Adverse Effects of Nonsteroidal Anti-inflammatory Drugs on the Gastrointestinal System*

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ABSTRACT

Two enzymes, cyclo-oxygenase (COX) and 5-lipoxygenase, act upon arachidonic acids to produce prostaglandins and leukotrienes. Inhibition of COX-2 by nonsteroidal anti-inflammatory drugs (NSAIDs) lowers synthesis of proinflammatory prostaglandins and produces analgesia. COX-2 is highly inducible by endotoxin, IL-1, hypoxia, epidermal growth factor (EGF), benzo[a]pyrene, and transforming growth factor beta 1 (TGF-β1). COX-1 is constitutively expressed. Conventional NSAIDs also inhibit the synthesis of cytoprotective prostaglandins by COX-1 in the gastrointestinal tract. Surplus arachidonic acids accumulate and enhance the generation of leukotrienes via the lipoxygenase pathway inducing neutrophil adhesion to endothelium and vasoconstriction.

The NSAIDs harboring a carboxyl group also inhibit oxidative phosphorylation (OXPHOS) lowering adenosine-triphosphate (ATP) generation leading to loss of mucosal cell tight junctions and increased mucosal permeability. Administration of NSAIDs that do not interfere with OXPHOS, and concomitant use of prostaglandin analogues to restore cytoprotection reduces complications of NSAID use. However, no NSAID that lacks potential for serious gastrointestinal toxicity is currently available. Selective inhibitors of COX-2 and 5-lipoxygenase are newer, promising drugs. Surprisingly, COX-2 null mice are able to mount an inflammatory response, suffering however, from kidney dysfunction and a shortened life span. Results of clinical studies on the long-term use of NSAID drugs such as selective inhibitors are still pending.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective analgesic1 and antiphlogistic agents.2,3,4 Worldwide, physicians write over 100 million prescriptions for NSAIDs annually. Additional use arises from patient self-medication with one or more of a large number of non-prescription drugs containing NSAIDs.5 In the United States over-the-counter drug use of NSAIDs is 7 times the prescription use. Over 2 billion dollars are spent for NSAIDs annually. The gastrointesti-
nal tract remains the most acceptable and popular route of administration of NSAIDs. It offers the advantage of convenience and results in good absorption of the therapeutic compounds.6

Uses include the short-term treatment of dental7 or perisurgical pain8 and long term treatment of painful musculoskeletal disorders such as rheumatoid arthritis. Aspirin is beneficial in the treatment of coronary heart disease, and prophylactic aspirin use significantly reduces the risk of myocardial infarction.9,10 Newer studies suggest that certain NSAIDs may find further uses. Sulindac, for instance, can induce regression in rectal adenomatous polyps.11 Aspirin and other NSAIDs may prevent or inhibit colonic cancer.12,13 Treatment with NSAIDs exerts a stronger protective influence than steroids in Alzheimer's disease.14,15

However, between 20 and 30 percent of patients under NSAIDs therapy develop digestive symptoms.16 Adverse effects of NSAIDs involve all segments of the alimentary tract. For example, patients with esophageal reflux taking NSAIDs have an increased risk of esophageal stenosis.16 The more common, serious adverse effects of NSAIDs involve the stomach, duodenum, and the lower gastrointestinal tract. The NSAID-induced gastrointestinal effects range from nausea, vomiting, dyspepsia, diarrhea, constipation, mucosal irritation, erosions to peptic ulcerations and massive, fatal gastrointestinal hemorrhage. Gastropathies consist of erythematous, erosive or ulcerative lesions located mainly antral or prepyloric.17,18 The NSAID-induced gastropathy may be asymptomatic despite a broad spectrum of abnormal endoscopic findings, but in the majority of cases there are clinical symptoms.19 Most importantly, NSAID exposure is strongly associated with both upper and lower gastrointestinal perforations.20 Life threatening hemorrhage may be the first clinical presentation.

