Review Article

The Gastroduodenal Toxicity of Nonsteroidal Anti-Inflammatory Drugs. A Review of the Literature

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Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular and important for the treatment of inflammation and pain. However, conventional NSAIDs are intrinsically toxic to the gastroduodenal (GD) mucosa. The literature can, and should, guide us towards safer prescribing of NSAIDs. Factors known to increase the risk of GD toxicity include: history of peptic ulcer disease; advanced age; high doses; and coadministration of aspirin, anticoagulants or corticosteroids. Patients with any one of these risk factors, with the possible exception of age alone, should receive gastroprotective prophylaxis with proton pump inhibitors or misoprostol. Standard dose H2 antagonists do not protect against NSAID-induced gastric ulcers and are unsuitable for prophylaxis. Awareness of risk factors and appropriate prophylactic agents will minimize the risk to patients. Whether the new generation of highly selective COX-2 inhibitors and nitric oxide–donating NSAIDs are safer drugs in long-term use be remains to be proven, though initial clinical trial data are positive. J Pain Symptom Manage 2000;20:140–151. © *U.S. Cancer Pain Relief Committee, 2000.*

Key Words
Nonsteroidal anti-inflammatory drugs, peptic ulcer, proton pump inhibitors, misoprostol, histamine H2 antagonists, gastroprotection

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to be the most widely used drug group worldwide.[1–3] Over 70 million prescriptions for NSAIDs are written each year in the United States[4] and approximately 20 million are written annually in the United Kingdom.[1] In addition to their anti-inflammatory properties, NSAIDs are highly effective analgesics[5,6] and are increasingly used in this context. While there are no large randomized controlled trials directly comparing the efficacies of commonly used NSAIDs, oral diclofenac and ibuprofen have proved superior to acetaminophen (paracetamol), "weak" opioids, and intramuscular morphine in single dose studies of acute pain.[7] Both single- and multiple-dose trials have demonstrated the efficacy of NSAIDs in cancer pain.[8]

NSAIDs are well recognized as causing upper gastrointestinal (GI) complications, ranging from dyspeptic symptoms in up to 40%[9,10] to life-threatening complicated ulcers (hemorrhage, perforation, or pyloric obstruction). Gastroduodenal (GD) damage related to NSAID

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use is thought to be the most frequent and, in aggregate, the most serious complication of any drug therapy.[11] The prevalence of peptic ulceration in chronic NSAID users is 20–30%,[12–14] with gastric ulcers approximately six times more common than duodenal ulcers.[12,15] The risk of hospitalization for serious upper GI complications (bleeding or perforation) from NSAID use is 1–2% per year.[16] In the US, this translates to over 100,000 hospital admissions for serious NSAID-related GI complications each year.[17] It is important to remember that upper GI symptoms do not match GD pathology. At least 50% of NSAID users with dyspepsia have no significant mucosal abnormalities,[12] whereas up to 60% of life-threatening complicated ulcers induced by NSAIDs have no preceding symptoms.[18]

Mechanism of Gastroduodenal Damage

NSAIDs disrupt the normal gastric mucosal barrier of bicarbonate and hydrophobic mucus by two mechanisms. The principal mechanism, independent of route of administration, results from disturbance of prostaglandin synthesis by inhibition of the constitutive cyclo-oxygenase (COX) isoenzyme, COX-1.[19,20] In the stomach, prostaglandins have a vital protective role, maintaining mucosal blood flow, stimulating secretion of bicarbonate and mucus and regulating mucosal cell turnover and repair.[20] Loss of protection by inhibition of prostaglandins renders the stomach vulnerable to damage by gastric acid.

