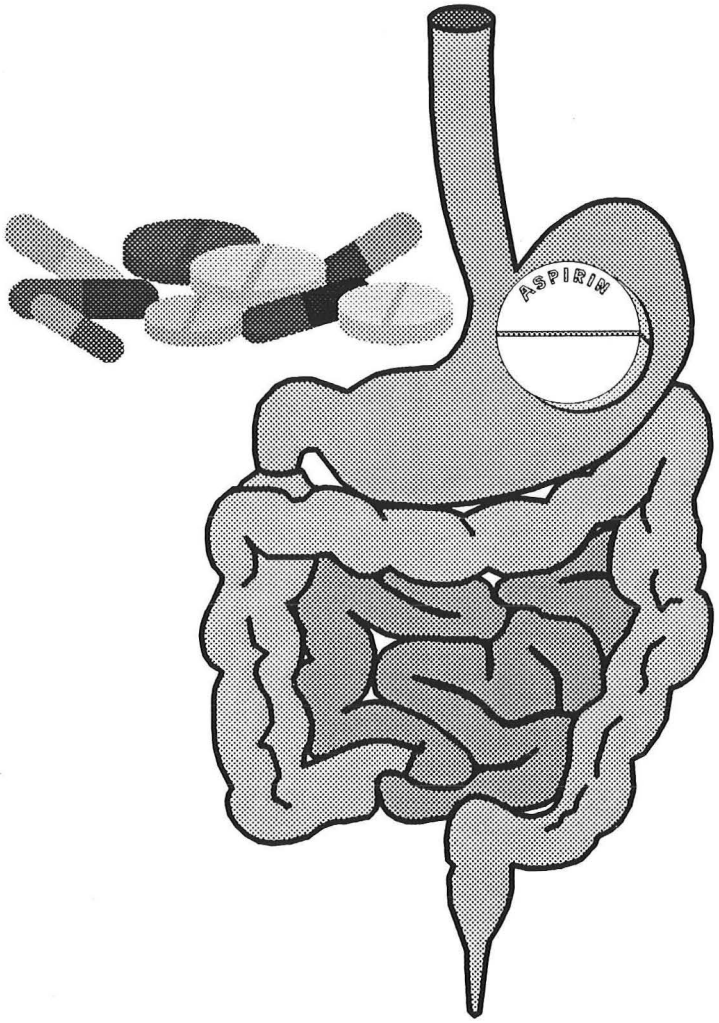
NSAIDs and the Gastrointestinal Tract



Internal Medicine Grand Rounds
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INTRODUCTION

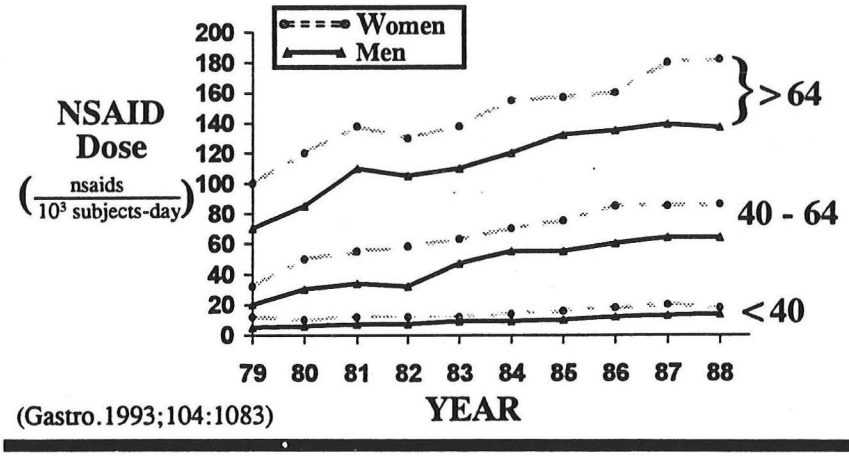
Nonsteroidal antiinflammatory drugs (NSAIDs) are one of the most widely used groups of drugs. They are quite effective as antiinflammatory, antipyretic and analgesics. Their widespread use is, in large part attributed to the a high prevalence of osteoarthritis and rheumatoid arthritis, conditions for which NSAIDs are very effective. Although these compound represent a very effective class of drugs, their use is associated with a broad spectrum of untoward reactions especially in the liver, kidney, skin and gastrointestinal (GI) tract. Since the gastrointestinal side-effects constitute the greatest of the untoward effects of NSAIDs, this review will concentrate on the untoward effects of NSAIDs in the various regions of the gastrointestinal tract beginning at the esophagus and ending with the colon.

EPIDEMIOLOGY

Worldwide, nonsteroidal anti-inflammatory drugs are prescribed more frequently than any other group of medicines[1]. It is estimated that nearly one in seven Americans is treated with an NSAID[2]. In 1991, 70 million prescriptions for NSAIDs were filled in the US at a cost of 2.2 billion dollars[3]. The phenomenon of widespread NSAID usage, in large part, is a reflection of the high prevalence of rheumatic diseases. Furthermore, at any point in time, 8 percent of people experience a rheumatic symptom which will likely be treated by an NSAID[4].

During the past 25 years there has been a substantial increase in the variety and number of prescriptions for NSAIDs worldwide. This increase in prescription rates was particularly dramatic in the 1970s and early 1980s, especially for older females[5,6] **(Figure, below)**. While in recent years, the rate of increase for prescription NSAIDs has begun to level off, the market for non-prescription (over-the-counter) NSAIDs has been rapidly expanding.

NSAID Prescription Rates by Age & Gender



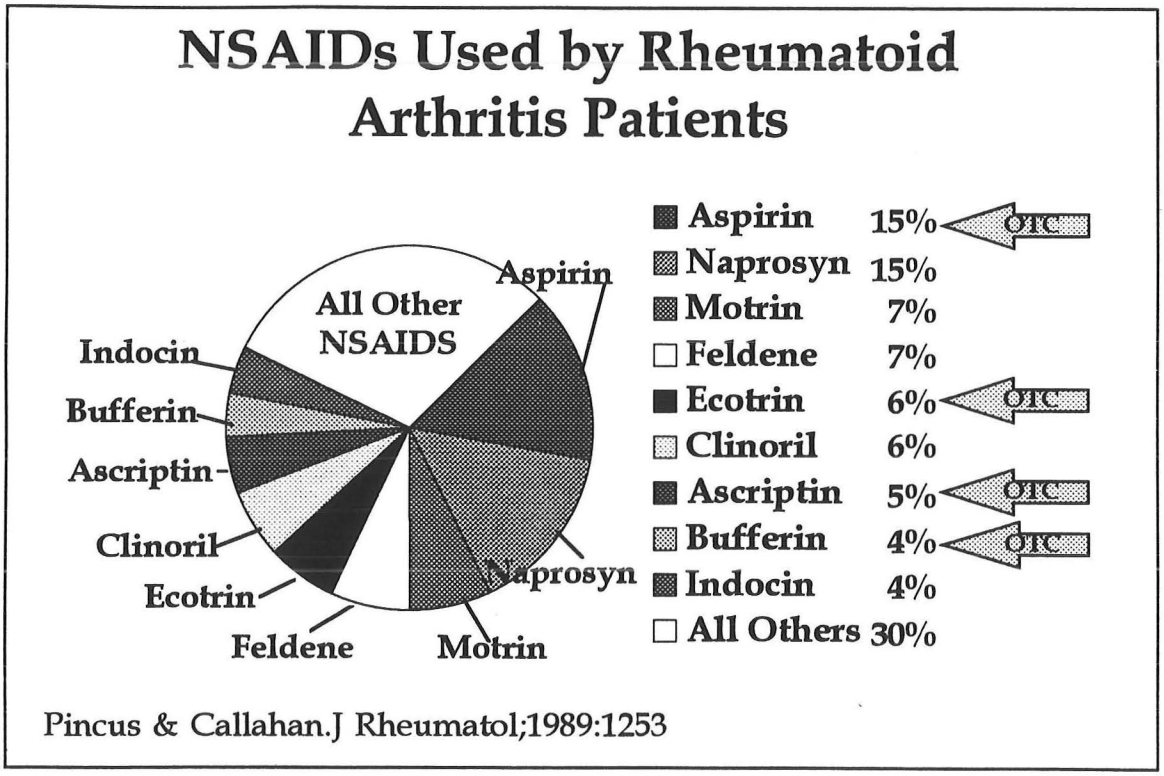
(Gastro.1993;104:1083)

In the 1995 edition of *The Physician's Desk Reference*, there are 21 different NSAIDs available by prescription, 7 of them salicylate-based compounds **(Table, below)**[7].

List of NSAIDs Available by Prescription

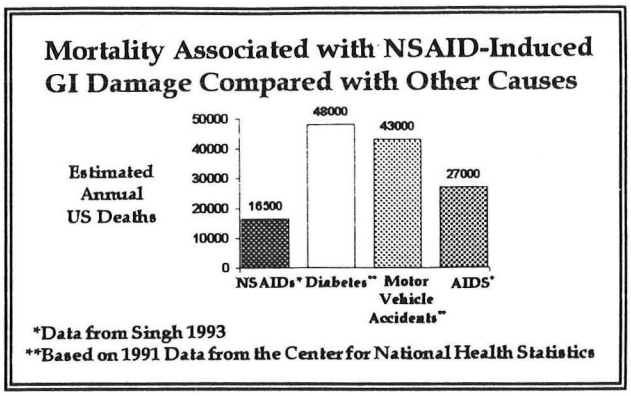
Nonsalicylate	*Salicylates*
Diclofenac (*Voltaren*)	**Aspirin**
Etodolac (*Lodine*)	**E-CAspirin** (*Zorprin*)
Fenoprofen (*Nalfon*)	**Diflunisal** (*Easprin*)
Flurbiprofen (*Ansaid*)	**Salsalate** (*Disalcid, Salfex*)
Ibuprofen (*Motrin*)	**Choline Magnesium Trisalicylate** (*Trilisate*)
Indomethacin (*Indocin*)	**Magnesium Salicylate** (*Magan*)
Ketoprofen (*Orudis*)	
Ketorolac (*Toradol*)	
Mefenamic Acid (*Ponstel*)	
Nabumetone (*Relafen*)	
Naproxen (*Naprosyn*)	
Oxaprozin (*Daypro*)	
Piroxicam (*Feldene*)	
Sulindac (*Clinoril*)	
Tolmetin (*Tolectin*)	

Actual NSAID consumption, however, is much greater than accounted by the 21 prescription NSAIDs. Over-the-counter (OTC) NSAID use is estimated to be as much as 7 times the rate for prescribed NSAIDs, with particularly high usage for non-prescription aspirin preparations. In spite of the vast number of NSAIDs available, prescription and non-prescription, in 1989 only 9 NSAIDs accounted for 70% of total NSAID consumption, at least in rheumatoid arthritis patients[8] **(Figure, below)**. Notably, four of these most commonly taken NSAIDs are available OTC.