**Epidemiology and Nosology**

The NSAID use is associated with hepatic, renal, hematological, and hypersensitivity reactions and with serious upper gastrointestinal disorders.21 Spontaneous reports of adverse effects from diclofenac, nabumetone, naproxen, and piroxicam show higher association of gastrointestinal events with nabumetone and piroxicam.22 It has been estimated that there is one hospital admission per 2,823 NSAID prescriptions.23 Endoscopic data and review of clinical histories of NSAID use by patients within one week of admission showed that a history of NSAID use was approximately equal in patients with upper and lower intestinal bleeding and significantly greater than controls.24 The risk of diverticular bleeding was higher than that of duodenal ulcer bleeding. The study included 461 patients with upper and 105 with lower GI bleeding and 1,895 controls.

One half of the patients taking NSAIDs regularly have gastric erosion and 10 percent to 30 percent have gastric ulcers.25 NSAID exposure is more common in gastric than in prepyloric, pyloric and duodenal perforation and accounts for 20 to 35 percent of ulcer bleedings.26 About 70 percent of a study group of 76 consecutive patients with gastrointestinal (GI) perforations had used aspirin or other NSAIDs.27 Twenty percent were lower GI and 80 percent upper GI perforations.27 Low dose aspirin therapy may precipitate myocardial infarction or unstable angina by inducing upper gastrointestinal bleeding, especially in patients with ischemic heart disease.28 Patients suffering fatal bleeding from gastric or duodenal ulcerations may experience no pain at all because of the analgesic effect of NSAIDs.

Results of a study on the exposure to NSAIDs in 272 patients with bleeding or perforated peptic ulcer documented by endoscopy are shown in figure 1. The NSAIDs are widely used for the treatment of chronic arthropathies, such as rheumatoid arthritis. A study of 2,400 consecutive patients with rheumatoid arthritis followed prospectively for an average of three and a half years indicated that NSAID gastropathy in patients with rheumatoid arthritis accounts for at least 20,000 hospitalizations and 2,600 deaths annually in the United States.29
Overall, there are more than 20,000 NSAID-induced fatalities a year in the United States. In England, NSAID use leads to the premature death of over 3,000 patients annually. Of 65,000 emergency upper gastrointestinal admissions per annum in the UK, 12,000 are attributable to NSAID use resulting in 2230 deaths. Another 330 deaths attributable to NSAID exposure occur in the community. In the Nordic countries, 20 to 50 percent of patients using NSAIDs have an ulcer at some time, and 1 to 2 percent on continuous therapy are hospitalized for ulcer complications resulting in 450 deaths annually.

A one-year prospective study of the natural history of dyspepsia in 545 adult primary care patients indicated that exposure to NSAIDs increased the risk for gastrointestinal bleeding by a factor of 7. The NSAID-associated serious gastrointestinal events in 2,747 patients with rheumatoid arthritis and 1,091 patients with osteoarthritis resulted in an annual hospitalization incidence of 1.58 percent during NSAID treatment in rheumatoid arthritis patients. The risk of gastrointestinal related death was 0.19 percent per year with NSAIDs. The hazard ratio of patients taking NSAIDs to those not taking NSAIDs was 5.2.

Major risk factors in patients with rheumatoid arthritis include age over 60 years, concomitant therapy with corticosteroids, and longer duration or larger dose of NSAID treatment. Another study shows a relative risk of gastroduodenal ulceration 4 to 5 times higher in the NSAID user. Higher doses of NSAIDs and concomitant use of corticosteroids further increases the risk. A seven-fold higher risk of gastric bleeding in elderly patients than in younger patients is associated with failure of normal mucosal adaptation. Evidence from a population-based retrospective case-control study of 1,377 cases of upper gastrointestinal bleeding and perforation (UGIB) and 10,000 control subjects reveal that age is the most important predictor of UGIB. The risk varies widely with the individual drug. Administration of azapropazone and piroxicam carries the highest risk of UGIB. Ibuprofen, naproxen, diclofenac, ketoprofen, and indomethacin has relative risks similar to that for overall NSAID use. The risk is higher in the female than the male patient.

