The Impact of NSAID Selection on Gastrointestinal Injury and Risk for Cardiovascular Events: Identifying and Treating Patients at Risk

Richard L. Ruffalo, MD, PharmD, Robert L. Jackson, MD, and Joshua J. Ofman, MD, MS(Health Services)

Educational Objectives

- Describe the pharmacological mechanisms of NSAIDs.
- Compare and contrast the effects of different types of NSAIDs on the gastrointestinal mucosa.
- Define patients at risk for NSAID-associated complications.
- Recall appropriate therapeutic recommendations with respect to cardiovascular and gastrointestinal patient risk factors.

Introduction

Between 10% and 15% of older Americans use a prescription nonsteroidal anti-inflammatory drug (NSAID) at least once daily. In addition, it is estimated that the use of over-the-counter nonprescription NSAIDs, which include aspirin, may be five to seven times greater than for prescribed NSAIDs. Numerous studies have confirmed that NSAIDs are clinically effective analgesic agents and that, when given specifically in the form of cardioprotective doses of aspirin (75–325 mg/day), they significantly reduce the risk for cardiovascular events. Although NSAIDs do not differ significantly in terms of their ability to relieve pain, they do differ in their side-effect profiles, which are probably related to their mechanism of action.

NSAIDs may be classified as agents that inhibit both isoforms of cyclooxygenase (COX-1 and COX-2) and as agents that are more selective for COX-2. Until recently, all marketed NSAIDs inhibited COX-1 and COX-2, a property that contributed to the gastrointestinal mucosal injury profile of these agents. This injury profile and its associated complications have been estimated to result in more than 100,000 hospitalizations and more than 16,000 deaths annually.

The recent availability of the COX-2 selective agents has demonstrated a reduced risk of gastrointestinal mucosal injury. However, there appears to be a delicate balance between the ability to protect the gastric mucosa and the effect on thrombotic events. Although selective COX-2 inhibitors appear to protect the gastric mucosa as a result of their selectivity, this same mechanism may cause an increased tendency toward thrombosis; several analyses suggest that these agents, compared with traditional NSAIDs, may increase a patient’s risk for cardiovascular events.

Gastrointestinal mucosal injury and complications associated with the use of COX-1/COX-2 NSAIDs, along with the risk of cardiovascular effects associated with selective COX-2 NSAIDs, have left clinicians in a quandary as to the ideal analgesic cardioprotective regimen to use. This dilemma has been further complicated by recent studies demonstrating that naproxen (Naprosyn®, Roche) is more cardioprotective than other NSAIDs.

This article reviews the pathophysiology of the inflammatory response and the pharmacological mechanisms of NSAID activity. Criteria that identify patients at risk for gastrointestinal mucosal injury or cardiovascular events are also presented. In a separate article in this issue, Drs. Fendrick and Garabedian-Ruffalo present a clinician’s guide to selecting NSAID therapy and, if applicable, antisecretory-gastroprotective therapy, as determined by the patient’s risk for gastrointestinal injury and his or her concurrent use of aspirin.

The Inflammatory Response

The physiological reaction to injury, noxious agents, and autoimmune-triggered substances consists of an innate, non-immunologic response and an acquired, specific immune response. During this highly complex repertoire of responses, referred to as the inflammatory reaction (Figure 1), numerous mediators of inflammation (e.g., eicosanoids, histamine, platelet-activating factor [PAF], bradykinin, and cyto...
Cyclooxygenase has been found to exist as two distinct isomers, the constitutively expressed COX-1 (found in nearly all tissues) and the inducible enzyme COX-2 (found primarily in inflammatory cell types).\textsuperscript{12-14} COX-1 mediates the production of prostaglandins, which maintain the integrity of the gastric mucosa, mediate platelet function, and regulate renal blood flow,\textsuperscript{15} and thromboxane A$_2$. COX-2 expression is increased by inflammatory stimuli (e.g., cytokines) and increases synthesis of prostaglandins that mediate inflammation, pain, and fever.\textsuperscript{15}