Neutrophils also are believed to have a central role in the development of NSAID-induced GD damage, although this is yet to be proven in humans. Animal studies have shown that neutropenia[21] or blockage of neutrophil adhesion to the vascular endothelium[22] will dramatically reduce the severity of NSAID-induced GD damage. Impaired production of protective prostaglandins in the gastric mucosa appears to increase the expression of neutrophil adhesion molecules.[23] This results in reduced mucosal blood flow from capillary obstruction[24] and local free radical damage from activated neutrophils.[25]

Some NSAIDs can damage the gastric mucosa by a second, direct effect. Acidic NSAIDs, including aspirin, become lipid soluble at low pH. Taken orally, they can cross the lipid barrier into gastric mucosal cells. At intracellular pH, they lose lipid solubility and become trapped, disrupting cell function, perhaps by inhibiting mitochondrial oxidative phosphorylation.[20,26] Damage to surface mucosal cells compromises the normal protective mechanisms, reducing resistance to acid damage. Mucosal erosions and hemorrhages can be seen within 90 minutes of ingestion of a single 75 mg tablet of aspirin.[27] However, this direct irritant effect is not believed to make a significant contribution to the development of NSAID ulcers,[28] nor are the submucosal hemorrhages and erosions thought to be of great clinical relevance.[12] While the use of prodrugs and enteric-coated formulations limit the direct irritant effect of NSAIDs, these formulations are not associated with a reduced incidence of GD ulceration.[28,29]

Factors Increasing the Risk of NSAID-Induced Gastroduodenal Damage

Overall, the use of NSAIDs increases the risk of developing a complicated peptic ulcer approximately four-fold.[26,30] Widely accepted additional risk factors are listed in Table 1. The elderly are clearly at greater risk of NSAID-induced GD toxicity. This may be related to impaired mucosal defenses, but may also be associated with a reduced renal clearance of the drug leading to increased plasma levels.[37] Gender, smoking, alcohol intake and cardiovascular disease have also been reported as risk factors in some studies.[30,31,38] The influence of *Helicobacter pylori* on the development and healing of NSAID-induced ulcers remains disputed, with trials producing conflicting data.[39–41] The effect of severe illness on the risk of NSAID-induced GD toxicity is also unclear. Increasing disability related to rheumatoid arthritis has been shown to be associated with an increased risk of serious GI events with NSAID use.[37] However, whether advanced malignancy is, in itself, a risk factor is not known.

NSAIDs vary considerably in their intrinsic potential to damage the GD mucosa. Ibuprofen is associated with the lowest incidence of GD toxicity, whereas the use of azapropazone and piroxicam carries much greater risk. This

Table 1
Risks of Complicated Peptic Ulcer in Patients Taking NSAIDs Compared With Non-Users of NSAIDs

	Relative risk	Reference
Use of NSAID (overall risk)	4	26, 30
Past history peptic ulcer disease	17	30
Age > 60 years	3–13	30, 31
Azapropazone	23–31	30, 32
Low dose NSAID:high dose	2:8	30, 32, 33
Multiple NSAID use	9	30
Co-prescription of corticosteroids	10	34
Co-prescription of anticoagulants	13	35
Co-prescription of aspirin (75–300 mg daily)	8 (odds ratio)	36

'NSAID spectrum' is illustrated in Figure 1. There is, in addition, a clear dose response, with higher doses leading to greater toxicity.[30–33] Ibuprofen used in doses above 1600 mg daily appears to have an incidence of GD toxicity comparable to diclofenac and naproxen.[30,32,33,43]

A recent audit of the use of NSAIDs in the palliative care setting[44] showed this population to be at very high risk of GD toxicity. NSAID use was high (36% of 200 patients in the audit) and additional risk factors were frequently present. In particular, coadministration of corticosteroids was noted in 45 (62.5%) patients taking NSAIDs.

Although factors that increase risk are becoming clearer, the definition of a patient at 'high risk,' and, therefore, warranting prophylaxis, remains unclear. Undoubtably, the presence of multiple risk factors puts the patient at much greater risk;[38] patients in this category are obvious choices for prophylaxis. Whether identification of a single additional risk factor for NSAID toxicity defines the patient as 'high risk,' necessitating prophylaxis, is contentious. Certainly, it can be argued that prophylaxis is warranted if any one of the factors listed in Table 1 is present.[45,46] It has been suggested, however, that the cost of prescribing prophylaxis for all patients over the age of 60 years is prohibitive[47] and elderly patients should receive prophylaxis only if other risks are identified. The selection of patients for gastroprotective prophylaxis according to risk factors requires further clarification.

