REVIEW ARTICLE

Drug Safety 2006; 29 (2): 119-132
0114-5916/06/0002-0119/$39.95/0

NSAID-Associated Adverse Effects and Acid Control Aids to Prevent Them

A Review of Current Treatment Options

Jørgen Næsdal[1] and *Kurt Brown*[2]

1 AstraZeneca R&D, Mölndal, Sweden
2 AstraZeneca LP, Wilmington, Delaware, USA

Contents

Abstract

NSAIDs are central to the clinical management of a wide range of conditions. However, NSAIDs in combination with gastric acid, which has been shown to play a central role in upper gastrointestinal (GI) events, can damage the gastroduodenal mucosa and result in dyspeptic symptoms and peptic lesions such as ulceration.

NSAID-associated GI mucosal injury is an important clinical problem. Gastroduodenal ulcers or ulcer complications occur in up to 25% of patients receiving NSAIDs. However, these toxicities are often not preceded by indicative symptoms. Data obtained from the Arthritis, Rheumatism, and Aging Medical Information System have shown that 50–60% of NSAID-associated peptic ulcer cases can remain clinically silent and do not present until complications occur. Therefore, prophylactic treatment to prevent GI complications may be necessary in a substantial proportion of NSAID users, especially those in groups associated with a high risk of developing these complications.

Use of cyclo-oxygenase (COX)-2 selective NSAIDs, also known as 'coxibs', substantially reduces the incidence of upper GI toxicities seen with non-selective NSAIDs. However, there are concerns regarding the cardiovascular safety of coxibs. For this reason, the US FDA recommends minimal use of coxibs and only when strictly necessary. Additionally, rofecoxib has been removed from the US market and sales of valdecoxib have been suspended. Furthermore, upper GI toxicities still occur in patients receiving coxibs. Therefore, cotherapies are required to prevent and/or heal upper GI effects associated with NSAID use. Effective prophylactic and treatment strategies include misoprostol, histamine H_2 receptor antagonists and proton pump inhibitors (PPIs). The key role that gastric acid plays in upper GI adverse events among NSAID users suggests that it is important to choose the most effective agent for acid control to alleviate symptoms, heal mucosal erosions and improve the reduced quality of life in this patient population. PPIs provide effective acid suppression, which is essential to avoid GI mucosal injury, and they are, therefore, capable of dramatically decreasing the morbidity and mortality associated with this disorder.

Since many serious GI complications are not heralded by any previous symptoms, physicians need to be aware of risk factor profiles that predispose patients to serious GI problems. Physicians also need to initiate the appropriate preventative acid suppressive therapy to minimise the burden of NSAID-associated GI adverse effects.

NSAIDs are among the world's most widely administered drugs, with an estimated 30 million people benefiting from their anti-inflammatory and analgesic effects each day.[1] Most NSAIDs are primarily prescribed for osteoarthritis, rheumatoid arthritis, and other musculoskeletal and soft tissue conditions.[2] NSAIDs are commonly prescribed to elderly patients, with 35% of all prescriptions administered to individuals >60 years of age.[3] However, the use of NSAIDs is increasing in all age groups because of the greater availability of over-the-counter (OTC) preparations and the growing use of low-dose aspirin (acetylsalicylic acid) for prevention of thrombotic conditions such as myocardial infarction or stroke.[4] In a review of UK prescribing practices, approximately 4% of patients were receiving a low-dose aspirin prescription.[5] However, when OTC aspirin use is included in estimates, exposure to low-dose aspirin has been estimated to be as high as 12% of the general population.[6]

Despite their beneficial effects and widespread use, NSAIDs are associated with significant toxicities and particularly those affecting the gastrointestinal (GI) tract. These adverse GI effects pose significant risks to patients and place a considerable economic burden on healthcare providers. For example, the management of NSAID-associated upper GI adverse effects has been estimated to add >45% to the cost of arthritis treatment.[7] In a retrospective cohort study involving >75 000 US patients aged ≥65 years it was calculated that the mean annual cost of medical care of GI disease in non-NSAID users was US$134 per patient, compared with US$191 for patients receiving NSAID treatment ($p < 0.001$).[8]

The relative risk (RR) has been estimated to be 2.5–5.5-fold greater for GI-related hospitalisation and 4-fold greater for death among patients receiving NSAIDs compared with patients who do not use NSAIDs.[9] Importantly, the upper GI adverse effects of NSAIDs can be successfully managed in many patients.[10]

This review discusses the upper GI adverse effects of NSAID therapy, associated risk factors and management options for preventing and/or treating these adverse effects.