**COX-1 and COX-2 NSAIDs: Pharmacological Effects**

Traditional NSAIDs are nonselective inhibitors of COX-1 and COX-2, albeit to differing degrees. Although it is difficult to assess selectivity, two groups of investigators have measured the extent to which traditional NSAIDs inhibit COX-1 and COX-2 in healthy volunteers.\textsuperscript{16,17} Vane and Botting found aspirin, indomethacin (Indocin®, Merck), sulindac (Clinoril®, Merck), and piroxicam (Feldene®, Pfizer) to be relatively selective for COX-1, with ratios of COX-1 to COX-2 greater than 60.\textsuperscript{17} Ibuprofen and acetaminophen were less selective for COX-1, with ratios of 15 and 7.5, respectively. Agents such as naproxen (with a ratio of 0.6) and diclofenac (with a ratio of 0.7) were relatively equipotent against both isoforms of cyclooxygenase.\textsuperscript{16,17}

The pattern of COX selectivity may explain the differences observed between the various NSAIDs with respect to their relative risk (RR) of gastrointestinal mucosal injury. Agents more potent for COX-1 versus COX-2 inhibition are associated with higher relative risk for gastrointestinal mucosal damage.\textsuperscript{11,17-19} However, although the selective COX-2 inhibitors offer a decreased risk for serious gastrointestinal mucosal injury, compared with traditional COX-1/COX-2 agents, the effect on the more common gastrointestinal symptoms such as dyspepsia is less clear.\textsuperscript{20}

This difference in COX selectivity also offers a physiological explanation for the more recently noted potential difference in cardiovascular events that have been observed between the COX-1/COX-2 agents and the selective COX-2 NSAIDs.\textsuperscript{5,7,8,9,21,22} COX-1/COX-2 NSAIDs, including aspirin, alter the balance between thromboxane A$_2$ (which promotes platelet aggregation) and PGI$_2$ (which inhibits it).\textsuperscript{11} The overall result of these two

---

**CE: NSAID Selection**

**Figure 1** Prostaglandin biosynthesis pathway. (Adapted from Rang HP, Dale MM, Ritter JM, Gardner P. Pharmacology, 4th ed. Edinburgh: Churchill Livingstone; 1999:198–228. Copyright 1999, with permission of Elsevier Science.\textsuperscript{11})
opposing actions and this "balance shift" is an antiplatelet effect
and a decrease in the number of cardiovascular events. In
contrast, as a result of their selectivity, COX-2 NSAIDs have no
effect on thromboxane A2 production and little to no effect on
platelet function, but they do cause a decrease in PG2 produc
tion. Therefore, patients receiving COX-2 inhibitors may not
benefit from the vasodilatory and antiplatelet aggregatory ef
fects of the COX-1/COX-2 agents. In addition, the decreased
production of PG2, and possibly of other prostaglandins, may
tip the physiological balance toward thromboxane A2, thereby
resulting in increased risk for thromboembolic events.

Epidemiology and the Mechanism of NSAID-
Induced Gastrointestinal Injury

Gastrointestinal side effects associated with NSAID and aspirin
use range in severity from minor, superficial mucosal injury to ul
ceration, perforation, gastric outlet obstruction, and hemorrhage.
These effects represent a substantial source of drug-induced mor
bidity and mortality among Americans. Hospitalizations resulting
from gastrointestinal disorders are at least six times more frequent
in patients with arthritis who are taking NSAIDs compared with
patients who are not. Up to 20% of patients taking long-term trad
itional NSAIDs have gastroduodenal ulcers, which can be observed
by endoscopy, between 2% and 4% have symptomatic gastric ul
cers; and between 1% and 2% have ulcer complications. COX-1/COX-2 NSAIDs impart gastrointestinal damage via
topical injury as well as by a systemic effect resulting from COX
inhibition and a decrease in prostaglandin production. Infection
with Helicobacter pylori (H. pylori) is an independent risk factor
for gastrointestinal injury in patients receiving NSAIDs.

