

# Effects of Nonsteroidal Anti-inflammatory Drugs on Endogenous Gastrointestinal Prostaglandins and Therapeutic Strategies for Prevention and Treatment of Nonsteroidal Anti-inflammatory Drug-Induced Damage

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● Although nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for pain relief and treatment of arthritis, they can induce gastric and duodenal ulcers and life-threatening complications. The mechanisms of their anti-inflammatory action and their gastroduodenal toxic effects are related, in part, to inhibition of prostaglandin synthesis. This review article discusses prostaglandins, their functions in the gastrointestinal tract, anti-inflammatory actions of NSAIDs, and mechanisms by which NSAIDs produce gastroduodenal ulcers. Also reviewed are risk factors associated with the development of NSAID-related ulcers and pharmacologic strategies for the prevention and treatment of NSAID-induced ulcers.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain relief and for treatment of arthritis (including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and gouty arthritis). A partial list of NSAIDs is shown in the Table. Although NSAIDs are effective as therapeutic agents, their major toxic effect is induction of gastroduodenal ulcers. Mechanisms for their anti-inflammatory action and their gastroduodenal toxic effects are probably related to an inhibition of prostaglandin synthesis. The purposes of this article are to review the effects of NSAIDs on the gastroduodenal mucosa, including their effects on mucosal prostaglandins, and to review the effects of therapeutic agents that can be used to prevent and treat NSAID-induced gastroduodenal damage.

## PROSTAGLANDINS AND RELATED COMPOUNDS

Prostaglandins (PGs) are a family of related fatty acids that are produced by nearly all of the body's cells. Prostaglandins participate in a variety of activities, including mediation of inflammatory responses, protection of the

gastrointestinal mucosa against injury, and regulation of renal blood flow. The general chemical structure of PGs is an oxygenated, 20-carbon, unsaturated fatty acid (eicosanoid) composed of a five-carbon ring, with two carbon side chains, one composed of seven carbon molecules and the other composed of eight.<sup>1</sup> Nomenclature used to describe individual PGs is based on two distinguishing features. First, the letter designation of PGs (ie, their family) is determined by the structure of the five-carbon ring. For example, all PGEs have a double-bonded oxygen (=O) at carbon 9 and a hydroxyl group (-OH) at carbon 11, while all PGFs have a hydroxyl group at both carbon 9 and carbon 11.<sup>2</sup> Second, the number of double bonds in the side chains determines PG classification as 1-, 2-, or 3-series and is reflected by a subscript (eg, PGE<sub>2</sub> [2-series] or 6-keto-PGF<sub>1α</sub> [1-series]) (Figure).

Prostaglandins are not stored within cells in any significant quantities, but are stored as precursor molecules. Prostaglandins of the 2-series are the most plentiful and biologically important and are derived from arachidonic acid, a component of phospholipids present in all cell membranes. In response to a mechanical or chemical perturbation of the cell membrane, arachidonic acid is released from membrane phospholipids into the cytoplasm of the cell through the action of a plasma membrane-bound enzyme, phospholipase A<sub>2</sub>. Once released, arachidonic acid may be acted on by cyclooxygenase, a membrane-bound enzyme, resulting in synthesis of PGs; alternatively, it may be metabolized by another enzyme, 5-lipoxygenase, to a group of closely related compounds, the leukotrienes (LTs) (Figure). The relative activities of the cyclooxygenase and 5-lipoxygenase pathways, and thus the relative amounts of eicosanoids produced, vary with cell type.<sup>3</sup> In gastric and duodenal mucosa, most arachidonic acid is converted into PGE<sub>2</sub>, PGF<sub>2α</sub>, and PGI<sub>2</sub>.<sup>4-6</sup>

## FUNCTION OF PROSTAGLANDINS IN THE GASTROINTESTINAL TRACT

Although PGs were first identified in the human body in the 1930s, it was not until the mid-1960s that PGs were identified in the gastrointestinal tract.<sup>7-9</sup> The earliest recognized effect of PGs on gastric mucosal function was an

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# Partial List of Nonsteroidal Anti-inflammatory Drugs

Salicylates  
Aspirin\*  
Diflunisal (Dolobid)\*  
Salsalate (Disalcid)\*

Indoles  
Indomethacin (Indocin)\*  
Sulindac (Clinoril)\*  
Tolmetin (Tolectin)\*  
Zomepirac (Zomax)

Pyrazoles  
Apazone (Rheumox)  
Feprazone (Methrazone)  
Phenylbutazone (Butazolidin)\*

Fenamates  
Flufenamic acid (Meralen)  
Mefenamic acid (Ponstel)\*  
Meclofenamate (Meclomen)\*  
Tolfenamic acid (Clotam)

Propionic acid derivatives  
Carprofen (Rimadyl)  
Fenbufen (Cinopal, Lederfen)  
Fenoprofen (Nalfon, Fenopron)\*  
Flurbiprofen (Ansaid, Froben)\*  
Ibuprofen (Motrin, Advil)\*  
Ketoprofen (Orudis)\*  
Naproxen (Naprosyn, Anaprox)\*  
Pirprofen (Rengasil)

Phenylacetic acid derivatives  
Diclofenac (Voltaren, Voltarol)\*  
Fenclofenac (Flenac)