1. Mechanism of Action of NSAIDs

The anti-inflammatory effects of NSAIDs, particularly aspirin, have been recognised for centuries. However, it was not until the early 1970s that the mechanism of action of these drugs was elucidated. Pioneering work by Vane[11] showed that NSAIDs inhibit the production of prostaglandins, which are involved in regulating many physiological processes, including inflammation, cytoprotection of the GI tract, platelet aggregation and renin release.[12] Specifically, NSAIDs act by inhibiting the cyclo-oxygenase (COX) activity of prostaglandin H synthase, which catalyses a step in the conversion of the unsaturated fatty acid arachidonic acid to prostaglandins (figure 1).[13] Two COX isozymes, encoded by separate genes, have been identified. These enzymes act as homodimers that are located at the intraluminal surface of the nuclear envelope and the endoplasmic reticulum. COX-1 is constitutively expressed in most tissues, but particularly in platelets, the GI tract and the kidneys. COX-2 expression is constitutive in the kidney and brain, but may be induced in other tissues by a variety of ligands (including cytokines and growth factors) and particularly at sites of inflammation.[14]

Aspirin covalently modifies COX-1, thus blocking access of substrates to the catalytic site of the enzyme.[12] Other NSAIDs act by competing with arachidonic acid for binding to the COX-1 and/or COX-2 active site. The chemical structure of a specific NSAID determines whether it binds to COX-1, COX-2 or both of these isozymes. The COX-1 : COX-2 inhibitory ratio of NSAIDs is important in determining their relative GI toxicity. This is because although both COX-1 and COX-2 appear to be necessary for prostaglandin-mediated

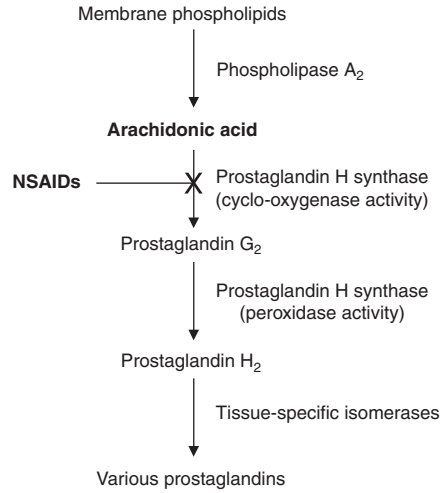

Fig. 1. Synthesis of prostaglandins. Arachidonic acid is produced from membrane phospholipids by the activity of phospholipase A_2. Arachidonic acid is then converted to prostaglandin H_2 via the cyclo-oxygenase (COX) and peroxidase activities of prostaglandin H synthase. Prostaglandin H_2 is further modified in tissues to yield a variety of prostaglandins. NSAIDs inhibit the COX activity of prostaglandin H synthase.

cytoprotection of the GI tract in animal models,[15,16] COX-1 is likely to be more important in this respect, since under normal physiological conditions COX-2 is expressed at only very low levels in the GI tract. The assumption that inducible COX-2 is responsible for the inflammatory effects of prostaglandins, whereas COX-1 is responsible for 'housekeeping' functions such as GI cytoprotection, led to the development of COX-2 selective NSAIDs, also known as 'coxibs'. It was assumed that coxibs would have the same anti-inflammatory properties as non-COX selective NSAIDs but with improved GI tolerability.