Topical Mucosal Injury

Topical mucosal injury secondary to NSAID use may be minor
(e.g., focal or diffuse injury, typically limited to superficial cells lin
ing the gastric lumen) or major (e.g., involving superficial cells as
well as deeper glandular structures). Topical injury occurs
rapidly, with one study documenting acute mucosal erosions and
hemorrhage within 30 minutes of a single 75-mg dose of aspirin.
Minor injury usually undergoes quick repair via restitution, a
continuous process involving migration of cells from the under
lying gastric glands. Major topical injury may occur when
NSAIDs, which are weak acids, diffuse across the gastric mucosal
barrier and become ionized and sequestered in the mucosal cells,
leading to cytotoxicity and an altered local immune response.
Mucosal adaptation and a reduction in major mucosal injury may
occur with chronic administration of damaging agents. Despite
this, most patients who receive chronic high-dose NSAIDs exhibit
major mucosal injury, a phenomenon that suggests that the mu
cosal adaptation process might be overwhelmed by these agents
and cannot impede or reverse the damage-inducing process.

Systemic Effects

Agents that affect COX not only inhibit this portion of the in
flammatory response but also have widespread physiological re
sults from a decreased production of the beneficial eicosanoids
(e.g., PG2, prostaglandin E2 [PGE2] and thromboxane A2). The
depletion of eicosanoids by agents that inhibit COX-1 com
promises a variety of physiological gastroprotective mecha
nisms, including mucosal blood flow, secretion of mucus and bi
arbonate, and maintenance of a hydrophobic mucosal sur
face. Blocking the formation of PGI2 and PGE2 also has im
portant implications in vascular homeostasis. Both PGI2 and
PGE2 are important vasodilators in renal vascular beds; there
fore, their inhibition may increase renal vasoconstriction, lead
ing to sodium and water retention, edema, and hypertension.

Risk of NSAID-Related Gastrointestinal Injury

During the past two decades, numerous studies have quantified
the relative risk for the development of gastrointestinal injury in
patients receiving aspirin or nonselective COX-1/COX-2 NSAIDs.

Aspirin

Aspirin ingestion increases the relative risk of gastrointesti
nal injury by approximately threefold to fourfold. Virtually all
healthy individuals exhibited gastric mucosal injury following
aspirin ingestion. In a controlled study of 2,250 ulcer-free pa
tients given aspirin 1 g/day for four years, the incidence of gas
tric and duodenal ulcers was nine to 11 times more prevalent
among those receiving aspirin. In a meta-analysis of 21 pri
mary and secondary myocardial and stroke-prevention trials,
the Antiplatelet Trialists’ Collaboration found that the risk of sig
nificant gastrointestinal bleeding and hospitalization resulting
from peptic ulceration was approximately twofold higher in pa
tients treated with aspirin (in doses of 75–1,500 mg/day) com
pared with those receiving placebo. The odds ratios (ORs) for
selected gastrointestinal symptoms and complications were as
follows: all ulcers, 1.3; ulcers serious enough to lead to with
drawal, 3.2; all gastrointestinal symptoms, 1.7; and symptoms
severe enough to cause a patient to withdraw, 1.6.

A meta-analysis of 24 randomized, controlled trials by Derry
and Loke found that gastrointestinal hemorrhage occurred in
2.47% of individuals taking aspirin for one year compared with
1.42% of patients taking placebo (OR = 1.68). At doses below
163 mg/day, gastrointestinal hemorrhage occurred in 2.3% of
patients taking aspirin compared with 1.45% of those taking
placebo (OR = 1.59). No relationship was observed between
gastrointestinal hemorrhage and aspirin dose, although pa
tients receiving modified-release aspirin formulations were at
slightly lower risk (OR = 1.93).

These findings as well as those of others indicate that
aspirin at any dose or formulation increases the risk of gastro
intestinal injury and complications. In a study by Weil and col
leagues, the odds ratios of upper gastrointestinal events by a
daily dose of aspirin were as follows: 2.3 with a dose of 75 mg,
3.2 with a dose of 150 mg, and 3.9 with a dose of 300 mg. Kel
ley and associates found a similar risk (RR = 2.4–2.6) among
those given plain aspirin, coated aspirin, or buffered aspirin.
The relative risk of gastric bleeding was 2.6 with plain aspirin,
3.2 with coated aspirin, and 3.6 with buffered aspirin.