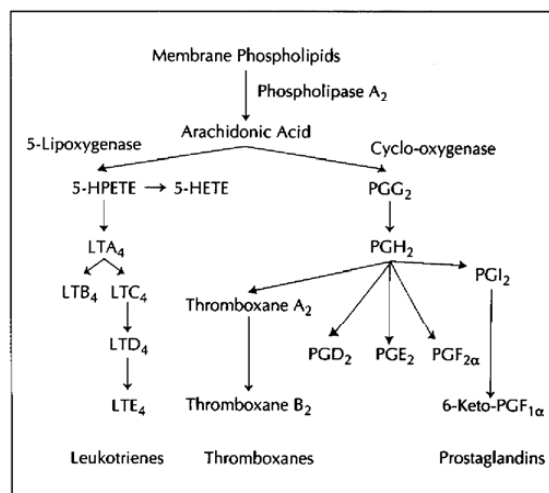
Oxicams  
Isoxicam (Maxicam)  
Piroxicam (Feldene)\*

\*Available in the United States in 1991.

inhibition of gastric acid and pepsin secretion.<sup>10-13</sup> Intravenously administered PGs of the E, F, and A classes and orally administered synthetic analogues of these compounds have potent antisecretory effects, PGs of the E class being the most potent.<sup>14-20</sup>

In the 1970s, investigators began to demonstrate that PGs could protect the gastric mucosa from injury and ulceration against a wide variety of damaging agents, such as alcohol, bile salts, acid, hypertonic saline, boiling water, stress, aspirin, and other NSAIDs.<sup>21-28</sup> Robert et al<sup>21</sup> performed the earliest of these experiments, in which they demonstrated that pretreatment with PGs could prevent mucosal damage from various noxious agents in rats. It was demonstrated that mucosal protection could be observed at doses of PGs that did not inhibit acid secretion.<sup>22</sup> This protective property of PGs was called "cytoprotection."<sup>29</sup> Even though pretreatment with PGs may protect against macroscopic injury, there is usually microscopic evidence of mucosal injury to surface epithelial cells after exposure to alcohol or other noxious agents.<sup>30</sup> Because of persistent surface cell damage despite PG pretreatment, the term *cytoprotection* is not entirely accurate and has for the most part been replaced by *mucosal protection*. Mucosal protection by prostaglandins has not only been demonstrated in the stomach, but has been shown in the duodenum.<sup>31-38</sup> Protection has been demonstrated with PGs of all classes and is separate from any effects the compounds may have on gastric acid secretion. In fact, in animals, mucosal protection has been demonstrated with PGs, such as 6-keto-PGF<sub>1α</sub>, that have no demonstrated

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Metabolism of arachidonic acid after its release from membrane phospholipids. HPETE indicates hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid; PG, prostaglandin; and LT, leukotriene.

effect on acid secretion.<sup>31</sup> However, in humans, it is not certain that the protective effects of PGs are due to mechanisms separate from inhibition of gastric acid secretion, since PGs, at doses employed in human trials, have antisecretory effects as well.

How is mucosal protection by PGs mediated? Integrity of the gastroduodenal mucosa is maintained by a balance between aggressive factors, such as acid and pepsin, and protective factors, such as bicarbonate and mucus.<sup>39,40</sup> When there is an imbalance between aggressive and protective factors, such that the extent of mucosal protection is lowered in relation to the level of offending agents, mucosal injury ensues. Persistence of this imbalance could lead to mucosal erosions and ulceration. Some of several putative mechanisms proposed through which PGs may provide their mucosal protective effects include the following: stimulation of mucosal bicarbonate secretion, mucus secretion, increased 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.<sup>24,28,29,41-45</sup> Soll et al<sup>46</sup> categorized various protective mechanisms according to their location with respect to the surface epithelial cells. They have been accordingly described as preepithelial (mucus and bicarbonate secretion), epithelial (surface epithelial cell continuity and migration), and postepithelial (mucosal blood flow).

## INFLAMMATION AND ANTI-INFLAMMATORY ACTIONS OF NSAIDs

Inflammatory cell recruitment is achieved through the release of a number of chemical mediators, such as PGs, LTs, histamine, serotonin, kinins, complement factors, and other peptides.<sup>47,48</sup> Evidence implicating PGs in this process was not obtained until 1971, when Vane<sup>49</sup> pro-

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posed PGs as substances that could elicit an inflammatory response. Prostaglandins were demonstrated to be associated with inflammation in a variety of experimental situations. For example, after subcutaneous PG administration, edema and erythema as well as some of the histologic changes of inflammation were observed.<sup>50</sup> After administration of aspirin, biosynthesis of PGs decreased in proportion to the decrease in the amount of inflammation,<sup>49,51,52</sup> and then, if exogenous PGs were later administered, there would be a return of inflammation.<sup>49</sup> Experimental administration of PGs could induce fever<sup>53</sup> and potentiate pain,<sup>54</sup> and subsequent administration of an NSAID could decrease fever and pain while also decreasing PG concentrations. It soon became clear that the anti-inflammatory effects of such drugs as aspirin could be explained by their suppression of PG synthesis and that such inhibition could also explain the actions of these drugs as analgesics and antipyretics.