2. Gastrointestinal (GI) Adverse Effects of NSAIDs

GI adverse effects are particularly common among NSAID users and have been reported to account for 103 000 GI-related hospitalisations[1] and 16 500 deaths per year in the US alone.[17] These adverse effects often manifest as upper GI symptoms such as heartburn, nausea, vomiting, abdominal pain or dyspepsia,[18,19] which lead to discontinuation of NSAID therapy in 5–15% of patients.[18] There are also well documented links between NSAID use, GI mucosal injury and associated com-

plications. Approximately half of the patients receiving NSAIDs develop gastric erosions, whilst 10–30% of long-term NSAID users develop a peptic ulcer.[20,21] A study of 235 patients with life-threatening complications of peptic ulceration found that nearly 80% of all ulcer-related deaths occurred in NSAID users.[22] Importantly, there appears to be no correlation between the incidence of upper GI symptoms and the presence of endoscopic ulcers.[22-24] Larkai et al.[23] performed an endoscopic evaluation of the gastric mucosa in 65 patients and found that only 30% of patients with NSAID-associated ulcers had dyspeptic symptoms. Furthermore, Armstrong and Blower[22] found that in >58% of patients receiving NSAIDs who developed a peptic ulcer, the first sign of this was a life-threatening complication. Therefore, the presence of NSAID-associated mucosal abnormalities appears to be symptomatically silent in the majority of patients.

NSAIDs have also been shown to increase the risk of lower GI adverse events such as bleeding, perforation, obstruction, ulceration and symptomatic diverticular disease.[25-27] NSAIDs may also play a role in the relapse of inflammatory bowel disease.[28] However, this review focuses on the upper GI toxicities associated with NSAID therapy.

3. Pivotal Role of Gastric Acid in the Upper GI Adverse Effects of NSAIDs

Although NSAIDs may have topical effects on the gastric mucosa, the predominant adverse GI effects induced by NSAIDs are a result of their systemic ability to depress prostaglandin levels and consequently alter GI biology.

The gastric mucosa is protected against the acid in the gastric lumen by a mucus layer that contains bicarbonate, which neutralises acid at the epithelial surface.[29] Prostaglandins are important for maintaining the integrity of the mucus-bicarbonate layer, which means that inhibition of prostaglandin synthesis by NSAIDs is likely to lead to compromise of this protective barrier. If small mucosal erosions do occur, these are normally repaired by proliferation of surface epithelial cells, which is a process that is also partly regulated by prostaglandins. A mucoid cap, comprising mucus, fibrin and cell debris, forms over regions of superficial mucosal damage and provides a less acidic (pH 4–6) environment that allows healing to proceed.[30] In a rat model, intraperitoneally administered NSAIDs (indometacin or naproxen) led to a rapid dissipation of the mucoid cap covering sites of mucosal damage, with the subsequent appearance of haemorrhagic erosions.[31] NSAID-induced dissipation of the mucoid cap did not occur in the presence of prostaglandin E_2, suggesting that prostaglandins are important in maintaining the stability of the mucoid cap. Therefore, inhibition of prostaglandin synthesis by NSAID therapy is likely to disrupt the defences that protect the gastric mucosa against acid damage.

In addition, prostaglandin depletion leads to an increase in gastric acid synthesis and, therefore, a reduction in the pH of the gastric lumen.[32,33] Gastric pH was measured over a 24-hour period in ten patients with rheumatoid arthritis who received either indometacin 150 mg/day or ketoprofen 300 mg/day for 1 month.[33] There was a significant increase in the number of 24-hour pH measurements during which a pH <3 was observed following 1 month of NSAID therapy in these patients (11 440 pH readings vs 10 339 at baseline; $p < 0.001$). The NSAID-associated increase in gastric acidity appears to occur rapidly following the start of therapy. In a study of 11 healthy volunteers, indometacin 50mg, taken every 8 hours for ten doses, led to a significant increase in acid secretion from 4.9 mmol to 7.4 mmol/75 minutes ($p < 0.05$).[34]