The NSAIDs induce or exacerbate damage of the distal gastrointestinal tracts. Seventy percent of patients receiving long term NSAID therapy have evidence of inflamma-
ation of the small intestine. Patients may suffer from asymptomatic ileal dysfunction, increased mucosal permeability, protein and blood loss. Occasionally, diaphragm-like small intestinal strictures necessitating surgery may develop. The prevalence of NSAID-induced damage to the large intestine is unknown. It is associated with diarrhea, colonic bleeding, anemia, ulcerations and strictures, perforations, and death. Diarrhea occurs in 3 to 5 percent of patients on NSAIDs. The NSAIDs may trigger exacerbation of inflammatory diseases and can complicate diverticular disease of the large bowel. Rare cases of segmental ischemic colitis in two patients with no possible etiologic factors other than NSAID use have been reported. Use of slow release NSAIDs shifts adverse effects from the upper to the distal gastrointestinal tract.

Pathophysiology

The NSAIDs exert their analgesic, antiphlogistic, and antipyretic effects through peripheral and central inhibition of prostaglandin (PG) synthesis and through a variety of other peripheral and central mechanisms (table I). Aspirin was the first NSAID shown to inhibit the COX pathway in which arachidonic acid is converted to prostaglandins. Two cyclo-oxygenase isoenzymes, referred to as COX-1 and COX-2, are inhibited by conventional NSAIDs (figure 2). The COX isoforms share structural and enzymatic similarities. Human COX-1 and COX-2 genes consist of 599 and 604 amino acids, respectively, but exhibit only about 60 percent homology. Both are expressed to a similar extent in the human stomach. However, in the mouse stomach, COX-1 is more abundant. In the rat stomach, COX-1 and COX-2 are found in surface mucous cells and mucous neck cells, respectively. The COX isoenzymes exhibit cellular compartmentalization: COX-2 is located both in the nuclear envelope and the endoplasmic reticulum, COX-1 only in the latter.

The COX genes exhibit striking differences in their regulation due to differences in promoters and transcripts. The constitutively expressed COX-1 gene shows poor inducibility and is classified as a 'housekeeping gene.' However, gastric COX-1 is induced by endotoxin administration in the rat. It provides prostaglandins for mucosal cytoprotective functions in the normal mucosa. The COX-2 (prostaglandin H synthase-2, PGHS-2, EC 1.14.99.1) is a multifunctional enzyme. Its gene is highly inducible by agents such as proinflammatory endotoxins that enhance the

<table>
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<tr>
<th>Group</th>
<th>Agent</th>
<th>Function</th>
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<tr>
<td>1</td>
<td>Flurbiprofen</td>
<td>COOH group lowers OXPHOS yield</td>
</tr>
<tr>
<td>2</td>
<td>NO-flurbiprofen</td>
<td>COOH group removed; OXPHOS intact</td>
</tr>
<tr>
<td>3</td>
<td>Sodium salicylate</td>
<td>No COX inhibition; inhibits PMN adhesion via adenosine release</td>
</tr>
<tr>
<td>4</td>
<td>Indomethacin</td>
<td>COX inhibitor; increases PMN β-2-integrin and PMN adhesion</td>
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<td>5</td>
<td>Flosulide</td>
<td>COX-2 selective inhibitor</td>
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<tr>
<td>6</td>
<td>Tepoxalin</td>
<td>COX and 5-LO inhibitor; NF kappa B inhibitor</td>
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<tr>
<td>7</td>
<td>Zileuton</td>
<td>Selective 5-LO inhibitor; inhibits PMN adhesion</td>
</tr>
<tr>
<td>8</td>
<td>Misoprostol</td>
<td>PG analogue; restores cytoprotection</td>
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OXPHOS = Oxidative phosphorylation.
COX = Cyclo-oxygenase.
5-LO = 5-lipoxygenase.
NF = Nuclear factor.
COX-2 transcript levels increasing the synthesis of proinflammatory prostaglandins at sites of inflammation.