Aspirin, an acetylated salicylate, was one of the first NSAIDs shown to be clinically effective as an anti-inflammatory agent.<sup>55</sup> Although many other NSAIDs have since been introduced, aspirin remains one of the most effective anti-inflammatory agents.<sup>55</sup> It is through the inhibition of cyclo-oxygenase that aspirin and other NSAIDs decrease PG synthesis. By acetylation of cyclo-oxygenase, aspirin inhibits this enzyme irreversibly, while other NSAIDs (flufenamic acid, ibuprofen, and sulindac, for example) inhibit cyclo-oxygenase in a reversible, concentration-dependent manner.<sup>56,57</sup> When cyclo-oxygenase is irreversibly inhibited within any particular cell, the capacity for PG synthesis does not return to normal until new enzyme can be synthesized.<sup>56</sup> This may explain why aspirin, in comparison with other NSAIDs, remains one of the most potent inhibitors of PG synthesis. It is hypothesized that cyclo-oxygenase exists in multiple forms throughout the body and that each form has its own drug specificity,<sup>58</sup> although this has not yet been verified by identification of structural cyclo-oxygenase variants. Cyclo-oxygenases obtained from different tissues have different sensitivities to inhibition by a particular NSAID, and different NSAIDs have variable abilities to inhibit a particular cyclo-oxygenase.<sup>57,58</sup> For example, acetaminophen is as effective as aspirin in the inhibition of brain cyclo-oxygenase, but is not nearly as effective as aspirin in the inhibition of cyclo-oxygenase from some peripheral sites.<sup>58</sup> This may explain why acetaminophen is an effective centrally acting antipyretic and analgesic but is not an effective peripherally acting anti-inflammatory agent. This may also explain why acetaminophen does not cause gastroduodenal toxic effects.

The LTs also play a significant role in the inflammatory response. They increase vascular permeability, are chemotactic for neutrophils, vasoconstrict arteries, stimulate bronchial wall constriction and mucus secretion, and increase intestinal inflammation.<sup>59,60</sup> Certain NSAIDs, in addition to inhibiting cyclo-oxygenase, also may inhibit 5-lipoxygenase.<sup>56,61</sup> The NSAIDs differ in their relative potencies to reduce inflammation,<sup>62</sup> and their anti-inflammatory effects do not always correlate with their ability to reduce PG synthesis. These observations may possibly be explained by different capacities of the various NSAIDs to inhibit cyclo-oxygenase, on the one hand, and 5-lipoxygenase, on the other hand. An NSAID such as indomethacin is predominantly a cyclo-oxygenase inhib-

itor, while other experimental NSAIDs of the fenamate class are effective inhibitors of both enzymes.<sup>63</sup> Whether differences in the relative amounts of cyclo-oxygenase/5-lipoxygenase inhibition by NSAIDs is indeed related to differences in anti-inflammatory actions of NSAIDs is currently under investigation.

Anti-inflammatory actions of NSAIDs are not only explained by inhibition of eicosanoid synthesis. For example, NSAIDs inhibit PG synthesis *in vivo* and *in vitro* at concentrations much lower than those required to achieve anti-inflammatory effects.<sup>64</sup> Moreover, some salicylates, including nonacetylated salicylates, are beneficial in inflammatory disease<sup>54,65-68</sup> even though they do not inhibit PG synthesis.<sup>66,69</sup> Inhibition of neutrophil function has been suggested as a second mechanism by which NSAIDs can exert their anti-inflammatory effects.<sup>62,70,71</sup>

#### MECHANISMS OF GASTRODUODENAL MUCOSAL INJURY BY NSAIDs

The mechanisms by which aspirin can cause gastrointestinal mucosal damage can be grouped into two categories: those independent of and those dependent on cyclo-oxygenase inhibition. Within a few minutes of aspirin ingestion, denudation of surface epithelial cells and increased mucosal permeability to sodium (Na<sup>+</sup>) and hydrogen (H<sup>+</sup>) ions can be observed,<sup>72</sup> reflected experimentally as a decrease in transmucosal potential difference.<sup>73,74</sup> Salicylic acid, the deacetylated metabolite of aspirin, does not inhibit cyclo-oxygenase activity in the gastric mucosa,<sup>75</sup> yet it reduces transmucosal potential difference as much as aspirin does.<sup>73</sup> Thus, surface epithelial cell disruption and a decline in potential difference are not dependent on cyclo-oxygenase inhibition, and epithelial cell disruption is not prevented by pretreatment with PGs.<sup>76</sup>

Endoscopic observation of the gastric mucosa after 1 to 2 weeks of enteric-coated aspirin therapy<sup>77,78</sup> or after 1 week of enteric-coated naproxen therapy<sup>79</sup> revealed considerably less gastric mucosal damage than with plain, non-enteric-coated formulations. Although gastric injury from a topical effect is decreased with enteric-coated formulations, their use on a long-term basis will result in gastric ulcers (GUs),<sup>80</sup> presumably the result of a systemic rather than topical effect. Gastric ulcers can be produced experimentally after NSAIDs are administered intravenously<sup>81</sup> or by rectal suppository<sup>82</sup> and without a change in gastric transmucosal potential difference.<sup>81,83</sup> It is likely that the NSAIDs were ulcerogenic because they reduced mucosal PG synthesis. This is supported by two observations: (1) small nonantisecretory doses of exogenous PGs prevent NSAID-induced ulcers<sup>23,24,28</sup> and (2) depletion of mucosal PGs by another mechanism, active or passive immunization with PG antibodies, leads to GUs.<sup>84</sup>