Increased acidity of the gastric lumen appears to be associated with an increased risk of mucosal damage. Shiotani et al.[35] investigated NSAID-associated GI mucosal damage endoscopically in 11 healthy volunteers. All subjects had normal-appearing gastric mucosa (no visible erosions) following 3 days of placebo. In contrast, after receiving naproxen 1000 mg/day for 3 days, one subject had mild damage (haemorrhages only), two had severe damage (three or more areas of gastric erosion) and three had very severe damage (widespread erosions, development of ulcers or erosions >4mm). Importantly, there was a significant inverse relationship between fasting gastric pH and the severity of naproxen-induced damage (figure 2).[35] Similarly, indometacin-induced gastric mucosal damage in rats was inversely associated with luminal pH (figure 3).[36] In this study, mucosal damage was signifi-

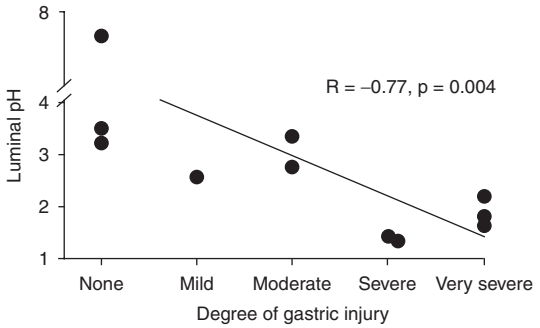

Fig. 2. The relationship between gastric luminal pH and the severity of gastric mucosal damage in healthy volunteers after receiving naproxen 1000mg for 3 days.[35]

cantly greater at a luminal pH of 2 or 4, compared with at a luminal pH of 5.5 or 7.0.

Therefore, NSAIDs have multiple effects on GI biology that may act in concert to potentiate the risk for GI mucosal damage. Firstly, the reduction in prostaglandin levels resulting from COX inhibition by NSAIDs leads to a compromise in the barrier that protects the gastric mucosa from acid damage. Secondly, prostaglandin depletion leads to increased gastric acidity, thus increasing the risk of mucosal damage. Increased gastric acidity may also contribute to the upper GI symptoms associated with NSAID therapy. The most convincing evidence that gastric acidity is a contributing factor to NSAID-associated mucosal damage and upper GI symptoms is found in the results of clinical studies that show acid-suppression therapies to be effective in the prevention and treatment of these outcomes. The findings of these studies are discussed later in this review.

4. Risk Factors for NSAID-Associated Upper GI Adverse Events

A number of risk factors have been identified that are associated with the risk of developing upper GI adverse events during NSAID therapy. These are discussed briefly in this section.

4.1 Age

Advanced age is a significant risk factor for developing upper GI adverse events while receiving NSAID therapy.[37-41] This is of particular importance, since NSAIDs are more commonly prescribed to elderly patients because of the higher incidence of arthritis and musculoskeletal syndromes in this population. In a meta-analysis by Gabriel et al.,[40] the summary odds ratio for GI complications associated with non-aspirin NSAID therapy was 5.52 among patients aged ≥60 years, compared with 1.65 for patients aged <60 years.

4.2 Choice of NSAID

It is apparent from many studies that individual NSAIDs are associated with different incidences of upper GI adverse events. A meta-analysis of 17 studies published between 1990 and 2001 demonstrated that aspirin carries an upper GI mucosal injury risk, even when taken at low thromboprophylactic doses, or in buffered or enteric formulations.[42] The overall RR of aspirin-associated upper GI complications was 2.2 for cohort and nested case-control studies, and 3.1 for non-nested, case-control studies. The study also found that although analgesic/anti-inflammatory doses of >300 mg/day aspirin carried a greater risk than cardiovascular doses of <300 mg/day, users of low-dose aspirin faced a 2-fold increased risk of upper GI complications with no clear dose-response effect.