Unfortunately, the major adverse consequences of the widespread use of NSAIDs are significant morbidity and mortality related to this class of drugs. In 1993, it was estimated that 16,500 deaths in the U.S. were attributed to NSAID use, a significant contribution to overall U.S. mortality when one compares this rate of death to other major causes of death in this country

such as diabetes, motor vehicle accidents, and AIDs[9] **(Figure, right)**. When considering morbidity, one quarter of all adverse reactions reported to the Committee on Safety of Medicines in the United Kingdom ago are due to NSAIDs [10]. Although the spectrum of these reactions is broad, the majority of the adverse effects reported after NSAID use are experienced within the gastrointestinal tract. The most serious of these complications, namely bleeding and perforation, account for almost all of the NSAID associated mortality and have increasing prevalence with advancing age [11-15]. Most of what has been written concerning NSAIDs' gastrointestinal effects has been in the stomach and duodenum. However, NSAIDs' effects can be found at all levels of the gastrointestinal tract.

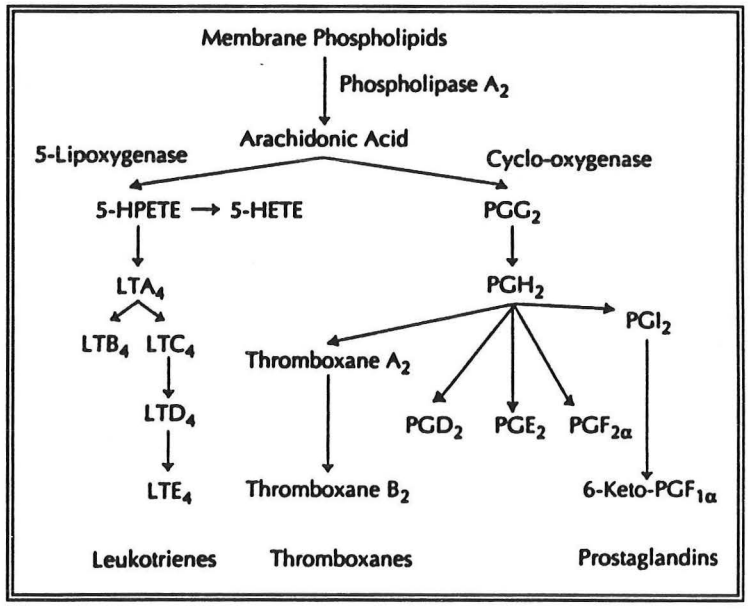


MECHANISMS OF TOXICITY OF NSAIDs

Irrespective of site of gastrointestinal damage, the mechanisms through which NSAIDs cause injury are similar throughout the tract. The general mechanisms 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.

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. Within the gastrointestinal tract, NSAID associated reduction in gastroduodenal mucosal prostaglandin concentrations is the major contributor towards NSAID mucosal toxicity. Cyclooxygenase, acts upon arachidonic acid to generate prostaglandins and thromboxane **(Figure, right [from ref [16]])**. Prostaglandins are a family of related fatty acids that are found in nearly all of the body's cell. In humans, prostaglandins E_2, I_2, and $F_{2\alpha}$ are the major prostaglandins produced by the



stomach and duodenum [17]. Prostaglandins participate in a variety of activities, including mediation of inflammatory responses and regulation of renal blood flow. Within the gastrointestinal tract, prostaglandins protect against injury. For example, if one pretreats the gastric mucosa with exogenously administered prostaglandins, protection is provided against a variety of damaging agents such as alcohol, bile, salts, acid, hypertonic saline, boiling water, stress, aspirin and other NSAIDs[18-24]. Some of the putative mechanisms through which prostaglandins provide their protective mucosal effects include: stimulation of mucosal bicarbonate secretion, stimulation of mucus secretion, increased mucosal blood flow, prevention of disruption of the gastric mucosal barrier, acceleration of cell proliferation, stimulation of cellular ionic transport processes, stimulation of cyclic adenosine monophosphate production, promotion of formation of surface active phospholipids, maintenance of gastric mucosal sulfhydryl compounds, stabilization of cellular lysosomes, and stabilization of cell membranes. There is emerging evidence suggesting that the mechanism which may be most responsible for the protective GI mucosal effects of prostaglandins is their ability to maintain mucosal blood flow [25-29].

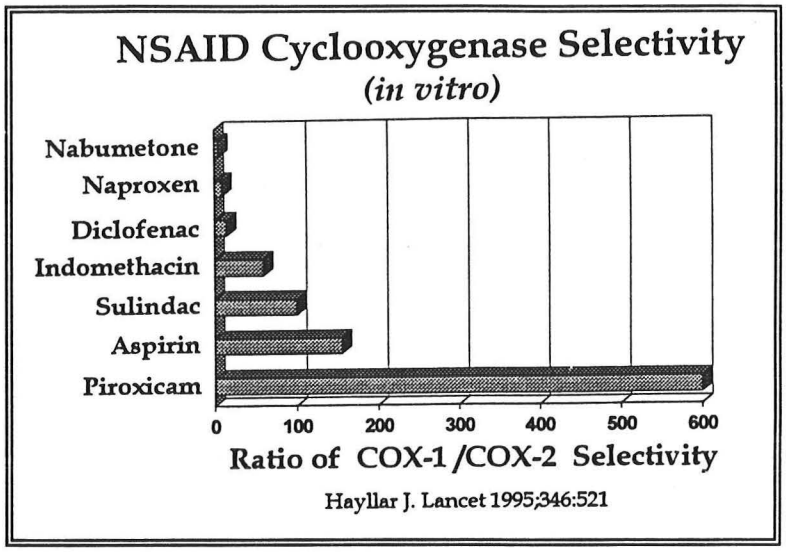
Cyclooxygenase (also called prostaglandin H synthase), the rate limiting enzyme in prostaglandin synthesis, is inhibited by NSAIDs. Thus, NSAIDs, via an inhibition of cyclooxygenase, will reduce gastroduodenal prostaglandin mucosal concentrations resulting in the loss of a major mechanism for protection against mucosal injury. With few exceptions, nearly all NSAIDs inhibit cyclooxygenase and, therefore, prostaglandin concentrations. Aspirin, by acetylation of cyclooxygenase, inhibits this enzyme irreversibly, while all other NSAIDS inhibit cyclooxygenase in a reversible, concentration-dependent manner[30,31]. With aspirin, when cyclooxygenase 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 inhibitors of prostaglandin synthesis.

Recently two structurally-related cyclooxygenase isoforms have been identified in mammalian cells, cyclooxygenase (COX)-1 and COX-2[32,33]. Based on data from animal studies, COX-1 is found in most of the body's tissues, including the stomach. COX-2, by contrast, is undetectable in most tissues under normal physiologic conditions. COX-2 is inducible through the action of cytokines and endotoxins. Thus, it is found in high concentrations in sites of inflammation. COX-2 is *not* found in the stomach[32] **(Table, above)**.

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

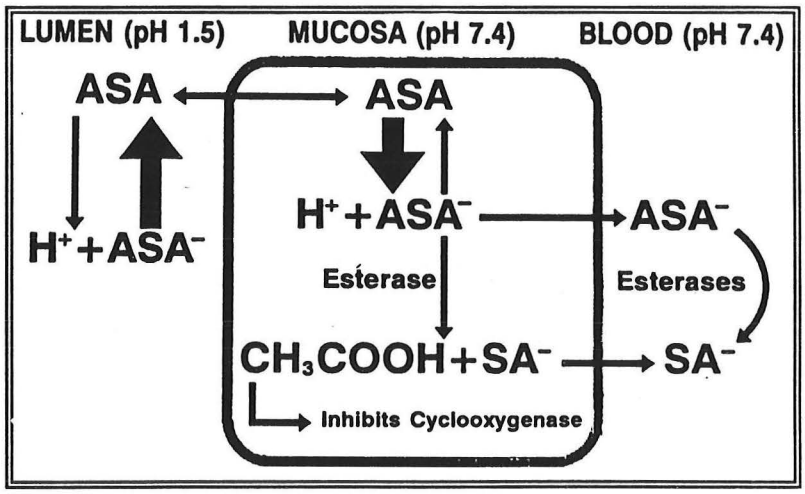
	COX-1	COX-2
Regulation	**Constitutive**	**Inducible**
Range of Expression	**2 to 4 fold**	**10 to 80 fold**
Tissue Expression	**Most tissues** **Notably found in:** **Platelets** **Endothelial cells** **Kidney** ***Stomach***	**Inflammatory Sites** **Synoviocytes** **Fibroblasts** **Monocytes**

All currently available NSAIDS inhibit both COX-1 and COX-2, although the ratio of their selectivity for COX-1/COX-2 widely varies[34] **(Figure, right)**. It has been reported that nabumetone, a recently introduced NSAID, selectively inhibits COX-2 while having much less of an effect on COX-1 expression in animal cell lines[33]. Interestingly, nabumetone is also clinically associated with fewer gastrointestinal side effects than other NSAIDs[35]. Current human investigation is underway to develop newer NSAIDs which will selectively inhibit COX-2 but not COX-1. Such NSAIDs could potentially decrease inflammation while possibly having minimal gastroduodenal effects.



Another advancement which may lead to NSAIDs which have less gastrointestinal toxicity is the recent development of NSAIDs which have a nitrous oxide moiety. Nitrous oxide (NO), or drugs that delivery NO, can reduce the severity of gastric mucosal injury in experimental models. In animals, NO-NSAIDs have recently been demonstrated to suppress gastric prostaglandins and to suppress inflammation yet have minimal gastric injury after short-term administration[25,36]. When tested in humans during long-term use, if similar observations are found, NO-NSAIDs may offer a future class of NSAID with less gastroduodenal toxicity.

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, some dependent upon cyclooxygenase inhibition and some independent of cyclooxygenase inhibition. The **figure (right)** demonstrates this process of intracellular trapping using aspirin (ASA) as a prototypical NSAID.



Topical Effects

Although prostaglandin suppression is believed to be the major mechanism of NSAID gastrointestinal injury, the initial type of injury which occurs is a direct topical effect [37-39]. Within a few minutes of aspirin ingestion, denudation of surface epithelial cells and increased mucosal permeability to sodium and hydrogen ions can be observed[40], reflected experimentally as a decrease in transmucosal potential difference[41,42]. Salicylic acid, the deacetylated metabolite of aspirin, does not inhibit cyclooxygenase activity in the gastric mucosa[43], yet it reduces potential difference as much as aspirin. Thus, acute surface epithelial cell disruption and the decline in potential difference are not dependent on cyclooxygenase inhibition, and, epithelial cell disruption is not prevented by pretreatment with prostaglandins[44].