Prophylaxis

Attempts to protect against GD damage by conventional NSAIDs have involved studies of mucosal coating drugs, gastric antisecretory drugs, and prostaglandin analogues.

Mucosal Coating Drugs

Sucralfate is the only mucosal coating agent that has been tested in the context of NSAID-induced GD toxicity. Although it has various characteristics which would suggest it may provide useful protection, including coating of ulcerated mucosa, adsorption of pepsin and bile acids, and the stimulation of endogenous prostaglandins,[13] studies have shown sucralfate to be of no benefit for prophylaxis.[12,13] A randomized controlled trial comparing sucralfate (1g four times daily) with misoprostol (200 mcg four times daily) for prophylaxis showed an incidence of gastric ulcers in the sucralfate arm of 16% at 3 months (equivalent to placebo in other studies), compared with only 1.6% in the misoprostol arm.[48] Sucralfate may, however, relieve NSAID-associated dyspepsia.[49]

Histamine H2 Antagonists

H2 antagonists in standard doses have been shown to provide some protection against NSAID-induced duodenal ulcers but minimal protection against the far greater problem of NSAID-induced gastric ulceration.[50–54] Two randomized, placebo-controlled trials have shown that patients receiving ranitidine 150 mg twice daily as primary prophylaxis had the

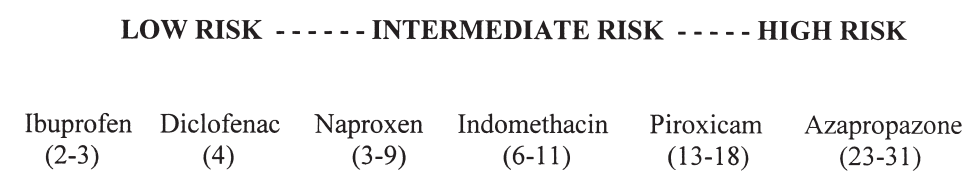

Fig. 1. Spectrum of NSAIDs according to intrinsic GD toxicity. Numbers in parentheses relate to relative risk of bleeding peptic ulcer compared with non-users of NSAIDs.[30,32,42,43]

same incidence of gastric ulcers at 8 weeks as patients in the placebo arm.[51,52] Comparison of ranitidine 150 mg twice daily with misoprostol 200 mcg four times daily[53] confirmed the much higher incidence of gastric ulceration in the ranitidine arm (5.7% vs. 0.6%) after 8 weeks. Use of famotidine in high dose, however, has been shown to significantly reduce the incidence of both duodenal and gastric ulcers induced by NSAIDs.[55] Interestingly, this was not duplicated by high dose ranitidine (300 mg twice daily) which failed to protect against NSAID-induced gastric ulcers in a small study.[56] This may suggest that NSAID-induced gastric ulceration is acid-independent, with high dose famotidine providing protection by another, undefined, mechanism.[28] According to the evidence in the literature, standard dose H2 antagonists do not provide adequate prophylaxis against NSAID-induced gastroduodenal toxicity and should be avoided in this context.

Proton Pump Inhibitors

Early reports suggested that omeprazole, like standard dose H2 antagonists, afforded moderate protection against NSAID-induced duodenal injury only.[57] More recently, four randomized controlled trials have studied the role of omeprazole in prevention and healing of NSAID-induced ulcers (Table 2). Two have looked at primary prevention of GD damage in patients receiving long-term NSAID therapy.[59,60] Both compared omeprazole 20 mg daily with placebo. Ekstrom et al.[59] recruited 177 patients with a history of dyspepsia or uncomplicated peptic ulcer; Cullen et al.[60] recruited 169 patients with mild dyspepsia. Both used endoscopic examination and symptom scores to assess response. The incidence of peptic ulcer at 3 months[59] was 4.7% in the omeprazole arm compared with 16.7% of patients taking placebo. At 6 months,[60] the incidences were 3.6% and 16.5% respectively. While the patient populations in these two