Henry et al.[43] performed a meta-analysis of 12 studies to compare the RR of serious upper GI complications in patients receiving 14 different non-selective NSAIDs (of which 11 were compared with ibuprofen). Ibuprofen was associated with the lowest risk, with other drugs producing a 1.6–9.2-fold increase in risk relative to ibuprofen (table I). In a further meta-analysis, the RR of developing GI

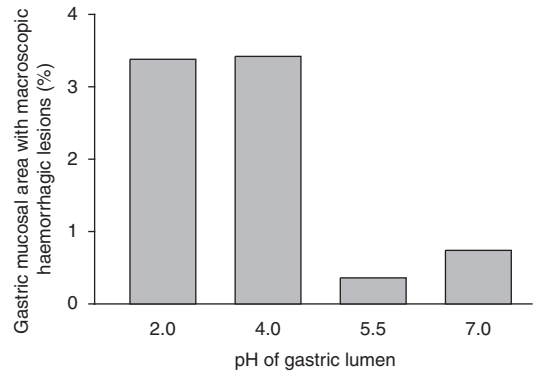

Fig. 3. The effect of gastric luminal pH on indometacin-induced mucosal damage in rats.[36]

Table I. Results of a meta-analysis to compare the risk of developing serious upper gastrointestinal complications while receiving various non-selective NSAIDs. Ibuprofen was associated with the lowest risk and so was used as a comparator in this analysis (reproduced from Henry et al.,[43] with permission from the BMJ Publishing Group)

Drug	No. of studies	Pooled relative risk (95% CI)	p-Value (heterogeneity)
Ibuprofen	NA	1.0	NA
Fenoprofen	2	1.6 (1.0, 2.5)	0.310
Aspirin (acetylsalicylic acid)	6	1.6 (1.3, 2.0)	0.685
Diclofenac	8	1.8 (1.4, 2.3)	0.778
Sulindac	5	2.1 (1.6, 2.7)	0.685
Diflunisal	2	2.2 (1.2, 4.1)	0.351
Naproxen	10	2.2 (1.7, 2.9)	0.131
Indometacin	11	2.4 (1.9, 3.1)	0.488
Tolmetin	2	3.0 (1.8, 4.9)	0.298
Piroxicam	10	3.8 (2.7, 5.2)	0.087
Ketoprofen	7	4.2 (2.7, 6.4)	0.258
Azapropazone	2	9.2 (4.0, 21.0)	0.832

NA = not applicable.

complications was significantly higher for patients receiving the indolic derivative indometacin (RR = 2.25) than for those receiving naproxen (RR = 1.83), diclofenac (RR = 1.73), piroxicam (RR = 1.66), tenoxicam (RR = 1.43), meloxicam (RR = 1.24) or ibuprofen (RR = 1.19) [all comparisons were relative to non-users of NSAIDs].[44]

The theory behind the development of coxibs, was that by sparing COX-1, these drugs would have equivalent efficacy but a better GI tolerability profile than non-selective NSAIDs. This hypothesis has been partially confirmed for the coxibs rofecoxib and celecoxib in clinical studies that assessed gastroduodenal damage (perforations/ulcers/bleeding) in patients with osteoarthritis or rheumatoid arthritis.[45-52] In patients with rheumatoid arthritis, treatment with rofecoxib was associated with significantly fewer clinically important upper GI events than treatment with naproxen, a non-selective NSAID.[47] Similarly, in a pooled analysis of 14 randomised, double-blind, controlled trials in patients with osteoarthritis or rheumatoid arthritis, and a separate open-label study in patients with arthritis, the incidence of upper GI ulcer complications associated with celecoxib was 8-fold lower than with non-selective NSAIDs.[48] Other studies have shown that treatment with coxibs is also associated with significantly fewer discontinuations as a result of overall GI adverse events than non-selective NSAIDs.[53,54]

Nevertheless, while the overall incidence of peptic ulcers and ulcer complications are reduced with coxibs relative to non-selective NSAIDs, the risk of gastroduodenal injury is not eliminated.[47,48] Additionally, although the use of coxibs is associated with less severe dyspeptic-type GI symptoms than non-selective agents and is better tolerated in this regard, it does not eliminate the risk of adverse upper GI symptoms.[55,56] In an analysis of eight randomised, double-blind studies, rofecoxib was associated with an increased incidence of upper GI symptoms compared with placebo.[56]