Although inhibition of PG synthesis contributes to NSAID-induced mucosal injury, it is not settled whether PG inhibition is the primary mechanism. In some studies, there has been poor correlation between gastric mucosal injury and PG suppression after NSAIDs.<sup>85-89</sup> Other factors probably work in combination with PG suppression to increase the propensity for mucosal injury by NSAIDs. For example, after indomethacin administration, gastric acid secretion has been shown to increase,<sup>89</sup> gastric mucosal blood flow to decrease,<sup>90,91</sup> and duodenal bicarbonate output to decrease.<sup>92</sup> Nonsteroidal anti-inflammatory drugs can also potentially affect mucus secretion, as



they have been shown to inhibit mucus synthesis, to reduce incorporation of radiolabeled precursors into mucus glycoprotein, and to alter thickness of the mucus layer.<sup>28,93</sup>

It has been hypothesized that, as a consequence of cyclo-oxygenase inhibition, arachidonic acid metabolism could alternatively be shunted toward the lipoxygenase pathway, resulting in increased LT synthesis.<sup>94-99</sup> The postulated mechanism by which increased activity of the 5-lipoxygenase pathway could enhance mucosal injury is by LT-mediated vasoconstriction or by direct vascular injury by oxygen radicals produced in this pathway.<sup>96,99</sup> The relative importance of LTs in NSAID-induced gastric mucosal damage is still unclear.

Since other pathogenetic mechanisms are potentially operative, one may ask whether significant NSAID-related mucosal injury can occur in the absence of suppression of mucosal PGs. After administration of salsalate, a nonacetylated salicylate that is anti-inflammatory, mucosal injury has been far less than after other NSAIDs.<sup>100-102</sup> Salsalate does not significantly inhibit cyclo-oxygenase activity or reduce mucosal PG content.<sup>69,102</sup> Thus, inhibition of PG synthesis is probably necessary but not sufficient for mucosal injury.

#### SHORT-TERM VS LONG-TERM NSAID ADMINISTRATION

After short-term administration, a variety of types of injury develop, ranging from petechial hemorrhages, diffuse hemorrhages, superficial erosions, and, less commonly, ulceration.\* On the basis of such observations, many claims have been made as to the superiority of one NSAID over another regarding the incidence of mucosal injury. Lanza<sup>112</sup> reported the largest experience with endoscopic mucosal observations after 7 days of NSAID ingestion. High doses of aspirin had the highest incidence of acute gastric mucosal injury, while the incidence of injury induced by other nonaspirin NSAIDs was less but also dose dependent. Among the nonaspirin NSAIDs, it was not easy to compare incidences of gastric mucosal toxic effects because of difficulties in determining equivalent doses. By compiling all of his NSAID data, Lanza observed a 6.7% incidence of GU and a 1.4% incidence of duodenal ulcer (DU) after 1 week of NSAID ingestion. The largest numbers of GUs were produced by aspirin and the lowest numbers by lower anti-inflammatory doses of ibuprofen.

The evolution of mucosal injury over time after short-term NSAID therapy also has been an interest of investigation. After a single dose of aspirin (650 mg), gastric intramucosal hemorrhages endoscopically visible as petechiae appear in as little as 15 minutes and gastric erosions in as little as 45 minutes.<sup>110</sup> Petechial lesions become most pronounced by 1 to 2 hours<sup>110,114</sup> and can occur in any location in the stomach.<sup>110,114</sup> After many repeated doses of aspirin, multiple erosions appear, mostly in the antrum,<sup>80,106,110</sup> but potentially in any gastric location. Endoscopic gastric mucosal injury peaks within the first 3 days and then tends to decrease despite continued aspirin administration,<sup>110,113,114</sup> despite the fact that mucosal PG content remains low.<sup>85,102</sup> This phenomenon has been referred to as gastric adaptation.<sup>114</sup> Increased epithelial cell regeneration and mitoses have been observed to occur in response to aspirin-induced injury.<sup>115-118</sup>

\*References 77-79, 82, 85, 87, 88, 101-114.

Mucosal petechiae and erosions are comparatively trivial, transient lesions that have low risk for major untoward effects.<sup>119</sup> Acute mucosal injury can be repaired rapidly through processes of restitution and gastric adaptation. With continued and frequent aspirin administration, the rate of mucosal injury may be greater than the rate of mucosal repair, ultimately resulting in a persistent epithelial defect.<sup>120</sup> Consequently, an erosion or an ulcer may develop, the distinction between the two being depth of damage.<sup>121</sup> An ulcer, once formed, has the potential to cause significant bleeding, luminal obstruction, or gastrointestinal perforation, all of which are not uncommon complications of long-term NSAID therapy.<sup>122-128</sup> Thus, the clinically important aspects of NSAID mucosal damage are primarily the consequences seen after long-term rather than short-term therapy.

Although there may be considerable differences in incidences of injury after short-term administration observed between the various nonaspirin NSAIDs, these differences cannot be used to predict injury after longer-term administration. Drugs that produce slight acute mucosal injury can still produce ulcers when given on a long-term basis. For example, sulindac produces little mucosal damage when given for a short term<sup>111</sup> but is associated with one of the highest rates of NSAID-related upper gastrointestinal bleeding.<sup>122</sup> Most data on consequences of long-term NSAID therapy come from epidemiologic studies or from prospective trials of patients taking these medications for therapy for chronic rheumatic diseases.