Table 2
Endoscopic Studies of Omeprazole in the Prophylaxis and Management of NSAID-Induced Peptic Ulcers

Patients	Drugs	Primary Prevention[a]	Healing of Established Ulcers[b]	Secondary Prevention[a]	Reference
541 - on long-term NSAIDs with ulcer or >10 erosions	Omeprazole (20 and 40 mg daily) versus Ranitidine 150 mg bid	NA	(at 8 weeks) Omep 20 – 80% Omep 40 – 79% Ranitidine – 63% (p = 0.001)	(at 6 months- Omeprazole 20 mg versus Ranitidine 150mg bid) Omep 20 – 72% Ranitidine – 59% (p = 0.004)	54
935 – on long-term NSAIDS with ulcer or >10 erosions	Omeprazole (20 and 40 mg daily) versus Misoprostol 200 μg qid	NA	(at 8 weeks) Omep 20 – 76% Omep 40 – 75% Misoprostol – 71%	(at 6 months - Omeprazole 20 mg versus Misoprostol 200 μg bid versus Placebo) Omep 10 – 61% Misoprost 48% (p = 0.001) Placebo – 27%	58
177 – on long-term NSAIDs with history of dyspepsia or uncomplicated peptic ulcer	Omeprazole 20 mg versus Placebo	(at 3 months) Omep 20 – 74% Placebo – 48% (p = 0.005)	NA	NA	59
169 – on long-term NSAIDs with current mild dyspepsia; no significiant endoscopic lesions	Omeprazole 20 mg versus Placebo	(at 6 months) Omep 20 – 78% Placebo – 53% (p = 0.004)	NA	NA	60

Ulcer defined as >0.3 cm in all studies.
[a]Treatment failure defined as development of any of the following: an ulcer, more than 10 gastric or duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in discontinuing treatment.
[b]Treatment success defined as disappearance of ulcer and the presence of fewer than 5 erosions in stomach or duodenum, and not more than mild dyspeptic symptoms.

studies were selected (either with a history of peptic ulcer disease or with current dyspepsia), the results suggest that omeprazole provides very useful prophylaxis for the wider population at increased risk of GD toxicity with NSAIDs.

Healing of established peptic ulcers in NSAID-treated patients, and secondary prophylaxis, were examined by two further studies.[54,58] Patients with peptic ulcers or more than 10 erosions at endoscopy were invited to participate. Omeprazole (20 mg or 40 mg daily) was compared with ranitidine 150 mg twice daily[54] and misoprostol 200 mcg four times daily [58] during the healing phase of the studies. Omeprazole was significantly more effective than ranitidine in healing established ulcers. Misoprostol appeared equally effective. There was no difference between the two doses of omeprazole. In the maintenance phase, omeprazole 20 mg daily was compared with ranitidine 150 mg twice daily,[54] misoprostol 200 mcg twice daily, and placebo.[58] Treatment failure was defined as the development of an ulcer, more than 10 erosions, at least moderate dyspeptic symptoms, or adverse events necessitating withdrawal of treatment. At 6 months, omeprazole was more successful than either ranitidine or misoprostol in maintaining remission (Table 2). It is worth noting that the dose of misoprostol used in the maintenance phase was lower than that used in the healing phase. Efficacy of misoprostol is dose-related but so, too, are side-effects.[61] Omeprazole was better tolerated than either dose regimen of misoprostol.[58] Overall, omeprazole appears to be effective in primary and secondary prevention of both gastric and duodenal injury and is better tolerated than misoprostol. Omeprazole also appears superior to both ranitidine and misoprostol in reduction of dyspeptic symptoms.[54,58] The efficacy of omeprazole in preventing serious complications of NSAID-induced peptic ulcers remains unclear.

To date, studies evaluating the efficacy of other proton pump inhibitors for primary or secondary prophylaxis of NSAID-induced GD toxicity are very limited. One small, randomized study found lansoprazole 15 mg daily to be as effective as misoprostol 200 mcg twice daily in patients taking indomethacin over a 3-week period.[62] A more recent study has also found lansoprazole to be as effective as misoprostol in primary prophylaxis with NSAIDs.[63] In the United Kingdom, omeprazole is the only proton pump inhibitor to have a license for prophylaxis of NSAID-induced ulcers, although related drugs appear to have similar effects.