More recently developed ('second-generation') coxibs (etoricoxib, valdecoxib, parecoxib and lumiracoxib) appear to have enhanced biochemical COX-2 selectivity compared with first-generation coxibs (rofecoxib and celecoxib).[57] The 'second-generation' coxibs have been demonstrated to produce a lower incidence of ulcer complications[58-62] or discontinuations as a result of dyspepsia[63] than non-selective NSAIDs. The enhanced COX-2 selectivity of these agents may lead to an improved GI safety profile over rofecoxib and celecoxib, although few prospective comparative studies have been performed to date. In one study, the risk of developing gastroduodenal ulcers with lumiracoxib was significantly lower than that for ibuprofen, but similar to that for celecoxib.[64]

Therefore, coxibs minimise, but importantly do not eliminate, upper GI complications associated with non-selective NSAIDs. However, concerns

have been expressed regarding the cardiovascular safety of coxibs.[65,66] COX-1 and COX-2 play an important role in the maintenance of cardiovascular haemostasis. COX-1-derived thromboxane A_2 (TxA_2) promotes platelet aggregation, vasoconstriction and smooth muscle cell proliferation.[67] In contrast, COX-2-derived prostacyclin inhibits platelet aggregation and smooth muscle cell proliferation, and promotes vasodilation.[68] Therefore, by inhibiting prostacyclin synthesis while having no effect on TxA_2synthesis, coxibs may shift the balance of cardiovascular haemostasis towards a prothrombotic or proatherogenic state. A review by Mukherjee et al.[69] found that annual myocardial infarction rates in patients taking coxibs were significantly higher than in those taking placebo. Furthermore, Bombardier et al.[47] investigated adverse events in 8076 patients who received rofecoxib or naproxen. The incidence of myocardial infarction was found to be 4-fold higher in the coxibs group.[47]

It was initially unclear whether the difference in cardiovascular events was due to an increased risk with rofecoxib or a cardioprotective activity of naproxen. However, recent data obtained from studies of patients with colorectal adenoma showed that both rofecoxib and celecoxib are associated with increased risk of cardiovascular events compared with placebo.[70,71] Furthermore, parecoxib and valdecoxib increased the risk of cardiovascular events following use in patients who had undergone coronary artery bypass graft surgery.[72]

Unfavourable cardiovascular risk data have led to an urgent re-evaluation of the use of coxibs in clinical practice, which may result in many patients currently receiving these agents being switched to non-selective NSAID therapy. Further studies are required to determine the relative cardiovascular safety of other coxibs to determine whether the increased risks are found for all drugs in the class. In the meantime, the US FDA requests that manufacturers of all marketed prescription NSAIDs revise product labelling to include a boxed warning highlighting the potential for increased risk of cardiovascular events.[73] The FDA is also specifically encouraging physicians to limit use of coxibs to the lowest dose for the shortest duration possible.[73] Rofecoxib has been removed from the US market and sales of valdecoxib have been suspended.

A further class of COX-inhibiting drugs is in development. This class, which includes the agent licofelone, inhibits COX-1 and COX-2, in addition to 5-lipoxygenase (5-LOX). The 5-LOX pathway acts on arachidonic acid to produce proinflammatory leukotrienes. Therefore, dual inhibition of both COX and 5-LOX simultaneously blocks two important inflammatory pathways. Licofelone 200mg or 400mg twice daily was assessed against placebo and naproxen 500mg twice daily in a 4-week study in 121 healthy volunteers.[74] Endoscopic data from this trial showed that subjects given licofelone or placebo did not develop any ulcers, whereas ulcers developed in 20% of subjects who were given naproxen.[74] Two separate studies in patients with osteoarthritis confirmed this favourable tolerability profile.[75] The efficacy of licofelone in the treatment of osteoarthritis was shown to be equivalent to naproxen in a long-term study conducted over 52 weeks.[75] Licofelone is currently in phase III trials, but the data available indicate that with its proven efficacy and favourable GI safety profile it could offer significant advantages over current anti-inflammatory therapies. Other drugs in the same class are also currently undergoing early phase clinical trials.