Enteric-coated NSAIDs produce considerably less acute gastric mucosal damage than plain, non-enteric-coated formulations during the first one to two weeks of administration[45-47], an observation in support of a local toxic effect of NSAIDS. However, with long-term administration of enteric-coated formulations, gastric ulcers develop [48], presumably as a result of a systemic contribution of prostaglandin suppression. Furthermore, gastric and duodenal ulcers occur after NSAIDS are administered intravenously[49,50] or by rectal suppository[51], further support of a systemic effect of prostaglandin inhibition.

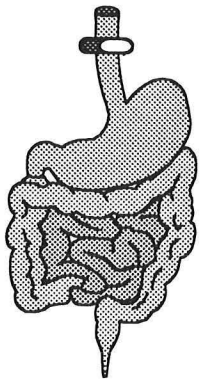
Although inhibition of prostaglandin synthesis contributes to NSAID-induced mucosal injury, it is not settled whether prostaglandin inhibition is the primary mechanism. In some studies, there has been poor correlation between gastric mucosal injury and prostaglandin suppression after NSAID administration[17,52-54]. Other factors probably work in concert with prostaglandin suppression to increase the propensity for mucosal injury by NSAIDs. For example, after indomethacin administration, gastric acid secretion has been shown to increase[55], gastric mucosal blood flow to decrease[56,57], and duodenal bicarbonate output to decrease[58]. NSAIDs can also potentially affect mucus secretion, as they have been shown to inhibit mucus synthesis, to reduce incorporation of radiolabelled precursors into mucus glycoprotein, and to alter thickness of the mucus layer[38,59]. Interestingly, since prostaglandins assist in the regulation of each of the above mechanisms, it is possible that all of the responses to NSAID administration could be prostaglandin mediated.

The strongest argument in support of prostaglandin depletion as an essential element of NSAID-induced ulcers is that depletion of mucosal prostaglandins, by active or passive immunization with prostaglandin antibodies, will lead to gastrointestinal ulcers, many of which will be complicated (perforated or bleeding) at the time of presentation[60]. Furthermore, NSAID-induced ulcers can be prevented by small doses of exogenous prostaglandins[38]. Overall, NSAID-induced gastrointestinal injury is not entirely explained by either a topical effect of prostaglandin suppression. The mechanism is likely a combination of both effects.

CLINICAL MANIFESTATIONS OF NSAID INJURY THROUGHOUT THE GI TRACT

The role of NSAIDs in gastrointestinal injury has been most extensively studied in the stomach. Although, in the stomach and duodenum, the evidence for a cause and effect association between NSAID use and mucosal injury is strong, in the other areas of the gastrointestinal tract the relationships are more speculative. Most studies of NSAID injury in these other areas have been in the form of case reports or series. Nevertheless, some recurrent observations have suggested, at the least, some very strong associations between NSAID use and gastrointestinal damage.

ESOPHAGUS



ULCERS

The principle toxic manifestations of NSAIDs in the esophagus are ulcers and strictures. However, esophageal ulcers are not specific to NSAIDs. Esophageal ulceration has been reported in association with at least 26 different medicines[61-63]. The most common of these medicines are listed **(Table, left)**. Considering all of the medicines associated with esophageal ulceration, the incidence of NSAID-associated ulceration falls about in the middle of the group. Antibiotics, particularly doxycycline and tetracycline, account for greater than 50% of reported cases of esophageal ulcers[61].

Cases of Pill-Induced Esophageal Ulcers

Drug	*Percent*	*No.*
Doxycycline	43%	96
Tetracycline	5%	12
Other Antibiotics*	5%	10
Emepronium bromide	16%	36
NSAIDs	**8%**	**17**
Potassium chloride	7%	16
Ferrous sulfate	5%	12
Alprenolol chloride	4%	9
Quinidine	3%	7
Ascorbic Acid	1%	2

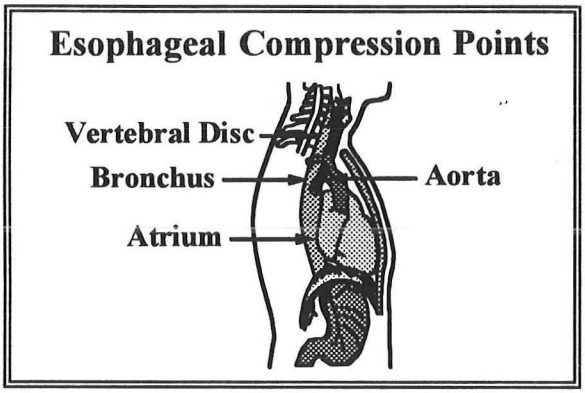
*Clindamycin (4); Minocycline (1); Ampicillin (1) Erythromycin (1); Penicillin (1); Lincomycin (1)

Many patients (approximately 50%) presenting with pill ulcers will give a history of having taken a medicine followed by a persistent sensation that the medicine is located substernally. Many case reports suggest that improper ingestion of pills may contribute to pill retention as

forty percent of these patients have a history of having taken their pills with no food or liquid or just prior to going to bed[61]. Odynophagia (74%) and dysphagia (20%) are the most common symptoms and, in some cases, major bleeding may occur. Also, patients with prolonged symptoms may experience significant weight loss.

As the pharmacologic properties of all of the various medicines in this group are quite diverse, there is not a likely single unifying mechanism to explain all pill-induced esophageal ulceration. Multifactorial etiologies are more probable as each of the various medicines has different chemical properties. With aspirin, esophageal ulcers are thought to be initiated by its disruption of the esophageal mucosal barrier to hydrogen diffusion, thus rendering the underlying esophageal mucosa more susceptible to refluxed gastric acid[62,64]. In animals esophageal ulceration can be experimentally induced after just a few oral doses of a NSAID[65]. The one unifying mechanism in all cases of esophageal pill ulceration is prolonged mucosal contact with a medicine which has relatively caustic physical properties.

Prior esophageal disease is not a prerequisite for development of injury. While most patients with this type of injury will have no apparent abnormality of esophageal transit, some of these patients will have an underlying esophageal motility abnormality. Moreover, preexisting esophageal compression by contiguous anatomical structures appears to predispose to pill ulceration and coincides with esophagal ulceration sites. Vertebral discs, main-stem bronchus, aorta, and left atrium, all may cause extrinsic esophageal compression, thus potentially setting up susceptibility for pill ulceration **(Figure, left)**.



The diagnosis of NSAID-induced esophageal ulceration is a diagnosis of exclusion based first on elimination of reflux disease, cancer, or infections as possible etiologies in patients who are concurrently taking NSAIDs. There is no specific therapy other than to heal the ulcer with acid suppressive medications and to advise patients against taking NSAIDs without food or water or prior to recumbency.

STRICTURES

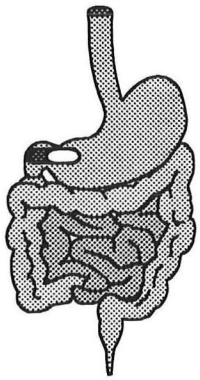
Esophageal stricture, as a complication of NSAID therapy, has been less widely appreciated than ulceration. All of the same medicines which are associated with pill-induced esophageal ulceration have also been associated with esophageal stricture. However, with stricture formation, quinidine and potassium chloride are the most frequently reported[62,63]. Risk factors for pill-induced stricturing are also similar and include recumbency, pill ingestion just prior to sleep or during the post-operative period. Extrinsic compression by contiguous structures also is a risk factor. Among individuals who develop pill-induced esophageal injury, strictures seem to have a greater likelihood of development in those with left atrial enlargement

or in those who take a sustained-release formulation[62]. Most pill-related esophageal strictures occur in the mid-esophagus (52% prevalence), with 26% and 22% of these strictures occurring in the proximal and distal esophagus, respectively[62]. Esophageal strictures, not related to medicines, are most commonly caused by gastroesophageal reflux of acid. For a diagnosis of NSAID-induced esophageal stricturing to be made, the mucosa which lies between the stricture and the gastroesophageal junction must be endoscopically normal and histologically normal, occurrences which would be very unlikely in acid reflux disease.

ESOPHAGITIS

The data suggesting a causal relationship between NSAID consumption and esophagitis is not as strong in esophagitis as in ulcer and stricture. Since gastroesophageal reflux disease (GERD) has a high prevalence in the general population, it would take a very large study to demonstrate that NSAIDs cause esophagitis, independent of acid. All studies reporting NSAID-induced esophagitis have been case reports or small series[66-68]. There are no controlled, prospective, well-designed trials which evaluate this potential relationship. It is of interest, however, that patients with esophagitis do have a much higher prevalence of NSAID use than controls[68]. Since the literature is not very clear as to the effects of NSAIDs independent of acid, my personal bias is that NSAIDs may exacerbate the tendency towards esophagitis in patients with GERD rather than independently cause most cases esophageal inflammation.

STOMACH AND DUODENUM



The Food and Drug Administration reports that symptomatic gastrointestinal ulceration (that is, ulcers associated with pain, perforation, or bleeding) occurs in approximately 2 to 4% of patients treated with a NSAID for one year[7]. When one considers the millions of people who consume NSAIDs annually, these seemingly small percentages translate into millions of symptomatic gastrointestinal ulcers, episodes of GI bleeding and perforations per year.

NSAID GASTROPATHY

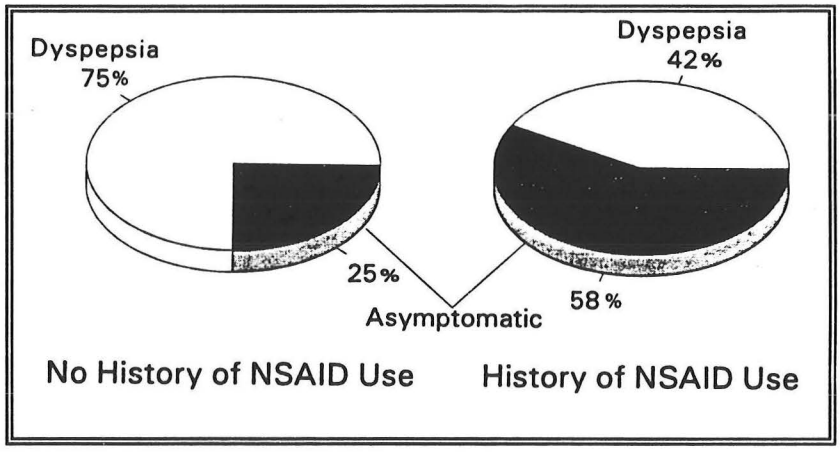
Ingestion of aspirin and other NSAIDs can produce acute gastric mucosal erosions and subepithelial hemorrhages. Although found in all gastric locations, these NSAID-associated lesions have a predilection for the gastric fundus and body. The constellation of multiple small erosions plus multiple small submucosal hemorrhages throughout the stomach is very suggestive of NSAID use. These endoscopic findings, although visually disconcerting, are usually asymptomatic. On microscopic evaluation of gastric biopsies of patients taking NSAIDs, the occurrence of a mucosal inflammatory infiltrate is not greater than expected for age-matched controls not taking NSAIDs. Thus NSAIDs do not actually cause a histologic gastritis. A more appropriate term for this condition is "NSAID gastropathy".