Retrospective reviews of records of hospital admissions for upper gastrointestinal bleeding have provided further evidence that long-term aspirin use is associated with GUs.<sup>123</sup> With the newer, nonaspirin NSAIDs, case-controlled studies also suggest that gastrointestinal bleeding from ulcers is strongly associated with NSAID use.<sup>122,124-131</sup> However, the incidence of serious ulcer complications with nonaspirin NSAIDs is less than that with aspirin. Patients presenting with bleeding ulcers are three to five times as likely as controls to have taken an NSAID, and 13% to 60% have a recent history of NSAID consumption.<sup>124-131</sup> Among subjects without a history of ulcer, patients taking NSAIDs have 1.5 times the risk of developing upper gastrointestinal bleeding than do controls not taking NSAIDs.<sup>127</sup> A dose-response relationship between NSAID consumption and development of mucosal ulcers may also exist. Cameron<sup>132</sup> found that a pattern of regular aspirin consumption (>15 aspirin tablets per week) had a significantly higher association with GUs than patterns of occasional (14 or less per week) or no aspirin consumption. On the basis of the distribution of aspirin use among these patients, it has been estimated that the relative risk of developing a GU rises dramatically above 15 to 20 aspirin tablets per week at an aspirin dose of 325 mg.<sup>120</sup>

Data on long-term mucosal effects of NSAID consumption come mostly from endoscopic studies of patients with rheumatoid arthritis or osteoarthritis.<sup>80,121,133-135</sup> McCarthy,<sup>136</sup> by combining data from all available point prevalence studies, estimated a GU point prevalence of 13% and a DU point prevalence of 11% for patients with arthritis taking long-term NSAID therapy. Enteric-coated aspirin appears to be associated with fewer GUs than plain aspirin.<sup>80</sup> However, incidences of DUs after use of either aspirin preparation are similar.<sup>134</sup>

Prospective, point-prevalence trials are limited by the fact that they look at the mucosa at only one point in time, after variable lengths of NSAID use. It is not certain whether the observed ulcer is truly a direct consequence of the NSAID or whether it was present before NSAID therapy began. To assess the risk of ulcer formation directly attributable to NSAIDs, a lesion-free mucosa needs to be observed at a zero time point, and the incidence of ulcers arising while the patient is taking NSAIDs as compared with placebo treatment is then recorded. Caruso and Bianchi-Porro<sup>133</sup> observed new gastric lesions in 31% of patients after 3 months of NSAIDs. The incidence of ulcers among these "lesions" was not reported, and there was no placebo-treated group for comparison. An alternative means to study the evolution of mucosal damage in long-term NSAID users is to use data from placebo-controlled trials of protective agents coadministered with NSAIDs. To date, there have been four large (ie, >100 subjects each) trials in which either a histamine<sub>2</sub> (H<sub>2</sub>) blocker, a synthetic PG, or placebo was coadministered with one of various NSAIDs to patients with arthritis who were without mucosal abnormalities at initial endoscopy.<sup>137-140</sup> Again, there was no group of patients with arthritis who received placebo without NSAIDs. Nevertheless, it appears that, at least after 2 months of NSAID therapy, a new GU may develop in a little greater than 10% of NSAID users, and a DU will develop in somewhere less than 10%. It is likely that gastric and duodenal ulceration with NSAID usage beyond 2 to 3 months will continue to occur, since NSAID-related ulcer complications, such as bleeding or perforation, occur frequently in long-term NSAID users.<sup>128,131,141</sup>

#### RISK FACTORS FOR NSAID-INDUCED ULCERS

##### Dose

As the prescribed dose of an NSAID increases, the percentage of patients presenting with upper gastrointestinal bleeding or hospitalized for ulcers increases.<sup>127,131</sup> Griffin et al<sup>131</sup> recently reported that the relative risk of ulceration in older subjects who have consumed NSAIDs for less than 30 days is almost twice the risk for longer periods of consumption.<sup>131</sup> The authors stated that the estimated risk for development of an ulcer among an elderly individual who has recently begun a high dose of an NSAID is 10 times that of a nonuser.<sup>131</sup> Prospective data directly evaluating dose-response or duration-response relationships between long-term NSAID use and ulcer development are lacking.

##### Ulcer History

A history of idiopathic ulcer disease may increase the risk of ulceration during NSAID therapy. After 2 months of NSAID consumption, six of 11 patients with a history of peptic ulcers developed recurrent ulceration, compared with only 11 of 115 patients with no ulcer history.<sup>138</sup> More studies of this risk factor are required before previous ulcer disease can be accepted as a definite risk factor.

##### Age

Age is one factor that has been consistently associated with an increased risk for NSAID-related ulcer complications.<sup>124,125,128,131</sup> The risk of perforated ulcers may be high in elderly NSAID users, especially elderly women,<sup>124</sup> and mortality from ulcer complications is also markedly elevated in the aged.<sup>128</sup> One likely explanation for this asso-

ciation of greater age and risk of NSAID ulcerations is that NSAID use increases with advancing age, especially in those over 60 years old.<sup>124,125</sup> However, there may be other factors that predispose the elderly to damage by NSAIDs. For example, our group and a group from Japan recently showed that both gastric<sup>142,143</sup> and duodenal<sup>142</sup> mucosal PG concentrations decline with aging in humans. Thus, older patients, at baseline, may have an already compromised potential for mucosal protection, perhaps placing this group at high risk for the development of NSAID-induced ulcers.