Prostglandin Analogues

Misoprostol has been extensively studied as a mucosal protective agent in NSAID users. As an analogue of prostaglandin E1, it counteracts the inhibition of prostaglandin production by conventional NSAIDs, maintaining the gastric mucosal barrier and mucosal blood flow. It also has some effect in reducing the secretion of gastric acid.[64] Randomized controlled trials of misoprostol in chronic NSAID use have compared it with placebo,[38,61,65,66] sucralfate,[48] ranitidine,[53] and omeprazole.[58] Misoprostol has been shown to be effective for the primary prophylaxis of both duodenal and gastric ulcers induced by NSAIDs (Table 3).

Misoprostol has also been shown to reduce the serious complications of NSAID-induced peptic ulcers. A randomized, placebo-controlled study of over 8,800 patients with rheumatoid arthritis receiving chronic NSAID therapy reported a 40% reduction in serious upper GI complications using misoprostol 200 mcg four times daily.[38] Degree of protection with misoprostol appears to be dose-dependent with 200 mcg four times daily providing greatest protection against gastric ulcers.[61,66] A dose-response effect has not been seen with prophylaxis against duodenal ulcers.[66] GI side effects are dose-related, with up to 40% of patients reporting diarrhea on the higher dose regimen.[61] While the diarrhea is often self-limiting, it has led to high withdrawal rates from some studies.[38,66]

Studies of secondary prophylaxis of NSAID ulcers have shown lower rates of GD ulcers with misoprostol treatment than with placebo,[58,67] although misoprostol 200 mcg twice daily was less protective than omeprazole 20 mg daily.[58] Fixed combinations of diclofenac and misoprostol have also been assessed and have been reported to be associated with a lower incidence of GD ulcers and similar efficacy than diclofenac alone.[68,69]

Treatment of Established NSAID-Induced Ulcers

NSAIDs can interfere with the healing of damaged mucosa[26,28] and the ideal manage-

Table 3
Endoscopic Studies of Misoprostol in the Primary Prophylaxis of NSAID-Induced Peptic Ulcers

Patients	Length of Study	Drugs	Duodenal Ulcers Present	Gastric Ulcers Present[a]	Reference
420 patients with osteoarthritis and abdominal pain	3 months	Misoprostol 200 μg qid Misoprostol 100 μg qid Placebo	Not assessed	1.4% 5.6% 21.7% ($P < 0.001$)	61
253 patients with osteoarthritis abdominal pain, and normal endoscopy	3 months	Misoprostol 200 μg qid Sucralfate 1 g qid	Not assessed	1.6% 16% ($P < 0.001$)	48
638 patients with arthritis and normal endoscopy	3 months	Misoprostol 200 μg qid Placebo	0.6% 4.6% (p = 0.002)	1.9% 7.7% ($P = 0.001$)	65
1197 patients with upper abdominal pain and normal endoscopy	3 months	Misoprostol 200 μg qid Misoprostol 200 μg tid Misoprostol 200 μg bid Placebo	1.4% 3.3% 2.6% 7.5%	4% 3.9% 8.1% 15.7%[b]	66
374 patients with upper abdominal pain and normal endoscopy	2 months	Misoprostol 200 μg qid Rantitidine 150 mg bid	1.1% 1.08%	0.56% 5.67% ($P < 0.01$)	53

[a]Gastric ulcer defined as at least 0.3 cm diameter in: Agrawal 1991; Raskin 1995; Raskin 1996; and Graham 1998; and at least 0.5 cm diameter in Graham 1993.
[b]All doses of misoprostol significantly better than placebo. Statistically significant dose effect of misoprostol with gastric, but not duodenal, ulcers.

ment of NSAID-induced peptic ulcers is to stop the offending drug. When this is not appropriate, misoprostol,[58,70] omeprazole[54,58] and lansoprazole[71] have been shown to heal peptic ulcers while NSAID use continues (Table 2). H2 antagonists are less effective than proton pump inhibitors in this context,[54,71] although it has been suggested that high doses[72] or a prolonged course[73] may heal both gastric and duodenal ulcers adequately.

