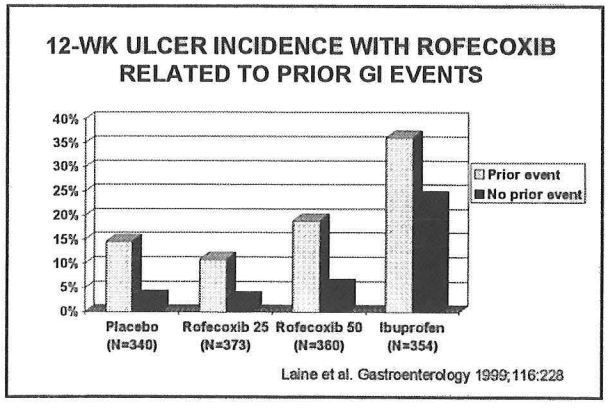


Figure 18.

These observations suggest that the safety profile of COX-2 inhibitors in patients at high-risk for NSAID-induced ulcers differs from safety profiles in patients who do not fall into a high risk category. Until further data are available it would be prudent to continue prophylatic co-therapies (misoprotsol, proton pump inhibitors or high-dose famotidine) in high-risk patients who are prescribed COX-2 NSAIDs.

As has been observed in a number of other NSAID studies, endoscopic ulceration is generally asymptomatic, is usually without untoward clinical consequences and usually would not have been clinically apparent if a controlled endoscopic study had not been performed. The more clinically meaningful data regarding the GI effects of a COX inhibitor are those which report incidences of clinically significant ulceration, that is ulcers associated with perforation, pain or bleeding, or "PUBs". Since very few patients who are exposed to NSAIDs will develop clinically significant ulceration, it generally takes thousands of patient-years of exposure before comparisons can achieve sufficient statistical power to make a statistically meaningful statement regarding incidences of PUBs. The clinical experience to date with specific COX-2 inhibitors has not been sufficiently long to be able to make statistically significant observations comparing their rates of clinically significant ulceration to those of comparator NSAIDs. In general, however, the investigational experience of accumulated significant GI events with specific COX-2 inhibitors suggests that their incidence of clinically significant ulceration (or PUBs) is likely to be about half that seen with traditional, non-selective NSAIDs (**Figure 19**).

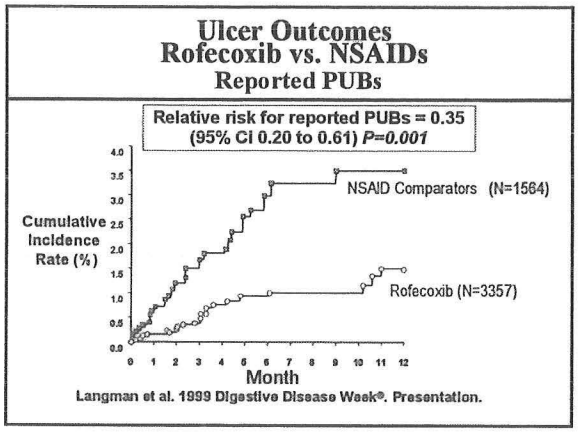


Figure 19. Data from *Gastroenterology* [100]

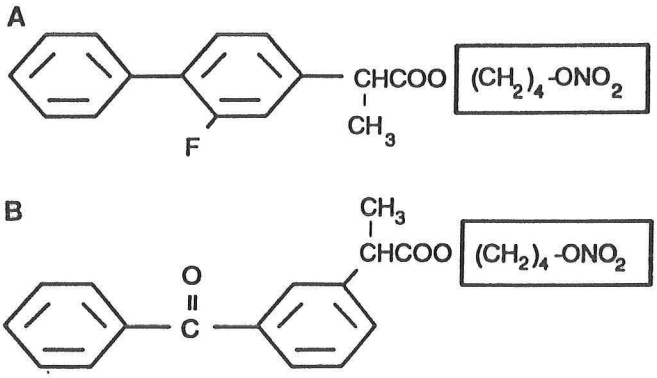
NSAID-induced dyspepsia is a symptom, which in clinical practice, drives diagnostic evaluations and increases the costs of therapy. The incidence of dyspepsia on a COX-2 inhibitor is 5 to 10% while dyspepsia in NSAID comparators is 10 to 15%. Thus, with regard to dyspepsia and other GI and non-GI symptoms, the specific COX inhibitors are well tolerated.