A recent article by Lai and colleagues found that initiation of
antisecreatory therapy (i.e., lanosoprazole [Prevacid®, TAP] 30 mg
once daily) in combination with low-dose aspirin significantly re
duced the risk of recurrent ulcer complications. The investi
gators enrolled 123 H. pylori–positive patients with ulcer com
plications after receiving low-dose aspirin for more than one
month. Following ulcer healing and cure of the H. pylori infec
tion, patients were randomly assigned to receive treatment with
the proton pump inhibitor (PPI) or placebo in addition to aspirin
In the VIGOR trial, patients with osteoarthritis (70%) and rheumatoid arthritis (20%) were monitored for a median of 9.0 months. Patients receiving rofecoxib 50 mg/day experienced significantly fewer upper gastrointestinal complications than those receiving naproxen 500 mg twice daily (cumulative incidence 2.1% vs. 4.5%, respectively; \( P = .005 \)).

The differences observed between the COX-2 agent and naproxen may have been caused by several study-related factors. For example, the VIGOR trial included a low percentage (8%) of individuals considered at high risk (with a history of a clinical gastrointestinal event) for a gastrointestinal event, and patients taking concurrent aspirin were excluded. In contrast, the CLASS study by Silverstein and colleagues found no statistically significant difference in the annualized incidence rate of upper gastrointestinal complications between patients treated for six months with celecoxib 400 mg twice daily or conventional NSAIDs (ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily) (0.76% vs. 1.45%, \( P = .09 \)). A statistically significant difference was observed in the annualized incidence rates of upper gastrointestinal complications combined with symptomatic ulcers in patients treated with celecoxib versus conventional NSAIDs (2.08% vs. 3.54%, \( P = .02 \)).

Unlike the patients in the VIGOR trial, patients taking aspirin therapy were not excluded from participating in the CLASS trial. In fact, when the percentage of patients with upper gastrointestinal ulcer complications, combined with symptomatic ulcers in patients using aspirin, was evaluated, no statistically significant differences were observed between patients receiving a traditional NSAID and patients receiving celecoxib (2.12 vs. 2.01, \( P = .92 \), and 6.0 vs. 4.7, \( P = .49 \), respectively).

**COX-2 Selective Inhibitors**

Clinical trial data suggest that the COX-2 selective NSAIDs, compared with nonselective COX-1/COX-2 NSAIDs, cause fewer serious gastrointestinal events; however, more recent case reports have cited serious gastrointestinal complications with the use of these agents. The relative safety of these agents, particularly in patients at high risk and in those requiring concurrent aspirin therapy, remains controversial.

Much of the debate regarding the safety of the selective COX-2 NSAIDs stems from the conflicting findings of two double-blind, randomized, prospective outcome studies, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which involved patients with rheumatoid arthritis, and the Celecoxib Long-Term Arthritis Safety Study (CLASS) trial, which involved patients with osteoarthritis (70%) and rheumatoid arthritis (30%). In the VIGOR trial, patients were monitored for a median of 9.0 months. Patients receiving rofecoxib 50 mg/day experienced significantly fewer upper gastrointestinal complications than those receiving naproxen 500 mg twice daily (cumulative incidence 2.1% vs. 4.5%, respectively; \( P = .005 \)).

The differences observed between the COX-2 agent and naproxen may have been caused by several study-related factors. For example, the VIGOR trial included a low percentage (8%) of individuals considered at high risk (with a history of a clinical gastrointestinal event) for a gastrointestinal event, and patients taking concurrent aspirin were excluded. In contrast, the CLASS study by Silverstein and colleagues found no statistically significant difference in the annualized incidence rate of upper gastrointestinal complications between patients treated for six months with celecoxib 400 mg twice daily or conventional NSAIDs (ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily) (0.76% vs. 1.45%, \( P = .09 \)). A statistically significant difference was observed in the annualized incidence rates of upper gastrointestinal complications combined with symptomatic ulcers in patients treated with celecoxib versus conventional NSAIDs (2.08% vs. 3.54%, \( P = .02 \)).