Cost-Effectiveness of Prophylaxis

GI damage caused by NSAID use in the elderly incurs an excess medical care cost estimated to be at least $2 billion/year in the United States.[17] A study of patients admitted to hospital with complicated peptic ulcer disease has shown that NSAID users are more likely to require blood transfusions and need longer hospital stays than non-users.[16] In the United Kingdom, it has been suggested that the cost of managing bleeding peptic ulcers induced by NSAID use confers an additional charge of £2 on every NSAID prescription, possibly more than the drug itself.[74]

Although the GI complications from NSAID use impose a costly burden on healthcare systems, it is unlikely to be cost-effective to prescribe prophylaxis for every NSAID user.[47,75,76] Studies of cost-effectiveness of misoprostol prophylaxis have produced contradictory information, from cost-saving[77–79] or cost-effective[80] to excessively costly.[81] The lack of consensus can be explained by differing assumptions made for each decision model, including the magnitude of the effect of misoprostol.[75] The studies also place emphasis on management guided by the presence of dyspeptic symptoms; because these do not match gastroduodenal pathology,[12,18] they are not an appropriate guide for the use of prophylaxis. Current consensus is to prescribe misoprostol or proton pump inhibitor prophylaxis for patients at high risk of gastroduodenal toxicity with NSAIDs.[2,3,47,76,82] The large proportion of chronic NSAID users who are over the age of 60 years may mean that prescription of prophylaxis to all elderly patients is not cost-effective. Restriction of prophylaxis in the elderly to those with additional risk factors has been proposed.[47]

The Future of NSAIDs

Selective COX-2 Inhibitors

Cyclo-oxygenase exists in two forms. COX-1 is expressed in most tissues, including stomach, kidney, and platelets, and is involved in

the synthesis of prostaglandins in response to physiological stimuli. COX-2, however, is induced at sites of inflammation, producing prostaglandins which mediate the inflammatory response and the perception of pain.[83] Conventional NSAIDs inhibit both isoenzymes. In theory, selective inhibition of COX-2 should result in an anti-inflammatory and analgesic effect without compromising mucosal integrity. In support of this, the risk of GD toxicity from any single NSAID is, to some extent, proportional to the degree of inhibition of COX-1.[20,84,85] For example, nabumetone, which is believed to be a preferential COX-2 inhibitor, has been shown to be equivalent in GD ulcerogenicity to a combination of ibuprofen and misoprostol.[86]

Studies of meloxicam, which is marketed in some countries as a preferential COX-2 inhibitor, have produced conflicting data concerning the value of preferential COX-2 inhibitors. Most studies demonstrate reduced gastrointestinal side effects when meloxicam 7.5 mg daily is compared with conventional NSAIDs, such as diclofenac,[87] naproxen[88] or piroxicam.[89] To date, meloxicam has not been compared with ibuprofen, the safest of the conventional NSAIDs. As with other NSAIDs, however, the GI side effects of meloxicam are dose-related, with meloxicam 15 mg daily reported to have a toxicity profile akin to piroxicam 20 mg daily.[90] Some studies of meloxicam 7.5 mg daily have raised concerns about its efficacy, with more withdrawals among meloxicam-treated patients because of lack of effect.[87,88] Recently it has been suggested that meloxicam 7.5 mg has a slightly lower therapeutic effect than diclofenac 100 mg,[91] which suggests that trials reporting an improved side effect profile with this dose of meloxicam may not have compared equi-effective doses. Overall, meloxicam 7.5 mg daily appears to be well tolerated, with evidence to support a better safety profile than some conventional NSAIDs. However, it does not appear to have a lower incidence of serious adverse gastrointestinal events than conventional NSAIDs[92] and warnings about gastrointestinal toxicity have been strengthened since its launch.[93]