Although the initial indications for specific COX inhibitors are the treatment of osteo-and rheumatoid arthritis and the relief of pain, there are also other very interesting possible future applications for the specific COX-2 inhibitors. Since COX-2 is up regulated in adenomatous colon polyps and in adenocarcinomas of the colon [101], it is possible that there will be a therapeutic benefit achieved with specific COX inhibitors for the prevention of adenomatous polyps and in the prevention of colon adenocarcinoma. Animal and cell culture models of each of these conditions have suggested that inhibition of COX-2 activity in the colon is associated with a reduction in adenomatous colon polyps as well as colon cancers [96,101-111]. Human studies of the effects of specific COX-2 inhibition in

adenomatous polyps and in colon cancer are currently underway. COX-2 inhibition may also be beneficial in the treatment of other cancers. In animal models of lung and prostate cancer, and in squamous cancer of the esophagus as well as in Barrettes esophagus, there is increased COX-2 expression. Specific inhibition of COX-2 in animal models of lung cancer has been associated with a reduction in primary lung tumors as well as a reduction in metastases.

Nitric oxide-releasing NSAIDs. The principal mechanism through which gastrointestinal mucosal prostaglandins are thought to protect against NSAID-induced injury is to maintain mucosal blood flow. After conventional NSAIDs are administered, mucosal prostaglandins are reduced, and, consequently gastrointestinal blood flow is lowered. Therefore, NSAID-induced ulceration, in large part can be considered ischemic ulceration which results primarily from reductions in prostaglandin-supported blood flow. Another major mechanism that appears important in the pathogenesis of NSAID-induced gastric damage is adherence of neutrophils to vascular endothelium.

Nitric oxide is now recognized as a critical mediator of gastrointestinal mucosal defense, exerting many of the same actions as prostaglandins within the gastrointestinal tract. In addition to other properties, nitric oxide increases mucosal blood flow and prevents neutrophil adherence to vascular endothelium [112]. These observations have led to the development of nitric oxide releasing-NSAIDs in which the native NSAID has been *coupled* to a nitric oxide-releasing moiety. The concept is that a vasodilating component is delivered by virtue of its attachment to the NSAID, directly to the gastrointestinal mucosal location that would be potentially damaged by the NSAID component. Nitric Oxide-NSAIDs, abbreviated "NO-NSAIDs" have been synthesized using diclofenac, naproxen and flurbiprofen. **(Figure 19).** These various NO-NSAIDs have been demonstrated to have anti-inflammatory, anti-pyretic, analgesic, and anti-thrombotic effects which are comparable to those of native NSAIDs [112,113]. However, the NO-NSAIDs are not associated with the NSAID-induced gastrointestinal toxicity that has been associated with the parent compounds [112,113].



Structures of NO-releasing derivatives of (*A*) flurbiprofen and (*B*) ketoprofen. The *rectangles* enclose the nitroxybutylester moieties that were added to the native NSAIDs.

Figure 19. Nitric-oxide releasing NSAIDs. *Gastroenterology* [112].

Interestingly, NO-NSAIDs inhibit both COX-1 and COX-2 and they reduce gastrointestinal prostaglandins to the same extent as native NSAIDs. This prostaglandin reduction is almost certainly attributable to the NSAID component of NO-NSAIDs. However, in spite of the marked prostaglandin reductions achieved with NO-NSAIDs, their use is not associated with the gastrointestinal

toxicity seen with the parent compounds.

NO-NSAIDs unfortunately have only been studied in animal models. There are no published reports of human studies on the effects of NO-NSAIDs on the gastrointestinal tract. The animal data, however, are very attractive. A major question is whether NO-NSAIDs, similar to any other new investigational agent in pre-clinical phases of investigation, will be without major toxicity when investigated in humans. This is currently unknown. Since the human studies have not yet been reported, any potential clinical applications for NO-NSAIDs will not be in the near future. Nevertheless the animal data suggest the potential for these to also be a safer class of non-steroidal anti-inflammatory drugs.

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