ULCERS

Prevalence

In endoscopic clinical research studies of patients who take NSAIDs, the incidence of new gastric ulcers ranges from 10% to 20% and the incidence of duodenal ulcers ranges from 4% to 10% during the first three months of NSAID use[69-72]. The reported incidence of NSAID-induced ulceration in endoscopic clinical trials probably overstates the actual risk of clinically significant NSAID-induced ulceration, which is probably closer to 1% during the first three months of NSAID use[7,73].

Over periods of NSAID usage of longer than 3 months, it has been difficult to ascertain the true risk of development of a NSAID-induced ulcer as many people who take NSAIDs have asymptomatic ulceration[14,74-76]. For example, in a prospective endoscopic study in which ulcer patients who were taking NSAIDs were compared to ulcer patients who had not taken NSAIDs (controls), significantly fewer NSAID-taking ulcer patients experienced ulcer symptoms than controls[76]. Asymptomatic NSAID-induced ulceration may be especially problematic in that asymptomatic patients will more frequently have bleeding or perforation as their first presentation of ulcer disease[14,76]. Among patients who present with bleeding ulcers, those who have been using NSAIDs are more than twice as likely to have been asymptomatic prior to presentation as those who have no history of NSAID use[14] **(Figure, right)**.



The reasons that NSAID use is associated with asymptomatic ulceration are not clear. It has been suggested that NSAIDs may induce analgesia or, alternatively, that NSAID use may exacerbate a previously existing "silent" ulcer causing it to perforate or bleed. NSAIDs are anti-coagulants due to their anti-platelet actions. Therefore, they can increase the tendency of an existing ulcer to bleed. Another possibility is that at initiation of NSAID therapy, many patients who are intolerant of the NSAID because of dyspepsia will discontinue the medicine. This would leave a large number of asymptomatic NSAID users to chronically continue NSAID consumption and be exposed to the continued risk of asymptomatic ulceration which may progress to an ulcer complication such as a bleed or perforation.

Ulcer Risk According to Type Of NSAID

Type of NSAID & Risk of Ulcer

Risk Group	*Drug*	*Relative Risk [Range]*
LOW	Ibuprofen (*Motrin*^{R})	2.0 [1.4-2.8]
	Diclofenac (*Voltaren*^{R})	4.2 [4.2-6.8]
MEDIUM	Naproxen (*Naprosyn*^{R})	9.1 [5.5-15.1]
	Indomethacin (*Indocin*^{R})	11.3 [6.3-20.3]
	Piroxicam (*Feldene*^{R})	13.7 [7.1-26.3]
HIGH	Ketoprofen (*Ketoprofen*^{R})	23.7 [7.6-74.2]
	Azapropazone (*Apazone*^{R})	31.5 [10.3-96.9]

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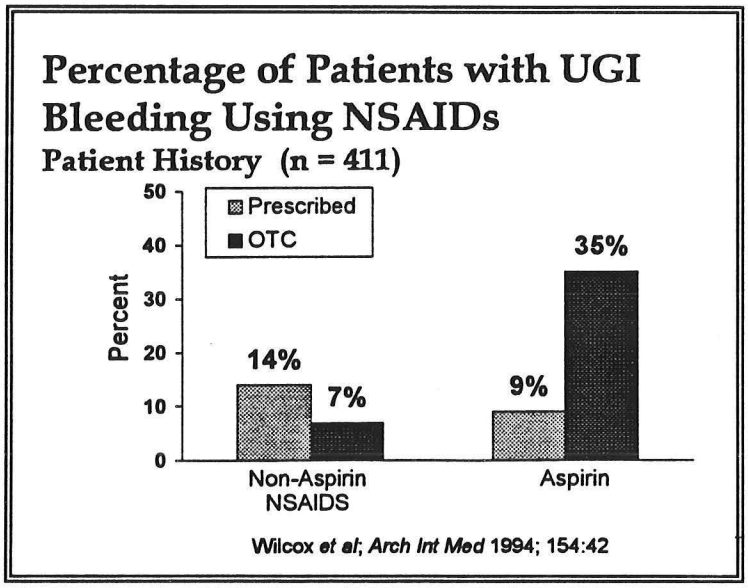
In the past it was stated that the risk of ulceration was equivalent for all types of NSAIDs. However, recent epidemiologic data have stratified NSAIDs by risk of NSAID-induced ulcer bleeding or perforation and have been ranked as shown in the **table (left)**[77,78]. Although not evaluated in the study shown here, other NSAIDs which might be considered as low risk include the nonacetylated salicylates and, possibly, nabumetone. Nabumetone, however, has had a relatively short clinical experience. It remains to be seen whether, over time, reported incidence of ulceration are truly lower with nabumetone than with other NSAIDs.

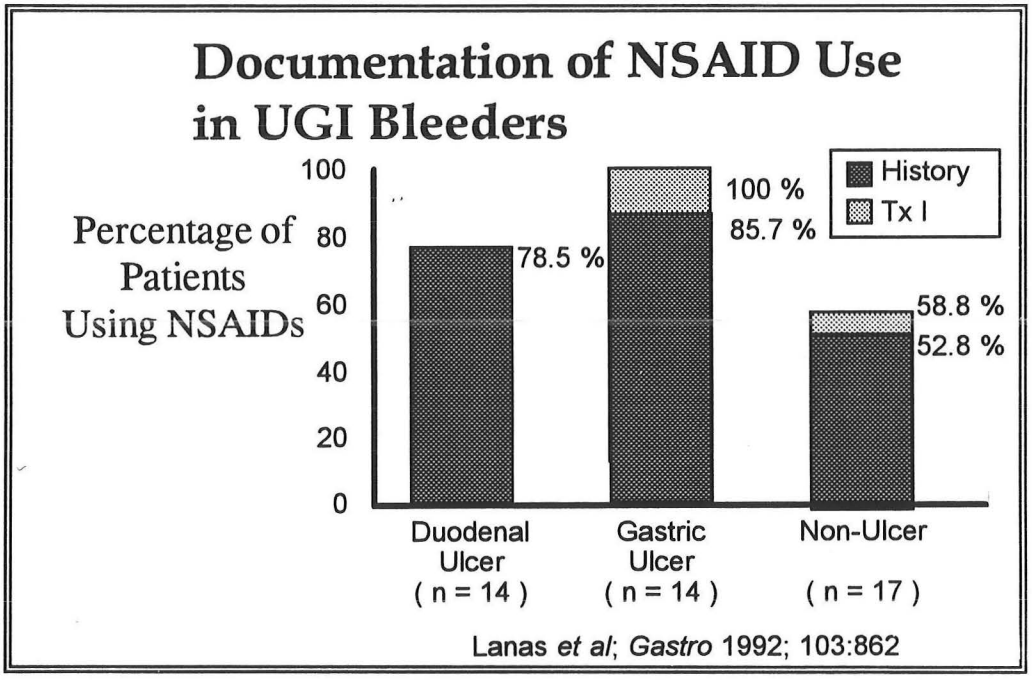
Undocumented Use and Over-the Counter NSAIDs

Precise quantification of NSAID-risk is further complicated by undocumented NSAID consumption. Total NSAID usage is probably underestimated given the recent over-the-counter (OTC) availability of NSAIDs. For example, the **figure (below)** shows results of a study in which the prevalence of NSAID use in patients who presented to the hospital with upper gastrointestinal bleeding was assessed by history[79]. In this urban population of upper gastrointestinal bleeders, 42% of the NSAIDs consumed were <u>not</u> prescribed (i.e., OTC). Notably, 35% of these bleeders were taking some form of non-prescribed aspirin, accounting for the overwhelming majority of NSAID use. Adding all forms of NSAID use, prescribed and OTC, and, aspirin and non-aspirin, NSAIDs were used by 65% of these gastrointestinal bleeders when use was assessed by history.



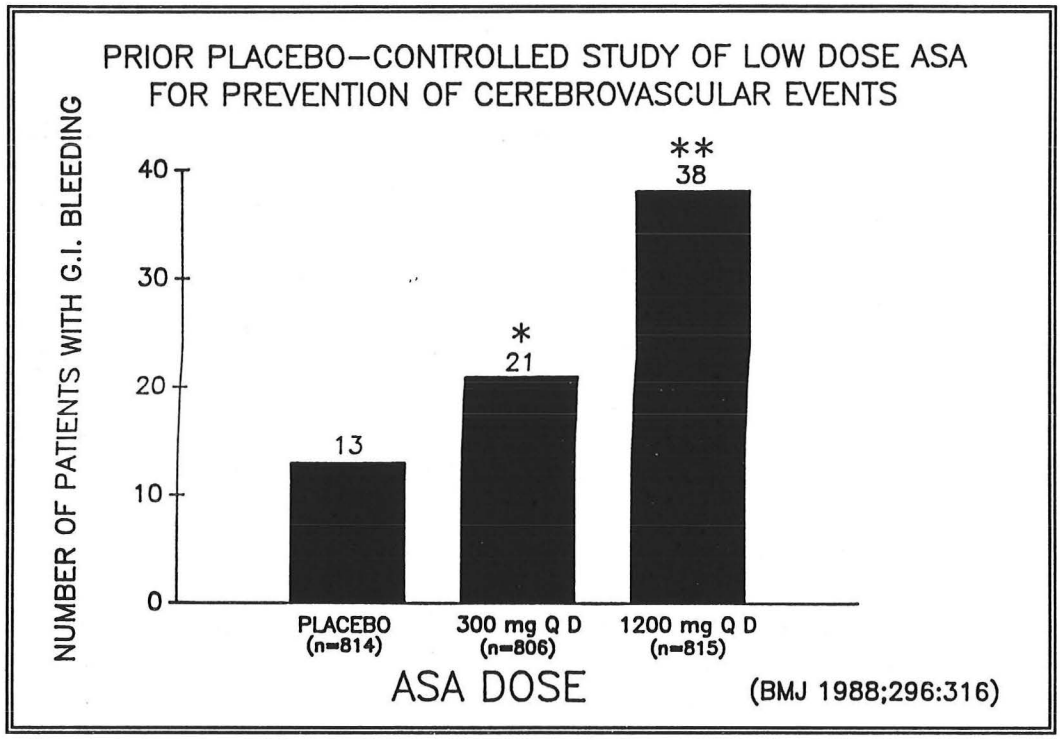
Numerous OTC compounds are available which contain aspirin or other NSAIDs. In the **Appendix**, is a list of currently available OTC and prescription products which contain aspirin, salicylates, ibuprofen or naproxen. Unfortunately, in many instances both the patient and physicians are unaware that such compounds are being taken.