Prostaglandins derived from arachidonic acid via COX-2, in particular PGE2, initiate inflammation and pain. Inhibition of COX-2 activity, partially by conventional NSAIDs and more completely by selective COX-2 inhibitors such as flosulide is therefore a major mechanism for the analgesic and anti-inflammatory action of NSAIDs. Treatment with monoclonal anti-PGE2 antibody fully reverses hyperalgesia in experimental models. Interference with G-protein-mediated signal transduction by NSAIDs forms a PG independent pathway for analgesic action.

Some NSAIDs also inhibit the lipoygenase pathway. However, conventional NSAIDs simultaneously inhibit COX-1 lowering synthesis of cytoprotective prostaglandins. The ratio of inhibition of the two COX isoforms varies for different NSAIDs (figure 3). Strong inhibition of COX-1 by NSAIDs such as piroxicam reduces mucosal prostaglandin cytoprotective functions, induces mucosal vascular injury, and leads to mucosal erosions and to ulcers. There may be local damage due to local effects where the NSAID tablet sits adjacent to the mucosa. But gastric ulcerations occur even when NSAIDs are administered intramuscularly or intravenously.

Ligation of the bile duct reduces NSAID damage in animal models indicating that enterohepatic recirculation is important in the pathogenesis of NSAID-induced pathologies. Diclofenac but not nitrofenac undergoes extensive enterohepatic circulation when administered to rats, exposing parts of the intestine repeatedly to the drug. Diclofenac but not nitrofenac induces frank intestinal

![Image of a diagram illustrating the effects of NSAIDs on prostaglandin synthesis and cytoprotection.](image-url)
ulcerations in such animals despite similar alterations in gastrointestinal permeability. Foods may have adverse effects. Refeeding after NSAID administration enhances macroscopic damage in animals.

Microbe involvement in the pathogenesis of lesions is suggested by experiments showing that pretreatment with antimicrobial drugs reduces damage in animals. Neutrophil adhesion to endothelial cells is damaging. Mucosal damage is limited when neutropenia is induced or when antibodies to adhesion molecules in experimental models limit neutrophil adhesion. The pathogenesis of NSAID-induced gastric ulcers is also associated with regionally disturbed gastric microcirculation and with the presence of acid.

The NSAIDs harboring a carboxyl moiety cause interfere with OXPHOS at micromolar concentrations in vitro. The carboxylic group acts as a proton translocator resulting in lower ATP generation. Intercellular tight junctions of mucosal cells are damaged increasing gastrointestinal permeability. Cells depleted of ATP are vulnerable to oxidant stress. The DNA synthesis is reduced, and mucosal cell proliferation is impaired. Mucosal cells are less able to generate components of the protective gastric barrier resulting in backflow of acid and pepsin into the mucosa. The NSAID-induced concomitant inhibition of prostaglandin synthesis further reduces the amount and quality of gastrointestinal mucosal protection.

All of 10 NSAIDs tested uncoupled rat liver mitochondrial respiration in vitro and decreased the mitochondrial membrane potential. Acetylsalicylic acid, diclofenac sodium, piroxicam, and mefenamic acid both uncouple and inhibit OXPHOS in rat renal cortex mitochondria in vitro. Dipyrone only uncouples and paracetamol only inhibits OXPHOS. Evidence of mitochondrial damage caused by NSAIDs in animal models include activation of mitochondrial marker enzymes after oral NSAIDs, damage to mitochondria shown on electron micrographs after oral NSAIDs, and reduced ATP generation. Flurbiprofen, ibuprofen, and ketoprofen significantly increase intestinal permeability in rats above that seen in untreated animals. Seventy five mg of indomethacin for one day significantly increases the permeability of the small intestine in healthy volunteers. All four drugs contain a carboxyl group. Other NSAIDs of this kind, for instance sulindac, etodolac, and flurbiprofen, are all associated with gastrointestinal toxicity. From the gastric lumen these NSAIDs rapidly penetrate the hydrophilic lipid-protective layer and reach a high level of concentration in the superficial cells of the mucosa.
Prostaglandins consist of a group of potent lipid mediators affecting gastrointestinal secretion, blood flow, and motility.\textsuperscript{63} Cytoprotective prostaglandins preserve the gastric mucosa by inhibiting acid secretion, raising bicarbonate output and mucus secretion, lowering mucosal permeability to $H^+$ ions, and maintaining mucosal blood flow. The NSAID-induced inhibition of COX-1 reduces synthesis of gastric cytoprotective prostaglandin. This results in increased acid production, decreased mucus production, back-diffusion of $H^+$ ions into the gastric mucosa, reduction in mucosal blood flow and delayed cellular repair. Consequently inhibition of COX-1 by NSAIDs results in an injured mucosa less able to cope with acid. Back-diffusion of acid from the lumen increases mucosal acidosis and enhances drug absorption.