##### Smoking

It is not known whether cigarette smoking influences the potential for NSAID-induced ulceration. The ability of the gastroduodenal mucosa to protect itself against injury may be decreased in smokers, since smoking is associated with reduced mucosal PG concentrations in humans.<sup>144,145</sup> Use of NSAIDs by smokers should further reduce their already low mucosal PG concentrations.

#### PREVENTION OF NSAID-INDUCED ULCERS

Initial attempts to lower gastroduodenal toxic effects seen with aspirin were directed toward development of alternative formulations. Newer NSAIDs, enteric-coated preparations, suppositories, and prodrugs disappointingly continue to be associated with significant ulceration. None has demonstrated conclusive superiority to the others for decreased gastroduodenal toxic effects. Consequently, a major research interest has arisen to investigate other drugs that, when coadministered with NSAIDs, will either protect against or prevent mucosal injury.

Evaluation of the efficacy of a coadministered agent to prevent mucosal damage is strongly influenced by the type of scale used to measure injury. Mucosal protection may or may not be observed, depending on which pattern of injury has been most heavily weighted in the scoring system. In a study of prevention of naproxen-induced acute gastroduodenal injury, cimetidine was demonstrated to be superior to placebo when a scale primarily reflective of mucosal hemorrhage was used, but cimetidine was not different from placebo when a scale in which erosions were incorporated into the scoring system was used.<sup>146</sup> Results of cotreatment trials are more reliably applied to clinical practice when erosions and ulcers are used as end points to define response to therapy. Here again, findings of the short-term trials may not be relevant to long-term administration and, thus, the weight of our conclusions should be based on results of trials of extended cotherapy in the long-term NSAID user.

##### H<sub>2</sub>-Receptor Antagonists

It has become common practice to prescribe H<sub>2</sub>-antagonists, such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid), along with NSAIDs for ulcer prophylaxis, even though supporting evidence from clinical trials is sparse. Nonetheless, coadministration of an antisecretory agent does, for the following reasons, have some theoretical merit: (1) after mucosal integrity has been interrupted by an NSAID, further cellular damage can occur through the back diffusion of acid; (2) during NSAID therapy, acid secretion may increase,<sup>89,147</sup> possibly because of decreased mucosal PG content; and (3) in animals, NSAID mucosal damage in the presence of acid is greater than when mu-

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cosa is exposed to a higher pH.<sup>148</sup> On the other hand, the fact that H<sub>2</sub>-antagonists have no known effects on gastric mucosal PGs theoretically argues against their possible benefit in a PG-deficient mucosa.<sup>149,150</sup>

Coadministration of H<sub>2</sub>-antagonists and aspirin, dosed for 7 days or less, to normal volunteers produced less gastric and duodenal mucosal injury than did administration of placebo.<sup>151-153</sup> Thus, in the short term, H<sub>2</sub>-antagonists are effective for prophylaxis against gastric and duodenal NSAID-induced injury. During longer periods of NSAID administration, H<sub>2</sub>-antagonists, such as ranitidine (150 mg twice daily), are effective for NSAID-induced ulcer prevention in the duodenum but not the stomach.<sup>138,139</sup>

There is limited information on ulcer prevention after an NSAID-induced ulcer has been healed by an H<sub>2</sub>-antagonist, assuming that coadministration of an H<sub>2</sub>-antagonist and the NSAID is continued.<sup>154-156</sup> Available data suggest that recurrence rates during cotherapy are low.<sup>136</sup> In these maintenance studies, however, repeated endoscopy was only performed for symptomatic recurrences. Since a considerable number of patients taking NSAIDs have asymptomatic ulcerations,<sup>121,128,129,138,139</sup> it is likely the recurrence rates have been underestimated. Given that full-dose H<sub>2</sub>-antagonist therapy does not effectively prevent initial NSAID-induced GUs, the ability of a maintenance dose of an H<sub>2</sub>-antagonist to prevent recurrent ulcers becomes suspect. Reliable data from well-designed maintenance trials of coadministration of H<sub>2</sub>-antagonist and NSAIDs are not available. Thus, H<sub>2</sub>-antagonists are not approved for the prevention of NSAID-induced ulcerations.

#### Sucralfate (Carafate)

Sucralfate, an aluminum salt of sucrose sulfate, provides mucosal protection in animals against a variety of noxious agents, including aspirin and indomethacin.<sup>157-160</sup> In humans given one to four doses of aspirin, mucosal protection with sucralfate has been observed.<sup>161,162</sup> Possible protective mechanisms of action include increased PG production,<sup>158,162,163</sup> stimulation of gastric mucus and bicarbonate secretion, and stimulation of gastric mucosal cell proliferation.<sup>163-166,190</sup>

Even though sucralfate can protect the gastric mucosa from injury after a few doses of aspirin, mucosal protection by sucralfate after more than 1 day of aspirin has not been consistently observed. When compared with placebo, fewer aspirin-induced gastric mucosal "lesions" occurred in normal volunteers treated with sucralfate for 5 days<sup>167</sup> or 7 days.<sup>168</sup> These findings are in contrast to other studies in which gastric mucosal protection was not seen with sucralfate after 1 week<sup>169</sup> or 2 weeks<sup>170</sup> of aspirin treatment. Sucralfate is inferior to misoprostol (Cytotec) in prevention of NSAID-induced ulcers over longer periods (3 months).<sup>171</sup>