The thromboxane index, an assay of platelet cyclooxygenase activity, is a test that has been investigationally employed to document NSAID ingestion when use is not apparent by history, but nevertheless suspected[68,80]. Since platelet cyclooxygenase is irreversibly inhibited by aspirin, and variably inhibited by other NSAIDs, a low serum platelet cyclooxygenase activity would suggest NSAID exposure. In a study of bleeding ulcer and non-ulcer patients, the thromboxane index improved documentation of NSAID use[80] **(Figure, below)**.



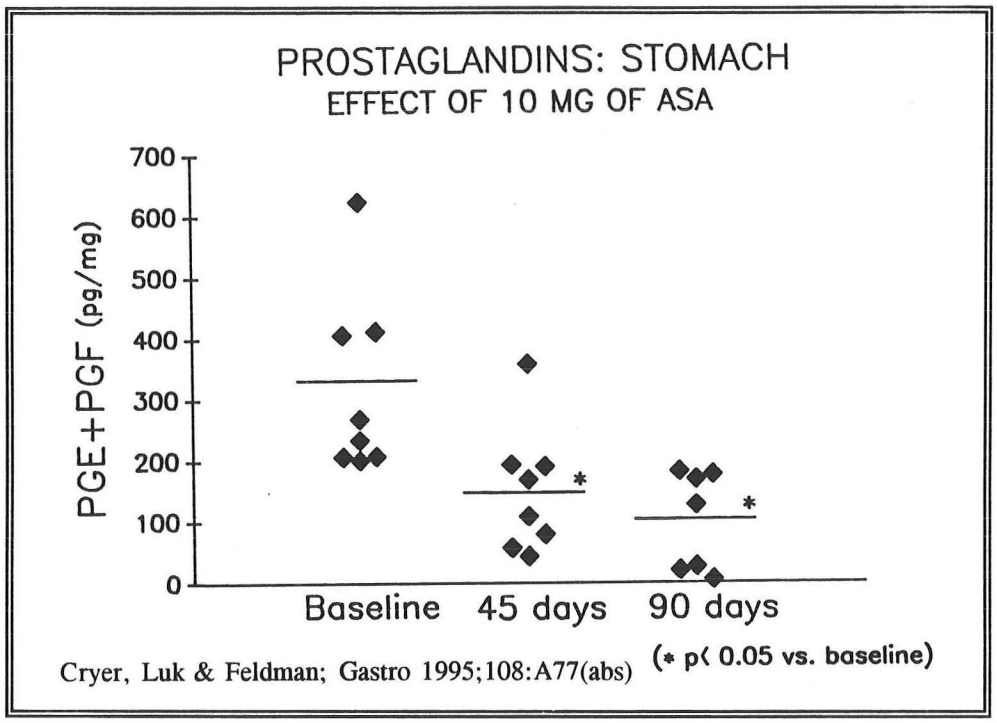
Low-Dose Aspirin

Low daily doses of aspirin (usually 325 mg per day) are very commonly prescribed for prevention of cardiovascular and cerebrovascular diseases [81-85]. In placebo-controlled studies of low-dose aspirin, aspirin therapy increased risks of GI bleeding [82] and increased the likelihood for hospitalization for ulcers[83]. Moreover, aspirin use as low as 75 mg per day has been associated with increased risk of GI bleeding[83]. Although it was suggested in many of these trials that low-dose aspirin may be associated with an increased risk of gastrointestinal toxicity, there are few data as to degree of risk. One placebo-controlled study of low-dose aspirin for prevention of cerebrovascular events reported increased rates gastrointestinal bleeding with aspirin when compared to placebo [85] **(Table, below)**.



In the above study, over the course of four years, greater than 2400 patients were randomized to placebo, aspirin 300 mg per day, or aspirin 1200 mg per day. With these doses, there was a significant dose-response relationship between aspirin dose and GI bleeding. Furthermore, this data suggests that an aspirin dose of 300 mg per day, while beneficial for vascular prophylaxis, is significantly associated with gastrointestinal complications. These findings have led to investigations evaluating toxicity of aspirin doses lower than 300 mg per day.

In a short-term study (1 week) of healthy subjects, 30 mg oral aspirin was found to significantly lower gastric juice prostaglandin concentrations[86]. In a more recent study of low-dose aspirin administered for 3 months, 10 mg of daily aspirin per day significantly lowered gastric mucosal prostaglandins and caused gastric ulceration[87] **(Figure, below)**.



NSAID-Induced Ulcers and *H. pylori*-Related Ulcers

NSAIDs and the bacterium, *Helicobacter pylori (H. pylori)*, are the two main etiologies for gastroduodenal ulcers. There are many characteristics of NSAID-induced ulcers and *H. pylori*-related ulcers to suggest that these two types of ulceration are separate pathophysiologic entities. First, NSAID-ulcers occur in individuals not infected with *H. pylori*[88]. Anatomic location, histology, patterns of recurrence, and symptoms also distinguish the two types of ulcer. In those who develop ulcers in association with NSAID use, gastric ulcers are about twice as likely as duodenal while *H. pylori*-related ulcers are more frequently duodenal. *H. pylori* nearly always is associated with a chronic active gastritis, while histologic gastritis is not an expected feature of NSAID-induced ulcers[89]. Experimental administration of an NSAID does not cause a histologic gastritis[90]. Since *H. pylori* is found in up to 50% of normal subjects older than age 60, NSAID use by older individuals can be expected to result in NSAID-induced ulcers which are associated with chronic active gastritis in about half of the older ulcer patients (assuming an equivalent predisposition for ulceration in *H. pylori*-infected and non-infected subjects). Indeed, in the literature about half of NSAID-associated ulcers are associated with chronic active gastritis [89].

Another notable difference between NSAID-induced and *H. pylori*-related ulcers is the pattern of their recurrence. When NSAID use is discontinued, NSAID ulcers should not recur. This compares to *H. pylori*-related ulcers which will have recurrence rates of 50% to 80% by one year if the organism is not eradicated by antibiotics[91-93]. Finally, dyspepsia is a common feature of *H. pylori* related ulcers, while most NSAID-induced ulcers are asymptomatic.

Since NSAIDs and *H. pylori* each may cause ulcers, a reasonable question is whether risk for ulceration is higher with combined *H. pylori* infection and NSAID consumption than with either of those factors alone. Two studies have suggested that *H. pylori* increases the risk for NSAID-induced ulceration[94,95]. However, since there was a small number of patients in each of these studies, confirmation is needed by additional studies of larger number of patients before a firm conclusion can be made regarding any additive effect between *H. pylori* and NSAIDs.

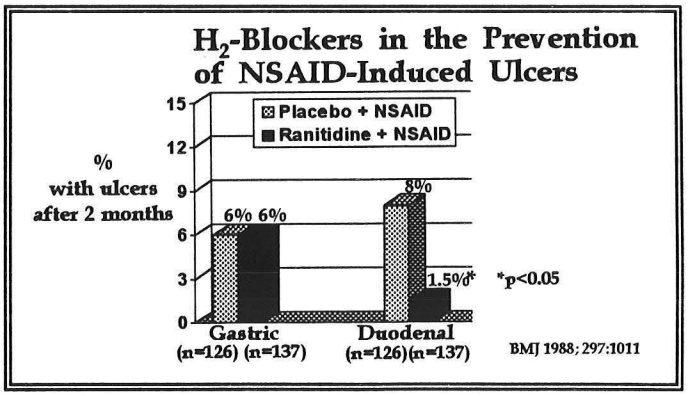
THERAPY FOR NSAID-INDUCED ULCERS

Therapy for NSAID-induced ulcers needs to be tailored depending on whether one is attempting to heal or to prevent NSAID-induced ulcers. Since therapeutic strategies differ, prevention and healing will be discussed separately.

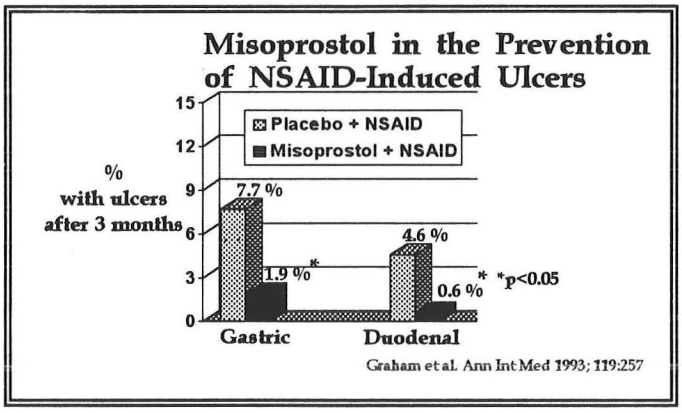
Prevention of NSAID-Induced Ulcers

Initial attempts to lower gastroduodenal toxic effects seen with aspirin and other NSAIDs were directed towards development of alternative formulations. Newer NSAIDs, enteric-coated preparations, suppositories, and prodrugs (e.g., sulindac) disappointingly continue to be associated with ulceration[49,50,96-99]. Consequently a major research interest has arisen to investigate other drugs, that when coadministered with NSAIDs, will either protect against or prevent mucosal ulceration.

There have been two major studies which have evaluated whether an H_2-receptor antagonist, when co-administered with an NSAID, can prevent NSAID-induced ulcers[70,71]. In both studies, after two months of co-administration of ranitidine (150 mg twice daily) to arthritis patients who were taking NSAIDs, the incidence of duodenal ulcer was significantly reduced in patients taking ranitidine compared to patients taking placebo[70,71] **(Figure, right)**. Gastric ulcer incidence, however, was similar in the two groups **(Figure, right)**. Since a) most NSAID-induced ulcers are gastric rather than duodenal, and b) one can not predict which type of NSAID-induced ulcer will develop, H_2-receptor antagonists are not ideal drugs for NSAID-ulcer prophylaxis.



A number of synthetic prostaglandins have been orally administered to prevent NSAID-induce mucosal damage. Most investigation of prevention of NSAID-related mucosal injury with prostaglandins has been with misoprostol, a synthetic PGE_1 analogue. 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 osteoarthritis[69]. 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 ($\geq$ 0.5 cm in diameter) had developed in 12.3% of placebo-treated patients compared to only 4.2% and 0.7% of patients treated with the lower and higher doses of misoprostol, respectively. In a second three month trial of similar design, the same investigators observed that misoprostol (200 μg four times daily) was more effective than sucralfate (1 gram four times daily) in the prevention of new gastric ulcers in arthritis patients who were taking NSAIDs. Gastric ulcers occurred in 9.2% of patients taking sucralfate with their NSAID and in only 0.8% of those taking misoprostol with their NSAID[100]. In the same study, duodenal ulcer incidence was equally low in sucralfate and misoprostol-treated patients[100].