The importance of reduced cytoprotective prostaglandin synthesis in the pathogenesis of mucosal injury is supported by experimental and clinical evidence. Oral indomethacin administered to rats (2 mg/kg daily for 4 days) induces intestinal adhesions, perforations, and neutrophil adhesion in mesenteric venules and inflammatory cell infiltration in the mesenteric interstitium.\textsuperscript{64} In patients, exogenous prostaglandin analogues such as misoprostol reduces the incidence of reactive gastritis\textsuperscript{65} and protects against both gastric and duodenal ulcers.\textsuperscript{66}

However, mice homozygous for COX-1 deficiency survive well and without gastric pathology.\textsuperscript{67} In spite of lack of measurable amounts of COX-1 in the gastric mucosa the gene knockout mice showed no increase in gastroduodenal ulcer development and surprisingly developed less indomethacin-induced gastric ulceration when compared with mice harboring intact COX-1 genes. These results in COX-1 null mice challenges the concept of cytoprotective prostaglandins and of NSAID-induced COX-1 inhibition in the pathogenesis of gastric injury.\textsuperscript{68}

In cell models IL-1\textsuperscript{69} and hypoxia\textsuperscript{70} induce COX-2 expression via nuclear factor-kappa B (NF-κB) p65 binding to matching sites in the COX-2 promoter region. Oncogenes src and ras up-regulate COX-2 promoter activity.\textsuperscript{52} Epi-dermal growth factor (EGF) induces both COX-2 messenger ribonucleic acid (mRNA) and protein, but has no effect on COX-1 expression.\textsuperscript{71} Benzo[a]pyrene up-regulates COX-2 expression,\textsuperscript{72} possibly explaining why tobacco smoking is a risk factor for NSAID induced ulcers. In rat intestinal cells, transforming growth factor beta 1 (TGF-β1) strongly induces COX-2 at both the mRNA and protein level, downregulating cyclin D1 and inhibiting cell growth.\textsuperscript{73} Human adenovirus E4 promoter binding protein (E4BP4) type elements, inducible by dexamethasone, are located in the COX-2 promoter, explaining a possible mechanism for glucocorticoid repression of COX-2.\textsuperscript{74} The COX-2 is induced in wounds, granulomas, ulcers, osteoclasts, proliferative phase endometrium, ovulation and parturition, and in colon carcinomas.\textsuperscript{75}

Transgenic COX-2 mice are able to mount an inflammatory response.\textsuperscript{76} They show no innate gastrointestinal pathology. However, they suffer from serious renal development anomalies and progressive deterioration of kidney function with age. Their life span is reduced. Such findings in COX-2 gene knockout mice raise significant questions of potential adverse renal effects of long-term COX-2 inhibition in humans. However, gene disruption during the development in utero is probably different from COX-2 inhibition in an adult patient with fully developed tissues.\textsuperscript{58}

An imbalance between the production of prostaglandins and vasoconstrictive leukotrienes is an important factor in the loss of mucosal integrity during NSAIDs absorption.\textsuperscript{40} The NSAID-induced inhibition of COX metabolism diverts arachidonic acids into the 5-lipoxygenase pathway that produces vasoconstrictor leukotrienes and generates oxyradsicals.\textsuperscript{64,77,78} Leukotrienes attract inflammatory cells to local sites of inflammation and produce ulcerations. Neutrophil adherence to the vascular endothelium increases and neutrophils release tissue-damaging mediators.\textsuperscript{79} Mucosal perfusion is reduced. Indomethacin, for example, increases leukotriene C-4 in the gastric efferent circulation in rats and pigs and induces mucosal lesions.\textsuperscript{80} However, oral dos-
ing of the selective 5-lipoxygenase inhibitor, MK-886, prevents development of both gastric and intestinal mucosal lesions.80