#### Prostaglandins, Including Misoprostol

A number of PGs have been orally administered to prevent NSAID-induced mucosal damage. Most investigation of prevention and/or treatment of NSAID-related mucosal injury has been with misoprostol, a PGE<sub>1</sub> analogue. Increasing evidence suggests that PG analogues can effectively prevent NSAID-induced gastric mucosal ulceration. In placebo-controlled trials of 1

week or less, misoprostol or enprostil (a PGE<sub>2</sub> analogue), when coadministered with NSAIDs, protected the gastric and duodenal mucosa from NSAID-induced injury.<sup>171-174</sup> With regard to ulceration, after only 1 week of NSAID therapy in normal volunteers, misoprostol significantly reduced the incidence of GUs and DUs.<sup>37</sup> Prostaglandin analogues appear to be more effective for the prevention of NSAID-induced GUs when compared with either H<sub>2</sub>-antagonists<sup>38</sup> or sucralfate.<sup>171</sup> In a multicenter trial, 420 patients with osteoarthritis who were taking one of three NSAIDs and who did not have GUs at the start of the study were randomized to receive either placebo, misoprostol (100 µg four times daily), or misoprostol (200 µg four times daily).<sup>137</sup> At the end of 3 months, GUs had developed in 30 of the 128 placebo-treated patients but in only eight of 143 and two of 139 patients treated with the lower and higher doses of misoprostol, respectively.

Data on use of misoprostol for prevention of NSAID-induced DUs come from two trials. In the above-mentioned trial, there was no significant difference in DU incidence at 3 months between misoprostol-treated and placebo-treated patients, possibly because the incidence of DU in the placebo group was very low. More recent results from another trial have suggested that misoprostol (200 µg four times daily) can significantly prevent NSAID-induced DUs.<sup>140</sup> Whereas 13 of 198 placebo-treated patients developed DUs after 12 weeks of NSAID, only two of 176 misoprostol-treated patients developed DUs by 12 weeks, a significant reduction.

Two aspects of these misoprostol studies<sup>137,140</sup> leave open questions about how to apply these data to clinical situations. First, patients with a history of previous ulcer disease were excluded. Because patients with a history of peptic ulcer disease seem to have a greater risk of recurrent ulceration,<sup>138</sup> it is especially important to know if misoprostol can confer a protective benefit to this group. Second, a protective benefit at 3 months does not predict long-term efficacy of misoprostol prophylaxis in patients taking NSAIDs on a long-term basis, nor does it predict with certainty a reduced morbidity or mortality from ulcer complications.

A reasonable assessment of the results of these trials is that misoprostol probably does provide a protective benefit against mucosal ulceration in patients who must ingest NSAIDs for a long period. Because misoprostol is available and has marketing approval for GU prophylaxis in NSAID users, certain questions should be investigated so that we may better define appropriate indications for its use: (1) Will a reduction in ulcer-related morbidity and mortality, the clinically important outcomes of gastric mucosal ulceration, be associated with misoprostol? (2) Which individuals among all long-term NSAID users should be singled out for prophylaxis? (3) How long and at what dosage should misoprostol prophylaxis be continued in such individuals?

#### Prevention Strategies

The optimal strategy for prevention of NSAID-related mucosal injury is not straightforward, given the uncertainties concerning pathogenesis of these ulcers and given the variety of available drugs that potentially could reduce ulcer frequency. An initial approach toward prevention should be directed toward identification of the individu-

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als who may be at greatest risk for NSAID-related ulceration. Elderly patients may possibly fall into this category. The risk of greater age may be further increased by a history of ulcer disease and, possibly, by female gender and a current habit of cigarette smoking. 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 patient has significant risk factors for NSAID-induced ulceration, as listed above, consideration should be given to prophylaxis with a coadministered agent. In our opinion, the strongest risk factor is a history of peptic ulcer disease. The impact of other risk factors, such as greater age, female gender, cigarette smoking, NSAID dosage, and number of various NSAIDs taken, is less certain, and physicians should use their judgment on a case-by-case basis, assessing potential benefits, risks, and costs. Misoprostol is the only drug approved for prevention of NSAID-induced GUs. We recommend a starting dose of 100 µg four times daily, since this dose seems to be almost as effective as the higher misoprostol dose and may reduce the incidence of diarrhea. If this dose is well tolerated, the physician may choose to increase the dose after a few weeks to 200 µg four times daily, although this dose may not be cost-effective.<sup>175</sup> These dosage recommendations are at slight variance with Food and Drug Administration guidelines, in which the higher dose is recommended initially and the lower dose is used if the higher dose cannot be tolerated. Doses higher than 800 µg daily should be avoided. Because of its abortifacient potential, misoprostol should not be used in pregnancy. If the patient has a history of DU, it might be worthwhile considering prophylaxis with an H<sub>2</sub>-antagonist. Whether sucralfate prevents NSAID-induced gastroduodenal mucosal ulceration awaits confirmation by placebo-controlled studies.