Misoprostol has also been shown to be effective in the prevention of NSAID-induced duodenal ulceration. In a recent study of arthritis patients who were taking NSAIDs who were also coadministered either misoprostol (200 μg four times daily) or placebo, misoprostol significantly reduced the incidence of duodenal ulcers as 4.6% and 0.6% of patients had duodenal ulcers in placebo-treated and misoprostol-treated groups, respectively, after three months of therapy **(Figure, above)**[72]. Thus, misoprostol appears to be superior to both ranitidine and sucralfate for the prevention of endoscopically diagnosed gastric ulcers and as effective as ranitidine and sucralfate in preventing endoscopically diagnosed duodenal ulcers.

The above trials have all involved assessment of ulcers which were defined endoscopically, many of which were asymptomatic. While these endoscopically-detected ulcers provide data which can be used to statistically compare the effects of various drugs, the more clinically relevant question is whether prophylaxis against NSAID-ulcers with any drug will prevent ulcer bleeding or perforation. This information is recently available. In 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[101]. Another question which remains to be answered regarding

prophylaxis with misoprostol is whether it will prevent more distal small intestinal ulceration (jejunal or ileal)[102,103].

There are no published data yet which support the use of proton-pump inhibitors (omeprazole and lansoprazole) for prophylaxis against NSAID-induced ulcers. However, omeprazole has been shown to prevent lesser forms of aspirin-induced injury (erosions and submucosal hemorrhage)[104] and data currently available only in abstract form suggest that omeprazole and lansoprazole may be effective for NSAID-ulcer prophylaxis[105,106].

Since only a minority of all NSAID users will develop an ulcer, it is not cost effective to provide prophylaxis to every person who takes a NSAID. Thus, there has been a large amount of debate concerning which subgroups of NSAID users are most appropriate to be given prophylactic therapy[73]. Many potential risk factors have been analyzed in a number of epidemiologic and prophylaxis studies **(Table, below)**. Patients with a previous history of ulcer disease appear to be at increased risk to develop a NSAID-induced ulcer[70,72]. Ideally, these individuals should not receive NSAIDs. However, many patients require NSAIDs for adequate pain control and mobility. Such patients who have a documented history of previous ulcers should be considered for prophylaxis, particularly if they have a history of previously complicated ulcers. Older age, dyspeptic symptoms, and co-morbid diseases have all be proposed as other variables which might place one at higher risk for NSAID-induced ulceration. However, there is less consensus regarding those variables. As stated previously, compared to non-NSAID users, patients who take NSAIDs will more frequently present with a perforated or bleeding ulcer which has previously been asymptomatic. Thus, the presence or absence of dyspepsia does not reliably identify NSAID-users who are at greatest risk for development of complications, and, therefore should not be used to guide our decision as to who should receive prophylactic therapy. In the NSAID-induced ulcer prevention studies, older age *per se* has not been a risk factor for NSAID-related ulceration[69-72]. Thus, older age, in and of itself, should not be used as an exclusive criteria for NSAID prophylaxis. Individuals with co-morbid diseases (such a functionally compromising heart or lung disease) are probably more likely to suffer poor outcomes from a complication of a NSAID-induced ulcer. Since older patients, in general, have a greater number of co-morbid diseases than younger patients, certain older (and selected younger) patients might be considered on a case-by-case basis for NSAID-ulcer prophylaxis[73].

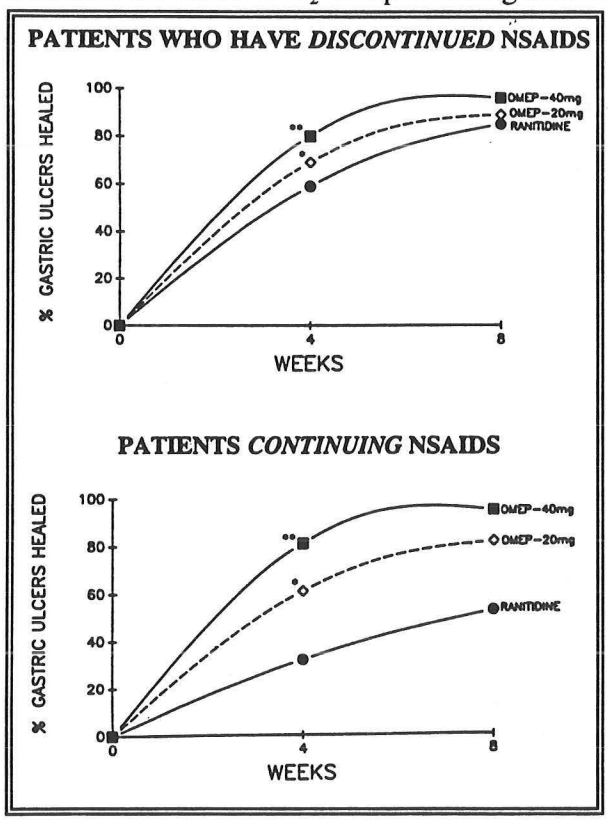
Possible Risk Factors for NSAID-induced Ulcer Complications

Patient-related	NSAID-related
History of Ulcer	Dose
Age	Duration of NSAID
Co-Morbid Diseases	Type of NSAID
Concomitant Steroids	
Concomitant Anticoagulants	
Unproven:	
gender, alcohol, smoking	
H. pylori, symptoms	

Treatment of NSAID-Induced Ulcers

Data regarding treatment of NSAID-induced ulcers is more straightforward than the prophylaxis literature. When attempting to treat an ulcer which has formed during NSAID use, the first step is always to stop the NSAID. Once an NSAID is stopped, high healing rates of NSAID-induced gastric and duodenal ulcers can be achieved by treatment with standard doses of H_2-receptor antagonists[107,108]. Ulcer healing rates after NSAID cessation shown are comparable to historical healing rates of ulcers not associated with NSAID use which were treated with H_2-receptor antagonists[109]. In some patients, however, NSAIDs cannot be discontinued. Most gastric or duodenal ulcers induced by NSAIDs can be healed with H_2-receptor antagonists while NSAIDs are continued[107,110-114]. However, in this situation, healing rates are lower than when NSAIDs are discontinued. Nevertheless, approximately 80% of gastric ulcers and approximately 90% of duodenal ulcers can be healed by 12 weeks while NSAID use continues[107]. Size of an NSAID-induced gastric ulcer is also a major determinant of success of H_2-receptor antagonist therapy. 90% of aspirin-induced gastric ulcers <0.5 cm in diameter can be healed by 2 months of a therapy with a H_2-receptor antagonist while aspirin is continued, while only 25% of gastric ulcers >0.5 cm in diameter will be healed at two months after comparable therapy[110].

Omeprazole is a potent anti-secretory agent which blocks gastric acid secretion at the level of the parietal cell by inhibiting H^+/K^+-adenosine triphosphatase pumps[115]. In patients in whom NSAIDs can be stopped, healing rates of NSAID-induced gastric ulcers are similar when treated with either a H_2-receptor antagonist or omeprazole **(Figure, below)**[114].



While statistically significantly higher healing rates can be achieved with omeprazole at 4 weeks in such patients, the actual percentage increment of healing is small, and, healing rates at 8 weeks with the two classes of medications are not significantly different. In patients with NSAID-induced gastric ulcers in whom NSAIDs **can not** be stopped, omeprazole is considerably more effective than ranitidine for ulcer healing **(Figure, left)**[114]. Notably, 95% of NSAID-induced gastric ulcers can be healed after 8 weeks of omeprazole (40 mg daily) in spite of continued NSAID use[114]. Further studies evaluating the use of omeprazole in the treatment of NSAID-induced gastric ulcers will be necessary to verify these initial observations. There are no published studies currently available evaluating omeprazole for healing of NSAID-induced duodenal ulcers while NSAID use continues. However, it is reasonable to presume that omeprazole should be at least as effective, if not more effective, for NSAID-induced duodenal ulcers as it is for NSAID-induced gastric ulcers since duodenal ulcers, in general, tend to be much more responsive to acid suppressive therapy than do gastric ulcers.

Management Summary for Therapy of NSAID-Induced Ulcers.

The initial approach toward **prevention** of NSAID-induced ulcers should be directed toward identification of individuals who may be at greatest risk for NSAID-related ulceration. Patients with a history of previous complicated peptic ulcers will certainly be included as high risk for NSAID-induced ulcers. Some elderly patients and some patients with co-morbid diseases may also fall into this category. If only, analgesia is desired, it might be prudent to initiate therapy with acetaminophen or a nonacetylated salicylate, thus avoiding other NSAIDs associated with more substantial gastroduodenal injury. However, many patients, especially those with inflammatory diseases, may require potentially ulcerogenic NSAIDs, in which case the lowest therapeutic anti-inflammatory dose should be started. If the NSAID-taking patient has significant risk factors for NSAID-induced ulceration, considerations should be given for prophylaxis with a co-administered agent.

Misoprostol is the only drug currently approved for the prevention of NSAID-induced ulcers. Unfortunately, misoprostol prophylaxis is poorly tolerated by many patients. Greater that 30% of patients may experience dose-related diarrhea on initiation of misoprostol[72]. Patients who are candidates for prophylaxis should be started at a low doe of misoprostol (100 μg four times daily) and the misoprostol dose should be incrementally increased to 200 μg four times daily as tolerated.

It is possible that the proton pump inhibitors (omeprazole and lansoprazole) may prove to be efficacious for prophylaxis of NSAID-induced ulcers. Prospective, placebo-controlled trials of omeprazole and lansoprazole are currently underway to evaluate their efficacy.

Prevention of NSAID-induced Gastric Ulcers

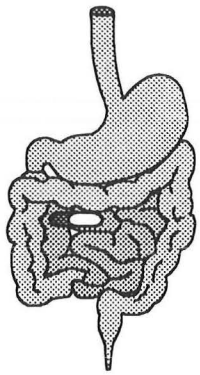
Medication	Effective
Antacids	?
Sucralfate (*Carafate*^{R})	No
H_2-Blockers	No
Misoprostol (*Cytotec*^{R})	Yes
Omeprazole (*Prilosec*^{R})	Possibly

Prevention of NSAID-induced Duodenal Ulcers

Medication	Effective
Antacids	?
Sucralfate (*Carafate*^{R})	?
H_2-Blockers	Yes
Misoprostol (*Cytotec*^{R})	Yes
Omeprazole (*Prilosec*^{R})	Possibly

The initial attempt at **treatment** of NSAID-induced ulcers should be cessation of the NSAID. Once the NSAID has been stopped, standard healing doses of any of the H_2-receptor antagonists (cimetidine, ranitidine, famotidine, or nizatidine) should be prescribed. However, complete withdrawal of the NSAID may not be possible in all patients, but they may tolerate a reduction in NSAID dose. In cases where NSAIDs need to be continued, omeprazole (40 mg daily) should be prescribed for 8 weeks. Patients who have continuously taken NSAIDs during the period of ulcer healing or those who need to restart previously discontinued NSAID therapy, should have follow-up studies to document healing of NSAID-induced gastric and, in some situations, NSAID-induced duodenal ulcers. Among patients with NSAID-induced duodenal ulcers, those who do not require resumption of their NSAIDs will not require follow-up endoscopy to document ulcer healing.