Research continues towards development of highly selective COX-2 inhibitors. Early clinical trials have been encouraging with toxicity during short-term use akin to placebo and efficacy similar to conventional NSAIDs. Compared with diclofenac[94] and naproxen,[95] celecoxib has been shown to have comparable analgesic and anti-inflammatory effects in patients with rheumatoid arthritis. The incidence of endoscopically-proven GD ulcers (at least 3 mm diameter) was significantly lower in patients treated with celecoxib (4–6% of patients on celecoxib 100 mg to 400 mg twice daily for up to 6 months; 15% of patients on diclofenac for 6 months; and 26% of patients on naproxen for 3 months). In patients with osteoarthritis treated with rofecoxib 25 mg or 50 mg daily, the incidence of peptic ulcers at 3 months has been shown to be equivalent to placebo and significantly less than ibuprofen 2.4 g daily.[96] Peptic ulcer bleeding is also significantly reduced in patients treated with rofecoxib compared with conventional NSAIDs.[97] Rofecoxib has also been shown to be effective in the management of post-dental surgery pain[98] and primary dysmenorrhea.[99] However, the use of highly selective COX-2 inhibitors primarily as analgesics is limited at present. Both rofecoxib and celecoxib are licensed in the United States for management of arthritis. Rofecoxib is also licensed for the management of acute pain at a dose of 50 mg daily (double the dose recommended for arthritis) with a recommended maximum duration of treatment of 5 days.

While the initial clinical trials have been consistent and encouraging, a recent case report described severe NSAID-induced gastropathy with celecoxib and highlighted the possibility of a role for COX-2 in mucosal protection and repair mechanisms.[100] More information is needed in order to ensure the safety and efficacy of highly selective COX-2 inhibitors.

Nitric Oxide-Releasing NSAIDs

Nitric oxide (NO) is now recognized as a vital mediator of GD mucosal defense, with the same effects on mucus production, mucosal blood flow, and neutrophil adherence and activation as the gastroprotective prostaglandins.[28] Evidence suggests that inhibition of one arm of mucosal defense may result in a compensatory increase in activity of the second.[28,101] Modifying conventional NSAIDs by adding a NO-donating moiety could, then, reduce toxicity while allowing non-selective COX-inhibition. Experimental models have corroborated this theory and shown efficacy

comparable to the parent compound.[102–104] Furthermore, while conventional NSAIDs impair healing of established ulcers, NO-NSAIDs have been shown to accelerate ulcer healing in an animal model.[105] Results of clinical trials of NO-NSAIDs are awaited.

Conclusions

NSAIDs will continue to be widely prescribed and useful drugs. Conventional NSAIDs are, however, associated with a high incidence of GD toxicity, which imposes a heavy financial burden on healthcare systems. Safer use of these drugs demands consideration of additional risk factors for each patient. Acetaminophen (paracetamol) should always be considered as an alternative to NSAIDs. In patients needing NSAIDs, low toxicity NSAIDs should be prescribed preferentially and commenced at the lowest recommended dose.[42] Gastroprotective prophylaxis should be considered for patients at increased risk of GD toxicity with NSAIDs (past history of peptic ulcer disease; advanced age; use of high toxicity NSAIDs or high doses; or coadministration of corticosteroids, aspirin, anticoagulants or multiple NSAIDs). Prophylaxis is warranted if any of these risks are identified, with the possible exception of age alone. According to the current evidence, the prophylactic agent chosen should be a proton pump inhibitor or misoprostol, but not standard dose H2 antagonists. Patients taking NSAIDs should also be educated about potential side effects and advised to discontinue the drug if upper GI symptoms develop.[106] New generation NSAIDs, including highly selective COX-2 inhibitors and NO-NSAIDs, are now appearing. These are likely to have a major impact on NSAID prescribing. Early experience is encouraging but their relative safety and efficacy in chronic pain is uncertain at present. For the time being, conventional NSAIDs will continue to be widely prescribed. An awareness of risks and responsible prescribing will enable safer use of these drugs.

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