Conventional NSAIDs injure the mucosal endothelium within minutes of administration by inducing neutrophil adherence to the mucosal vascular endothelium. Subsequently, neutrophils release oxygen-derived free radical and proteolytic enzymes. Reduced prostaglandins synthesis through inhibition of COX-1 combined with an increase in lipoxygenase products such as leukotriene B4 contribute to the damage.79 Prevention of neutrophil adherence or depletion of circulating neutrophils results in reduced susceptibility to NSAID-induced experimental mucosal injury.81 Sodium salicylate, indomethacin, and piroxicam all inhibit stimulated neutrophil adherence to the endothelium.82

Different NSAIDs differ in the mechanism of their effect on the interaction of neutrophils with the vascular endothelium. Indomethacin induces margination of circulating neutrophils (PMN) in the gastric microcirculation via up-regulation of beta-2-integrin on the surface of the PMNs.83 Sodium salicylate inhibits stimulated neutrophil adhesion to endothelium without inhibiting prostaglandin synthesis. The drug inhibits oxidative phosphorylation, thereby making more ADP available.

Adenosine inhibits stimulated neutrophil adhesion to endothelium. Adding adenosine deaminase (ADA) converts ADP to its inactive metabolite, inosine. Thus, ADA inhibits neutrophil adhesion induced by sodium salicylate but not by indomethacin and piroxicam. Pepsinogen is a possible growth factor promoting healing of NSAID-induced gastric ulcerations.84 Indomethacin increases pepsinogen production in isolated guinea pig gastric chief cells by enhancing LTB4 release from the cells.85 Pretreating the cells with a 5-LO inhibitor abolishes pepsinogen generation.

Infection with the bacterium Helicobacter pylori does not aggravate NSAID-induced gastric ulcers. They heal with routine treatment.86 Presence of H. pylori in the stomach is associated with diffuse histological injury of the gastric mucosa.86 Daily naproksen of 500 mg and etodolac of 400 mg with twice daily ingestion for 4 weeks versus a placebo given to 52 healthy volunteers with normal baseline endoscopy did not cause diffuse mucosal injury of the gastric mucosa. The NSAID use did not alter H. pylori-induced gastritis. Development of NSAID-induced gastroduodenal damage was not influenced by underlying H. pylori infection.

**Therapeutic Alternatives**

Younger patients without risk factors may adapt to NSAID use. However, NSAIDs should be used cautiously in elderly patients and in patients who smoke or have a history of peptic ulcer, or who use oral corticosteroids or anticoagulants.88 Strategies to reduce the side effects of NSAIDs include development of new drug classes, enteric coating, non-acidic drugs, and pro-drugs such as drossicam (a produg of piroxicam) and nabumetone.87 A lack of cytoprotective prostaglandin due to NSAID-induced COX-1 inhibition can be ameliorated by administration of synthetic prostaglandins.88

Patients given the prostaglandin E1 analogue misoprostol concomitantly with NSAID therapy have reduced gastric pathology compared to patients given NSAIDs without exogenous prostaglandin supplementation.89 Misoprostol protects against both gastric and duodenal ulcers and reduces the risk of serious complications by 40 percent.86 However, NSAID-induced bleeding is not affected by concomitant oral misoprostol treatment. One to two years of misoprostol treatment of 90 patients receiving NSAIDs significantly reduced the prevalence of reactive gastritis.65