SMALL INTESTINE



Although the duodenum is part of the small intestine, NSAID effects in the duodenum are more similar to effects in the stomach than the jejunum and ileum. Thus for purposes of this discussion, the small intestine will refer primarily to the jejunum and ileum. The variety and magnitude of clinical consequences within the small intestines of NSAID users have, until very recently, been under appreciated since the small intestine has traditionally been relatively inaccessible for investigation. In recent years, however, there has been a marked expansion of investigations which have better defined the magnitude and mechanisms of the small intestinal effects of NSAIDs.

ULCERS

It is quite common for patients to have gastrointestinal bleeding while taking NSAIDs yet have no endoscopically identifiable bleeding source in the stomach, duodenum or colon. Although the small intestine is clinically suspected as the site of blood loss, this is usually not confirmed by diagnostic radiologic studies. In addition to gastrointestinal bleeding, the other life-threatening consequence of the small intestinal effects of NSAIDs is perforation. Most evidence that NSAIDs cause perforation and hemorrhage of the small intestine comes from a case-control study[116], and several case reports[117-121]. In a retrospective study of infants born with a patent ductus arteriosus who were treated with indomethacin (as a prostaglandin inhibitor) or treated by surgical ligation, 10% of indomethacin-treated infants developed intestinal perforation while none of the surgically-treated infants experienced perforations[122].

There have been very few prospective studies evaluating the association of NSAIDs and small intestinal ulceration. Only one study has endoscopically-assessed the small intestines of rheumatoid arthritis patients who were taking NSAIDs and who had chronic gastrointestinal blood loss[123]. In this study, 4 ileal and jejunal ulcers (26% prevalence) were visualized. The major problem with this study is the methodology. Specifically, the type of endoscope used in this study has poor sensitivity for visualization of intestinal mucosa. It views about 1/3 of the circumference of the intestinal lumen, allows very brief inspection of any particular intestinal area, and, is not able to return to an area of suspicion for closer inspection. Just very recently, newer generation enteroscopes have been introduced which have a more extensive field of vision and allow controlled mucosal inspection.

More conclusive evidence for the association between NSAIDs and small intestinal ulcers was recently provided by an autopsy study which compared rates of ulceration in patients who had been taking NSAIDs prior to death to a control group of patients who had not taken NSAIDs

pre-mortem[124]. In this study, the small intestines were examined at autopsy of 713 patients, of whom 249 had been taking NSAIDs. Small intestinal ulcers were found in 8.4% of the NSAID group and in only 0.6% of the control group ($p < 0.001$), the strongest data available to suggest NSAIDs as a cause of small intestinal ulceration **(Table, below)**. In the same study, gastric and duodenal ulcers were seen in 22% and 12% respectively of NSAID users[124]. However, there was no correlation between ulcers in the stomach or duodenum and ulcers in the small intestine. These data suggest that one can not predict the absence or presence of small intestinal ulcers based on endoscopic assessment of the upper gastrointestinal tract. Of particular interest in this study, 25% of the NSAID users had been taking a single daily dose of aspirin at a dose of 300 mg per day or less. 3 patients in this study died of intestinal perforation. All of these patients were taking NSAIDs, rendering a 1% perforation rate related to NSAIDs.

Prevalence of Small Intestinal Ulceration

Control Group (*n*=464)	*NSAID Group* (*n*=249)
0.6 %	8.4 % *

* $p<0.001$

Allison et al. N.Eng.J.Med. 1992 ; 327:749

The mechanisms for NSAID-induced small intestinal perforation are the same as those in the stomach and duodenum, that is, a local mucosal toxic effect and prostaglandin inhibition. A higher than expected rate of intestinal perforation with slow-release NSAID preparations suggests a role for a local effect [117]. The observation that depletion of mucosal prostaglandins by active or passive immunization with antibodies directed prostaglandins will cause intestinal perforation in animals[125], argues in favor of prostaglandin inhibition as the principal mechanism.

STRICTURES

Similar to the effects of NSAIDs in the esophagus, NSAID use can result in strictures of the small intestine (and colon)[126-130]. However, there are some unique pathological aspects to the intestinal strictures. Their pathological configurations range from non-specific broad-based strictures, to intestinal diaphragms[126,127,129,130]. These diaphragms are usually multiple, thin (2 to 4 mm), concentric web-like septa, which may narrow the lumen down to the size of a pinhole. The lumen may become constricted to the point where patients on NSAIDs could develop symptoms of small intestinal obstruction[131-133]. These diaphragms are usually located in the jejunum. Their histology reveals submucosal fibrosis with normal overlying epithelium, except the central tip of the diaphragm, which contains acute and chronic inflammatory cells. Since these intestinal diaphragms have not been associated with conditions other than NSAIDs, their occurrence is now thought to be pathognomonic of NSAID use[126]. The prevalence of these diaphragms is rather low. In a retrospective review of surgically resected small intestinal specimens, out of 456 specimens resected over 11 years, diaphragms were detected in 7 (1.5% prevalence) and NSAIDs were associated with each case[134].

Small intestinal diaphragms are particularly difficult to diagnose since no conventional diagnostic procedure is very helpful. During barium studies the strictures may mimic exaggerated plica circularis. Because the diaphragms do not distort the intestinal wall, at laparotomy they are not apparent on visual inspection. To locate the diaphragms the surgeon may have to palpate the intestinal wall. If the small intestine is inflated with air, they can be more easily detected.

ENTEROPATHY

In addition to structural lesions such as ulcers, strictures and diaphragms, NSAIDs can cause a clinical entity of diffuse intestinal inflammation and increased intestinal mucosal permeability. This so called "NSAID enteropathy" may be characterized clinically by occult blood loss, iron deficiency anemia, malabsorption and a protein loosing enteropathy[135-141] **(Table, next page)**. Of these manifestations, the blood loss is the most clinically significant. Many patients who chronically take NSAIDs will present with hemeoccult positive stools and iron deficiency anemia and have no endoscopically-identifiable source in the upper gastrointestinal tract or colon which adequately explains their bleeding[137,142,143]. In many of these cases, the blood loss is occurring in the small intestine and may be of similar magnitude as in patients with intestinal malignancies who also present with severe iron deficiency anemia[142,144]. After blood loss, protein loss is the second most common clinical manifestation of NSAID enteropathy. Intestinal protein loss is usually mild and usually does not lead to major clinical problems. However, occasional patients with NSAID enteropathy have reported serum albumin concentrations as low as 1.7mg/dl[135]. Ileal dysfunction may also occur but is usually asymptomatic and not clinically relevant [141]. Occasionally, diarrhea secondary to fat or bile salt malabsorption may be experienced. Laboratory detection of vitamin B_{12} deficiency is common in rheumatoid arthritis patients[145], but clinical manifestations of B_{12} deficiency in this population

are rare. D-xylose (carbohydrate) and fat malabsorption are also mild and not clinically relevant[138-140]. Taking all of these various manifestations into account, it is estimated that up to 70% of patients taking NSAIDs will have some component of NSAID enteropathy,[126,135,136] although most of these presentations are mild and are not clinically apparent.

NSAID Enteropathy

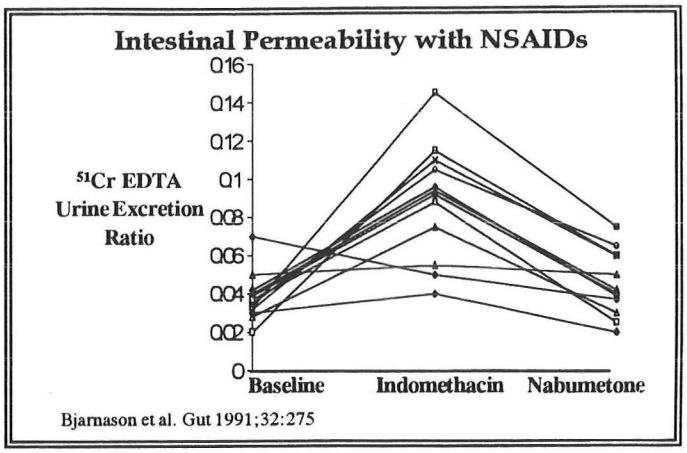
Abnormality	*Clinical Implication*
Chronic blood loss	May contribute to iron deficiency
Protein loss	May cause hypoalbuminemia
Ileal dysfunction	Asymptomatic, not clinically relevant
D-xylose malabsorption	Mild, not clinically relevant
Steatorrhea	Mild, not clinically relevant

Bjarnason, I et al. Gastroenterology 1993;104:1832

The pathophysiologic components which underlie NSAID enteropathy are increased intestinal permeability and intestinal inflammation. The precise mechanisms through which NSAIDs lead to these changes are uncertain. Techniques involving radionuclide and permeability probes have been used to examine small intestinal inflammation and permeability, respectively, in patients taking NSAIDS. Each of these pathologic processes and techniques is described in more detail in the following sections.

Permeability. Intestinal permeability is assessed experimentally by measurement of urinary recovery of orally administered test probes. In the normal, intact small intestine, these tests probes can not pass from the intestinal lumen to the blood stream. When intestinal mucosal integrity is interrupted, such as with inflammation or NSAIDS, these agents are able to traverse the intestinal wall and appear in the systemic circulation. Most studies assessing the effects of NSAIDs on small intestinal permeability have used chromium-labelled (^{51}Cr) EDTA[146-150]. In

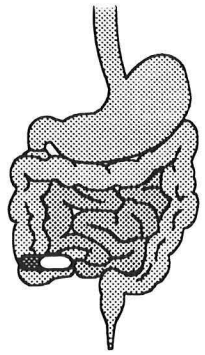
arthritis patients and normal volunteers, NSAID administration results in increased urinary appearance of ^{51}Cr-EDTA[149] **(Figure, right)**. In response to nabumetone, mean ^{51}Cr-EDTA urinary excretion is similar to baseline. This may explain nabumetone's low clinical incidence of intestinal ulceration. Changes in intestinal permeability can be detected after two doses of a NSAID and within 12 hours of administration[146]. After cessation of NSAID therapy, intestinal permeability usually reverts to normal within 4 days[149].