Unlike the patients in the VIGOR trial, patients taking aspirin therapy were not excluded from participating in the CLASS trial. In fact, when the percentage of patients with upper gastrointestinal ulcer complications, combined with symptomatic ulcers in patients using aspirin, was evaluated, no statistically significant differences were observed between patients receiving a traditional NSAID and patients receiving celecoxib (2.12 vs. 2.01, \( P = .92 \), and 6.0 vs. 4.7, \( P = .49 \), respectively).
tithrombotic/antiplatelet effect from naproxen (or possibly both).\(^3\) The differences observed between the VIGOR and the CLASS studies may be related to the characteristics of the enrolled patients; that is, the VIGOR trial enrolled only patients with rheumatoid arthritis, a population known to be at high risk for cardiovascular events, whereas the CLASS study enrolled a high percentage (21%) of patients who were receiving concurrent aspirin therapy.

Fueling the provocative nature of the findings in the Mukherjee study\(^2\) are the recent data from three case-control studies suggesting that naproxen, in contrast to other conventional NSAIDs, may reduce the risk of acute myocardial infarction\(^8,9\) and may lower the risk of acute thromboembolic cardiovascular events, including myocardial infarction, sudden death, and stroke.\(^7\)

Solomon and colleagues\(^8\) found no relationship between NSAID use in the preceding 180 days and acute myocardial infarction (OR = 1.0, \(P = .92\)) and no relationship between NSAID use on the index date and acute myocardial infarction (OR 1.04, \(P = .55\)). However, analysis of specific NSAID use found a 16% reduction in the odds of myocardial infarction among patients who were given naproxen. Etodolac (Lodine\(^®\), Wyeth-Ayerst) and fenoprofen (Nalfon\(^®\), Eli Lilly) were associated with an increased risk of acute myocardial infarction (OR = 1.28 and 1.95, respectively; \(P \leq .05\)); in contrast, ibuprofen use was not associated with acute myocardial infarction risk (OR = 1.02).

Rahne and colleagues\(^9\) also found that the incidence of acute myocardial infarction in individuals who were concurrent, chronic users of naproxen was lower than in patients using other NSAIDs (OR = 0.64).

Watson and colleagues\(^7\) found a 35% reduction in the risk of thromboembolic cardiovascular events (myocardial infarction, sudden death, and stroke) and a 60% reduction in the risk of myocardial infarction among patients with rheumatoid arthritis who received naproxen compared with other non-naproxen NSAIDs.

**Identifying Patients at Risk for NSAID-Associated Complications**

Numerous studies have defined the factors that increase the risk for NSAID-associated gastrointestinal injury (Table 1).\(^1,52,53,67,68\) The American College of Gastroenterology has published guidelines for identifying factors that place patients at increased risk for NSAID-induced gastrointestinal injury.\(^69\) Some of these patient factors include (1) age older than 60 years; (2) a history of ulcer disease or a gastrointestinal event; (3) the need for high-dose NSAID therapy or chronic use of NSAIDs, or both; and (4) the need for concurrent corticosteroids or warfarin therapy, or both. In addition, some recent studies suggest that the use of aspirin therapy, even at low doses, places patients at increased risk for gastrointestinal injury.\(^44,48–51\) and at an even greater risk if another NSAID, regardless of its cyclooxygenase selectivity, is added to the mix.\(^4\)

Because *H. pylori* infection is an independent risk factor for gastrointestinal injury, patients with a history of ulcer disease who require NSAID therapy should be tested for the presence of the bacterium; if the results are positive, cure of the bacterial infection is essential. Similarly, *H. pylori* infection and an ulcer have developed during NSAID therapy, it is clinically prudent to cure the bacterial infection.

Whether the choice between a traditional NSAID and a COX-2 selective NSAID changes a patient’s risk for cardiovascular events remains controversial. However, it is known that patients at risk for cardiovascular events, as defined by recently released guidelines,\(^70\) often require low-dose aspirin therapy, which increases their risk for gastrointestinal injury.\(^44,48–51\)

**Recommendations for Patients at Risk**

The patient’s current use of aspirin and past gastrointestinal history dictate the NSAID-selection process. The decision-making process is also influenced by the fact that many patients are receiving maintenance therapy with PPIs for gastroesophageal reflux disease.