Ornoprostil, a PGE1 analogue simultaneously administered with indomethacin prevents indomethacin-induced intestinal permeability.90 Synthetic prostaglandin analogues may have their own side effects. Mild diarrhea and gastrointestinal intolerance are prominent adverse reactions experienced by patients receiving arbaprostil and enprostil,91 misoprostol, on the other hand, is well tolerated.92
Cimetidine and ranitidine (H₂ blockers) showed minimal protective value in both short term (<2 weeks) and long term trials.⁸⁸ Meloxicam, a relatively selective COX-2 inhibitor, combines anti-inflammatory efficacy with improved tolerability.⁹³ Results from a double-blind, randomized, 28 day trial in more than 9,000 patients showed that meloxicam in therapeutic dosages causes less dyspepsia, abdominal pain, nausea, vomiting and diarrhea than diclofenac. Meloxicam caused fewer peptic ulcers and gastrointestinal bleeds than naproxen, diclofenac, or piroxicam and without any increase in renal or liver abnormalities compared to other NSAIDs.

The NSAIDs that are more COX-2 selective (from 3- to 10-fold more selective for COX-2 than for COX-1) have less gastrointestinal toxicity associated with their use. Highly selective inhibitors of COX-2 (300 fold or more selective for COX-2 over COX-1)⁹⁸ reduce the risk of adverse effects from NSAIDs. These therapeutically promising compounds with a high selectivity for COX-2 still require well-designed large clinical trials to adequately evaluate advantages versus potential drawbacks that may result from prolonged selective COX-2 inhibition.⁵⁰

Studies on selective 5-lipoxygenase inhibition using MK-886 (3-[1-(4-chlorobenzyl)-3-t-butylothio-5-isopropylindol-2-yl]-2,2-dimethylpropanoic acid) failed to demonstrate⁹⁴ or demonstrated⁸⁰ significant prevention of indomethacin-induced gastropathy in the rat.⁹⁴ The selective 5-lipoxygenase (5-LO) inhibitor nordihydroguaiaretic acid (NDHA) reduces the severity or indomethacin-induced ulcer formation in rats.⁹⁵ No correlation was evident between the antioxidant properties of NDHA and the ability to reduce the severity of gastric damage.⁹⁶

In another study, oral indomethacin (100 mg/kg) was employed to produce elevated levels of leukotriene (LT) B₄ (LTB₄) in rat gastric mucosa 90 minutes after administration; pretreatment with the selective 5-LO inhibitor zileuton and the COX/5-LO inhibitor tepoxalin [5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide]⁹⁷ prevented the increase in LTB₄ levels as well as indomethacin-induced neutrophil adhesion.⁶⁴ The LTD₄ receptor antagonists, such as MK-571, significantly reduce indomethacin-induced mucosal permeability increases.⁹⁶ Tebufelone is an NSAID of the di-tert-butylphenol class that inhibits both PGE₂ and LTB₄ generation.⁹₈ Long term use of single doses up to 800 mg was generally well tolerated.⁹₉

The carboxyl group can be chemically modified, such as in dimero-flurbiprofen and nitrobutyl-flurbiprofen (figure 4). The latter NSAIDs, as well as nabumetone and highly selective COX-2 inhibitors such as flosulide,¹⁰⁰ do not cause uncoupling in vitro and are reported to show increased gastrointestinal tolerability (figure 5). Some enteric-coated or prodrug formulations induce more side effects
than others. Kelly et al reported that use of low doses of enteric-coated aspirin carried a 3-fold increase in risk of major upper-gastrointestinal bleeding. However, administration of enteric coated naproxen to patients with either osteoarthritis or rheumatoid arthritis significantly reduced gastrointestinal complaints compared to ingestion of standard immediate release naproxen.

Fish oil has anti-inflammatory properties. Supplementation in the form of eicosapentaenoic acid (EPA) as an alternative substrate to arachidonic acid leads to the formation of less proinflammatory leukotrienes and prostaglandins. In a one year, placebo-controlled study of 64 patients with stable rheumatoid arthritis requiring NSAID therapy, EPA supplementation (171 mg/day) led to significantly reduced use of NSAIDs without any deterioration in the clinical and laboratory parameters of disease activity.