4.3 Dose of NSAID

In the meta-analysis by Henry et al.,[43] a positive correlation was found between the dose of ibuprofen, naproxen and indometacin, and the RR of GI complications. Although, overall, ibuprofen was found to have the lowest risk of GI complications among the 14 non-selective NSAIDs considered in this analysis, no advantage was observed with dosages of ibuprofen >1600 mg/day.

4.4 Duration of NSAID Therapy

The risk of developing GI adverse events while receiving NSAIDs appears to increase with the duration of therapy.[38] In an endoscopic study of patients with rheumatoid arthritis or osteoarthritis who had been receiving NSAIDs for between <1 and ≥15 years, a significant correlation was found between the prevalence of gastroduodenal ulcers and the duration of NSAID use ($p = 0.019$).[37] Gastroduodenal ulcers were found in 13.8% of patients

who had been receiving NSAIDs for <1 year, compared with 25.9% of patients who had received NSAIDs for ≥1 year.

4.5 Previous History of Peptic Ulcer Disease or GI Bleeding

A previous history of peptic ulcer disease or GI bleeding is a significant risk factor for developing GI adverse events while receiving NSAIDs.[40,76] In a registry-based cohort study, Hallas et al.[76] found a 5-fold higher risk of upper GI bleeding in patients taking NSAIDs who had a history of peptic ulcer, compared with patients who had no history of peptic ulcer.

4.6 Concurrent Corticosteroid or Anticoagulant Use

Concurrent use of either corticosteroids or anticoagulants is associated with a significant increase in the risk of GI symptoms during NSAID therapy.[40,77,78] Piper et al.[77] evaluated 1415 patients hospitalised with gastric ulcer, duodenal ulcer or GI haemorrhage and found that patients who were concomitant users of corticosteroids and NSAIDs were 15 times more likely to develop peptic ulcer disease. This increased risk was not observed in patients receiving corticosteroids alone. In a retrospective cohort study, the RR of haemorrhagic peptic ulcer disease was 12.7 in patients receiving concurrent NSAIDs and anticoagulants, compared with those receiving neither of these drugs.[78]

4.7 Infection with *Helicobacter pylori*

The relationship between *Helicobacter pylori* infection and the use of NSAIDs in the pathogenesis of peptic ulcer disease is controversial. A recent meta-analysis of 463 trials has shown that, compared with *H. pylori*-negative, non-NSAID users, *H. pylori*-positive NSAID users were >60 times more likely to develop peptic ulceration.[79] The authors also found that *H. pylori* and NSAID use significantly increased the risk of ulcer bleeding by 1.79-fold and 4.85-fold, respectively, and when the two factors were combined the RR increased to 6.13. The results of a study investigating the influence of *H. pylori* colonisation on gastric mucosal eicosanoid synthesis in patients taking NSAIDs have indicated that prostaglandin-independent mechanisms are likely to account for enhanced susceptibility to ulceration in *H. pylori*-positive patients.[80] In fact, *H. pylori* seemed to stimulate synthesis of prostaglandin E_2 by promoting mucosal inflammatory cell infiltration.

4.8 Other Factors

Other factors that have been suggested to be associated with a higher likelihood of developing GI adverse events while receiving NSAIDs include underlying rheumatic disease, cardiovascular disease, smoking and alcohol consumption.[81]

5. Options for the Management of NSAID-Associated Upper GI Adverse Events

Although the most obvious method of controlling NSAID-associated GI toxicity is discontinuation of NSAID therapy, this is rarely possible or tolerated in patients with chronic diseases such as osteoarthritis or rheumatoid arthritis because of the chronically painful nature of the underlying disease. Although NSAID-associated upper GI toxicities, and the consequent reduction in quality of life, cause many patients to discontinue NSAID therapy, this may lead to deterioration in the arthritic condition and increased pain. Therefore, in at-risk patients, therapeutic options are required that allow continued NSAID therapy by preventing or treating NSAID-related upper GI toxicity. Three classes of drug have shown efficacy in this treatment setting: prostaglandin analogues, histamine H_2 receptor antagonists and proton pump inhibitors (PPIs).