Inflammation. A significant increase in intestinal inflammatory cell infiltrate occurs within three hours of NSAID administration[151]. Unfortunately, this assessment requires biopsy and histology. A non-invasive method to assess intestinal inflammation involves intravenous injection of neutrophils labelled with ^{111}Indium (^{111}In) followed by abdominal imaging by scintigraphy. The labelled neutrophils localize to areas of active inflammation, thus providing a means to assess the intestinal effects of NSAIDs. Approximately 50% of patients on chronic NSAID therapy will have an ^{111}In-labelled leukocyte scintigram which demonstrates increased inflammation in an intestinal location[126]. Furthermore, over the four days which follow ^{111}In administration, these patients will have increased ^{111}In fecal excretion. While ^{111}In scintigraphy is qualitative, fecal excretion of ^{111}In is quantitative and is a sensitive index of inflammation throughout the gastrointestinal tract. 60% to 70% of patients on NSAIDs have increased ^{111}In fecal excretion[126]. Patients not treated with NSAIDs have normal ^{111}In excretion values.

THERAPY

There are no therapies which have been clearly documented as effective treatments for NSAID-induced intestinal ulcers, strictures, or NSAID enteropathy. Small intestinal perforation is surgically treated. Likewise, bowel obstruction secondary to NSAID-induced strictures or diaphragms may require surgery. NSAID enteropathy is usually not clinically apparent and, therefore, would not usually require any therapeutic intervention. When chronic intestinal blood and/or protein loss present with clinical manifestations, cessation of NSAID therapy should prove therapeutic. A small retrospective study has suggested that concomitant misoprostol administration may improve anemia in NSAID enteropathy[152]. If protein malabsorption is a problem, a change of NSAID therapy to nabumetone may improve mucosal permeability[149] and consequently reduce protein loss. Co-administration of metronidazole may also reduce NSAID-induced permeability changes[153]. Improvement in NSAID-induced permeability with metronidazole may be related to its antibacterial effects, a hypothesis which supports the theory that increased permeability to intestinal bacteria may contribute to the pathogenesis of NSAID-induced intestinal inflammation.

COLON 

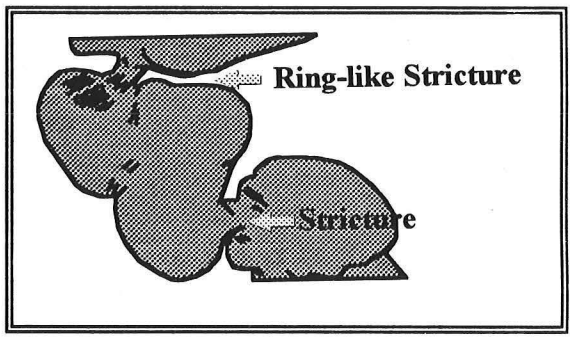
As in the small intestine, most of the effects of NSAIDs in the colon are asymptomatic. A convenient way to categorize these effects is to segregate findings which occur in individuals with no prior history of colonic disease from instances where NSAIDs exacerbate preexisting colonic pathology.

EFFECTS IN SUBJECTS WITH NO PRE-EXISTING COLONIC DISEASE

Similar to small intestinal processes, NSAID-induced ulceration, strictures and diaphragms occur in the colon. In the colon, however, there are fewer reported cases. The fact that a) NSAIDs have fewer adverse effects more distally in the gastrointestinal tract and, b) most NSAIDs are entirely absorbed in the upper gastrointestinal tract, support the argument that local mucosal effect of NSAIDs is a major pathogenetic component.

Ulceration. Colonic ulceration associated with NSAIDs has been reported in the cecum, transverse and sigmoid colon, although the left side of the colon is the most common site of ulceration[154-160]. Ulcer histology shows non-specific changes. All classes of NSAIDs have caused colonic ulceration, including aspirin at a dose of 325mg/day[154]. Ulceration may be complicated by bleeding[154,159,161] and perforation, especially in the cecum[161]. It is difficult to demonstrate a cause-and-effect relationship between NSAIDs and ulceration since almost all information comes from case reports. However, a role for NSAIDs in colonic perforation and bleeding is supported by epidemiologic observations that patients with these complications are more than twice as likely as controls to have taken NSAIDs[161].

Strictures. As shown diagrammatically in the **Figure (right)**, diaphragm-like strictures and broad-based strictures have also been described in the ascending colon of a patient taking a slow-release form of diclofenac[162]. These lesions macroscopically and microscopically resemble those in the small intestine. It has been suggested that the diaphragm-like lesions may represent a specialized mucosal response peculiar to the small and large intestine[162].



Colitis. NSAIDs can induce a variety of types of colitis. Cases of eosinophilic[163], collagenous[164-166], pseudomembranous[167], and non-specific colitis[166,168,169] have been associated with NSAIDs. A disproportionately high number of colitis cases have occurred in patients taking mefenamic and flufenamic acid[163,168,169]. The usual presentation is watery diarrhea which, on occasion, may be bloody. Significant weight loss may also occur. Colonoscopy is usually normal, although there may be diffuse ulcerations which may mimic inflammatory bowel disease. The extent of ulceration may range from proctitis to pancolitis. Histology usually reveals a non-specific mild colitis unless one of the other variants is present (eosinophilic, pseudomembranous, or collagenous).

Anorectal Disease. Rectal administration of NSAIDs in the form of suppositories has been frequently associated with inflammation, ulcers, and strictures of the anus and rectum[33,51,170-175]. Patients may complain of proctalgia, tenesmus or watery diarrhea[51]. Bloody and mucoid stools, fecal incontinence have also been described[170]. Approximately 10% to 30% of patients receiving NSAID suppositories will report a significant side effect[172,173].

EFFECTS IN SUBJECTS WITH PRE-EXISTING COLONIC DISEASE

Diverticular Disease. There are individual case reports suggesting NSAIDs as the cause of colonic diverticular perforation [117,176]. Many cases involved a sustained release preparation of indomethacin in which instances the perforations were attributed to a mechanical effect of the capsule being caught in a diverticulum. In one prospective study and in another case-control study, patients admitted with complications of diverticular disease has significantly greater NSAID consumption than controls[177,178]. Overall, these studies suggest that serious complications of diverticular disease may be associated with NSAIDs.

Inflammatory Bowel Disease. Not only can NSAIDs induce disease which mimics inflammatory bowel disease (IBD), they may also activate IBD which has been previously quiescent. This occurrence is more frequently observed in ulcerative colitis than Crohn's disease. One postulated mechanism through which NSAIDs may exacerbate colonic inflammation is by inhibiting cyclooxygenase and shunting arachidonic acid metabolism towards the pro-inflammatory leukotrienes. Of all IBD patients, only a subset experience symptomatic flares when placed on a NSAID. These patients, when they relapse, will do so within a few days of receiving a NSAID[179].

THERAPY

All of the colonic diseases associated with NSAIDs, pre-existing and de novo, should improve with NSAID discontinuation. There is no specific treatment for colonic ulcers. They usually have significantly healed by three weeks after NSAID discontinuation[154]. Endoscopic balloon dilation of strictures has been suggested for symptomatic patients[162]. This therapy offers an attractive alternative for patients who would otherwise proceed to surgery. With NSAID suppositories, anorectal stenoses have occurred that were so severe that serial rectal dilations were required. In spite of these treatments, a few patients developed bowel obstructions requiring protocolectomy[170].

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OVER-THE-COUNTER (OTC) & PRESCRIPTION PRODUCTS CONTAINING ASPIRIN, ASPIRIN-LIKE COMPOUNDS, IBUPROFEN, OR NAPROXEN

OTC PRODUCTS CONTAINING ASPIRIN AND/OR ASPIRIN-LIKE COMPOUNDS

Alka-Seltzer Antacid/Pain Reliever Effervescent Tablets
Alka-Seltzer Plus Cold Medicine Tablets
Anacin Caplets/Tablets
Anacin Maximum Strength Tablets
Arthritis Pain Formula Tablets
Arthritis Strength Bufferin Tablets
Ascriptin Caplets/Tablets
Ascriptin A/D Caplets
Aspergum
Bayer Aspirin Caplets/Tablets
Bayer Children's Chewable Tablets
Bayer Plus Tablets
Maximum Bayer Caplets/Tablets
8-Hour Bayer Extended-Release Tablets
BC Powder
BC Cold Powder
Buffaprin Caplets/Tablets
Bufferin Arthritis Strength Caplets
Bufferin Caplets/Tablets
Cama Arthritis Pain Reliever Tablets
Doan's Pills Caplets
Ecotrin Caplets/Tablets
Empirin Tablets
Excedrin Extra-Strength Caplets/Tablets
Midol Caplets
Mobigesic Analgesic Tablets
Norwich Tablets
P-A-C Analgesic Tablets
Pepto-Bismol Liquid/Tablets
Sine-Off Tablets, Aspirin Formula
St. Joseph Adult Chewable Aspirin
Therapy Bayer Caplets
Trigesic
Ursinus Inlay-Tabs
Vanquish Analgesic Caplets

OTC PRODUCTS CONTAINING IBUPROFEN

Advil Caplets/Tablets
Advil Cold/Sinus Caplets
Bayer Select Ibuprofen Pain Relief Formula Caplets
Dristan Sinus Caplets
Haltran Tablets
Ibuprohm Ibuprofen Caplets/Tablets
Midol IB Tablets
Motrin IB Caplets/Tablets
Nuprin Ibuprofen Caplets/Tablets
Sine-Aid IB

OTC PRODUCTS CONTAINING NAPROXEN

Aleve Caplets/Tablets

Important Note: *This list compiled Oct 1995. In the future, manufacturers may add new products which contain aspirin or NSAIDs or may reformulate some of the current products.*

APPENDIX

PRESCRIPTION PRODUCTS CONTAINING ASPIRIN AND/OR ASPIRIN-LIKE PRODUCTS

Darvon Compound-65
Disalcid Capsules/Tablets
Easprin Tablets
Empirin with Codeine Tablets
Equagesic Tablets
Fiorinal Capsules/Tablets
Fiorinal with Codeine Capsules/Tablets
Lortab ASA Tablets
Magsal Tablets
Mono-Gesic Tablets
Norgesic & Norgesic Forte Tablets
Percodan & Percodan-Demi Tablets
Robaxisal Tablets
Salflex Tablets
Soma Compound Tablets
Soma Compound with Codeine Tablets
Synalgos-DC Capsules
Talwin Compound Tablets
Trilisate Tablets/Liquid

PRESCRIPTION PRODUCTS CONTAINING IBUPROFEN

Children's Advil Suspension
Children's Motrin Suspension
Motrin Tablets

PRESCRIPTION PRODUCTS CONTAINING NAPROXEN

Anaprox/Anaprox DS Tablets
Naprosyn Suspension/Tablets

***Important Note**: This list compiled Oct 1995. In the future, manufacturers may add new products which contain aspirin or NSAIDs or may reformulate some of the current products.*

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