Avoidable NSAID-induced adverse effects may be iatrogenic or due to self-medication by over-the-counter (OTCD) NSAID containing drugs. Patient ignorance may lead to ingestion of NSAIDs in OTCD in addition to prescrip-
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Physician prescribing patterns may contribute to avoidable gastrointestinal morbidity. In a Canadian study, exposure to potentially inappropriate drug combinations (PIDC) in 51,587 elderly patients receiving NSAID therapy was 4 percent. About one quarter of the incidents resulted from contemporaneous prescribing by different physicians. The use of a single prescribing pharmacy but not the presence of a single prescribing physician lowered the risk of PIDC involving NSAIDs.

A separate prospective cohort study of NSAID prescriptions by 112 physicians concluded that unnecessary NSAID prescribing and less than optimal management of NSAID-related side effects were sufficiently common to cause concern about the appropriateness of NSAID use in the general population. Inappropriate prescription of NSAIDs was more common when contraindications to NSAID therapy were incompletely assessed. While NSAID-related gastropathy was diagnosed correctly in 93 percent of office visits, they were acceptably managed only in 77 percent of the visits.

The NSAID therapy should not be used or continued in elderly, high risk patients with a history of recent major gastric ulcer activity or bleeding ulcer. Age may represent a risk factor for damage to mitochondrial function caused by NSAIDs. Paracetamol generally does not impair kidney mitochondrial energy in young animals, however, in aged animals administration of the drug leads to impaired mitochondrial energy metabolism. Similar studies of the role of age in the impact of NSAIDs on gastrointestinal cell mitochondria have not yet been reported. However, NSAIDs which decouple OXPHOS should probably be avoided in the elderly.

Gastroduodenal ulcer disease consists of a heterogeneous group of different multifactorial etiologies. Some patients harbor genetic risk factors. For instance, blood groups A and O are associated with gastric and duodenal ulcers, respectively, and non-secretor phenotypes predispose to both type of ulcers. Peptinogen C may play a role in epithelial cell growth during healing of the gastric mucosa.

Patients with gastric body ulcers have a higher frequency of allele 4 of the pepsinogen gene, possibly reducing the rate of mucosal healing. An indomethacin-induced increase in pepsinogen production in isolated guinea pig gastric chief cells probably represents cellular adaptation to the toxic effects of the drug. Indomethacin enhances LTB4 release from the cell and pretreating the cells with a 5-LO inhibitor abolishes pepsinogen generation. The COX-1 gene is induced by endotoxin administration in the rat. This induction is important in gastric adaptation and healing, and is not related to H. pylori infection. Gliostatin is a protein factor related to rheumatoid arthritis disease activity. Gliostatin infusion delays experimental ulcer healing in rats. The precise mechanism of the interaction of these and other cytokines and growth factors in NSAID-induced gastrointestinal lesions and their healing still remain to be elucidated.

Conclusion

No NSAID that lacks the potential for serious gastrointestinal toxicity is currently available. Generally, some newer drugs are better tolerated than many conventional NSAIDs. Still, substantial morbidity and mortality owing to NSAID-induced adverse effects impart a high cost both to the patients and society. Long-term use of NSAIDs in high-risk patients should be avoided whenever possible. When NSAIDs are prescribed, the lowest effective dose of NSAID should be selected. The NSAIDs which do not affect mitochondrial function and are not exposed to enterohepatic recirculation are preferable. Weak COX-1 and strong COX-2 inhibitors are desirable. Patients at increased risk for upper gastrointestinal complications should be given a prostaglandin analogue such as misoprostol concomitantly with NSAID treatment to restore mucosal cytoprotective functions.

All gastric ulcers require biopsy and histological examination. Selective COX-2 inhibitors appear to provide an improved gastroin-
testinal safety profile compared to older NSAIDs. However, the COX-2 gene is inducible by several cytokines and growth factors. It codes for a multifunctional enzyme involved in wound healing, proliferative stage endometrium, osteoclasts, ovulation and parturition. The safety of long term use in patients of selective inhibitors of COX-2 and 5-lipoxygenase must therefore be carefully established. Adverse effects on the gastrointestinal tract due to non-prescription use of high dose aspirin and other conventional NSAIDs remain a considerable problem.

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