Among patients not receiving aspirin, those with no history of gastrointestinal injury may be treated with a traditional NSAID.\(^71\) Selection of NSAID therapy among patients not taking aspirin but who have a history of gastrointestinal injury should be based on their concurrent use of a PPI. For example, patients who are not receiving PPI therapy should be given a COX-2-selective NSAID; adding an antisecretory agent can be considered if gastric symptoms develop. Patients receiving a PPI may be given a traditional NSAID.\(^72\)

Among patients receiving aspirin therapy, the concurrent use of an antisecretory agent (e.g., a PPI or a histamine H\(_2\) receptor antagonist) or a gastroprotective agent should be considered, especially in those with a history of gastrointestinal complications.\(^50,73,74\) However, a trial comparing misoprostol (Cytotec\(^®\), Pharmacia) with histamine H\(_2\) receptor antagonists found that only misoprostol produced a significant and consistent reduction in the risk of NSAID-induced gastrointestinal lesions or ulceration.\(^75\)

A more recent study found PPI therapy to be superior to misoprostol, offering greater symptom relief and a more favorable tolerability profile with a positive effect on patient compliance.\(^73\) The choice between a traditional NSAID and a COX-2 NSAID in patients receiving concurrent aspirin should thus be based on the patient’s history of gastrointestinal injury.\(^50,72,74\) A traditional NSAID may be considered the first choice among patients without a history of gastrointestinal injury, whereas a COX-2 selective NSAID might be considered the first choice among those with a history of gastrointestinal injury,\(^72,74\) although many would argue that the concurrent use of aspirin negates or minimizes the gastrointestinal protection advantage.
tolerability than with misoprostol.\textsuperscript{79} If an ulcer develops during NSAID therapy, treatment with the offending agent should be discontinued, if possible, and the patient should receive an effective ulcer-healing regimen. In subsequent assessments of pain management, such individuals should be considered at risk for gastrointestinal injury and should be managed accordingly. For patients who are unable to discontinue their pain management regimens, several randomized, controlled, clinical trials have documented significantly higher ulcer healing rates with PPI regimens,\textsuperscript{78} some of which are discussed later in this article.

In all cases, it is prudent to prescribe the lowest therapeutically effective dose of the selective NSAID needed to reduce the risk of adverse events.\textsuperscript{76} If an ulcer develops during NSAID therapy, treatment with the offending agent should be discontinued, if possible, and the patient should receive an effective ulcer-healing regimen. In subsequent assessments of pain management, such individuals should be considered at risk for gastrointestinal injury and should be managed accordingly. For patients who are unable to discontinue their pain management regimens, several randomized, controlled, clinical trials have documented significantly higher ulcer healing rates with PPI therapy than with H2 receptor antagonist therapy\textsuperscript{77,78} and higher tolerability than with misoprostol.\textsuperscript{79}

**Summary**

Although NSAIDs are very effective in keeping patients pain-free, this benefit may occur at the expense of the gastrointestinal mucosa. The newer selective COX-2 NSAIDs were developed to provide pain relief without doing harm to the gastric mucosa; however, emerging data suggest that this advantage occurs at the expense of cardiovascular risk. Clinicians must carefully evaluate the patient’s medical history and assess the risk for gastrointestinal injury as well as cardiovascular events and any need for aspirin therapy before choosing between the traditional COX-1/COX-2 NSAIDs and the selective COX-2 NSAIDs.

Given the recent insights into the potential cardioprotective effects of naproxen, further research should focus on the optimal treatment strategy for patients who require antplatelet therapy and NSAID-antalgiesia therapy. If gastrointestinal symptoms develop, the addition of a gastrointestinal protectant, such as a PPI, should be considered. Clinicians should also note that the addition of even low doses of aspirin may negate the gastrointestinal benefits of selective COX-2 NSAIDs.

**References**


56. Ruffalo has indicated that he has no commercial relationships to disclose in relation to this article. Dr. Jackson has declared that he is an employee of TAP Pharmaceuticals, Inc., and he has received research grants from these companies. Dr. Ruffalo has indicated that he has no commercial relationships to disclose in relation to this article.