#### TREATMENT OF NSAID-INDUCED ULCERS H<sub>2</sub>-Receptor Antagonists

Although H<sub>2</sub>-antagonists do not effectively prevent NSAID-induced GUs, they are useful for accelerating GU healing.<sup>136,176</sup> A practical consideration is whether ulcer healing can occur while NSAID administration continues. After an NSAID-induced GU has appeared and NSAID therapy is discontinued, approximately two thirds of GUs will heal by 6 weeks of combined treatment with an H<sub>2</sub>-antagonist and antacid,<sup>154</sup> a healing rate that is similar to the healing rates of idiopathic GUs treated with H<sub>2</sub>-antagonists for 6 weeks.<sup>176,177</sup> In many patients, however, NSAIDs cannot be discontinued.

Gastric or duodenal ulcers induced by NSAIDs can be healed with H<sub>2</sub>-antagonists while NSAIDs are continued.<sup>178-183</sup> However, healing rates are lower than when NSAIDs are discontinued.<sup>179-181</sup> When 190 patients with arthritis were randomly assigned to continue or discontinue NSAIDs while their ulcers were being treated with ranitidine,<sup>182</sup> GU and DU healing rates after NSAIDs were discontinued were significantly greater at 4, 8, and 12 weeks than when NSAIDs were continued. Nonetheless, in those who continued NSAIDs, approximately 80% of GUs and approximately 90% of DUs were healed by 12

weeks. Size of an NSAID-induced GU is also a major determinant of success of H<sub>2</sub>-antagonist therapy.<sup>178</sup>

#### Omeprazole (Prilosec)

This agent inhibits gastric acid secretion by blocking H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase pumps in parietal cells. Omeprazole may be more efficacious than H<sub>2</sub>-antagonists for treatment of NSAID-related GUs.<sup>181</sup> With omeprazole therapy (40 mg daily), healing rates during continued NSAID use were only slightly lower than, and were not significantly different from, healing rates of conventional peptic ulcers also treated with omeprazole. Further studies evaluating the use of omeprazole in the treatment of NSAID-induced GUs will be necessary to verify these initial observations.

#### Sucralfate (Carafate)

In patients with arthritis, after 4 weeks of therapy for NSAID-induced erosions or ulcers, sucralfate-treated patients who were still taking NSAIDs had a greater improvement in their mean mucosal injury score than patients taking placebo.<sup>184</sup> Two problems in interpretation of these data are that (1) GUs were not separated from erosions and (2) sucralfate-treated patients, before initiation of therapy, had significantly worse mucosal injury than placebo users and, therefore, had greater potential for improvement in their scores with therapy. In another study, improvement in gastric erosions with sucralfate after 6 weeks of therapy was similar to improvement seen with cimetidine.<sup>185</sup> Again, outcomes for GUs were not described. Only one study, using sucralfate as treatment for NSAID-induced mucosal damage, specifically separated ulcer data from data for other mucosal lesions.<sup>179</sup> After 9 weeks of therapy for NSAID-related ulcers in patients with arthritis, sucralfate or ranitidine healed just over 80% of ulcers. However, difficulties again arise in drawing conclusions from these data, as GU and DU healing data were not separately mentioned. At initiation of therapy, most endoscopically observed ulcers were DUs. Thus, it is reasonable to conclude that the treatment success of sucralfate primarily reflected DU healing. No firm conclusions can be made regarding sucralfate as a therapeutic agent in NSAID-induced mucosal ulceration.

#### Misoprostol

For healing of conventional peptic ulcers (unrelated to NSAIDs), synthetic PG analogues are about as effective as, but not more effective than, H<sub>2</sub>-antagonists.<sup>186-190</sup> Healing of peptic ulcers with synthetic PG analogues can probably be entirely attributed to acid inhibition rather than to mucosal-protective effects. For example, misoprostol, at an oral dose of 200 µg, is as effective as 200 mg of cimetidine in the inhibition of acid secretion.<sup>191</sup> Since PG analogues and H<sub>2</sub>-antagonists have similar abilities to heal peptic ulcers, but PG analogues are associated with more frequent side effects,<sup>192</sup> H<sub>2</sub>-antagonists remain the treatment of choice for healing of conventional peptic ulcers.

Efficacy of misoprostol as treatment of NSAID-induced ulcers was addressed in one study of 239 patients with rheumatoid arthritis with endoscopically documented gastric or duodenal "lesions."<sup>193</sup> Patients were randomized to receive either misoprostol (200 µg four times daily) or placebo while continuing to take aspirin (650 to 1300 mg four times daily). The results suggest that misoprostol is

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effective in healing of NSAID-induced GU and possibly DU. However, further studies are needed to address this question, since in the above study the numbers of ulcers were relatively small and ulcer healing rates after cotherapy with misoprostol and aspirin may not equal healing rates after misoprostol and other NSAIDs. Moreover, trials directly comparing healing efficacy of misoprostol with other more traditional healing agents are also needed. Misoprostol is not currently approved for use for either GU or DU healing.

### Treatment Strategies

Initial attempts at treatment of NSAID-induced ulcers should be cessation of the NSAID. Complete withdrawal of NSAIDs may not be possible in all patients, but they may tolerate a reduction in NSAID dose. With continued NSAID use, many drugs might be useful ulcer-healing agents. The  $H_2$ -receptor antagonists, such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid), and the proton pump inhibitor omeprazole (Prilosec) effectively heal NSAID-induced GU and DU. Available data suggest that misoprostol (Cytotec) may heal NSAID-induced GUs and that sucralfate (Carafate) and misoprostol may heal NSAID-induced DUs. However, more studies are needed before sucralfate and misoprostol can be recommended for treatment of an active NSAID-induced ulcer.

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