5.1 Prostaglandin Analogues

The upper GI toxicity of NSAIDs is related to their inhibition of prostaglandin synthesis. Therefore, it would be expected that coadministration of prostaglandins or prostaglandin analogues would reduce the upper GI adverse effects of NSAIDs.

5.1.1 Prevention of Ulcers

Misoprostol is an analogue of prostaglandin E_1, which reduces the incidence of NSAID-associated gastric and duodenal ulcers.[82-84] In the MUCOSA (Misoprostol Ulcer Complications Outcome Safety Assessment) study, 8843 patients with rheumatoid

arthritis who were receiving NSAID therapy were randomised to receive misoprostol 200μg four times daily or placebo for 6 months.[82] In this study, misoprostol produced a 40% reduction in ulcer complications compared with placebo (odds ratio 0.598; 95% CI 0.364, 0.982; p = 0.049). However, misoprostol use is associated with adverse effects, particularly diarrhoea and dyspepsia, that limit patient acceptance of the drug. In the MUCOSA study, 20% of patients receiving misoprostol withdrew within the first month of treatment, of which 10% of total withdrawals were due to diarrhoea (compared with 4% of patients receiving placebo, p < 0.001) and 5% were due to dyspepsia (compared with 4% receiving placebo, p > 0.20).[82]

5.1.2 Conclusions

Misoprostol is effective in the prevention of NSAID-induced gastroduodenal ulcers and ulcer complications, but is poorly tolerated.

5.2 Histamine H_2 Receptor Antagonists

Histamine, acting via the H_2 receptor, is an important effector in gastric acid secretion. The key role that gastric acid plays in NSAID-induced ulcer complications provides a rationale for using antisecretory therapies in treating or preventing these adverse effects. Ranitidine and famotidine are H_2 receptor antagonists that have been studied as potential cotherapy for patients receiving NSAIDs.

5.2.1 Prevention of Ulcers

In two placebo-controlled studies, ranitidine 150mg twice daily provided significant protection against the development of NSAID-associated duodenal ulcers but not gastric ulcers.[85,86] NSAID-associated gastric ulcers occur more frequently than duodenal ulcers[37,87] and the relative lack of efficacy of standard ranitidine doses in preventing gastric ulcers may be a result of poor acid suppression. At a standard dosage of ranitidine, the median pH in the stomach over 24 hours is rarely >3.[88] Therefore, higher doses of H_2 receptor antagonists have been studied in this setting. In a 6-month study, famotidine 40mg twice daily significantly reduced the cumulative incidence of gastric and duodenal ulcers, compared with placebo.[89]

5.2.2 Healing of Ulcers

The effect of ranitidine on the healing of NSAID-associated ulcers was investigated among 190 patients with confirmed peptic ulcers who were randomised to continue or cease NSAID therapy; all patients received ranitidine.[90] After 8 weeks of treatment, gastric ulcers had healed in 95% of patients who had stopped NSAID therapy, compared with 63% in the patients who continued NSAID therapy (p = 0.001). For duodenal ulcers, the healing rates were 100% and 84% in patients who had ceased or continued NSAIDs, respectively (p = 0.006). Famotidine 40mg twice daily has also been shown to be effective for the healing and maintenance of NSAID-associated gastroduodenal ulcers.[91] After 12 weeks of treatment, gastroduodenal healing rates associated with famotidine were 100% and 89% for 16 patients who had ceased NSAIDs and 88 patients who continued NSAIDs, respectively. The rate of relapse over the next 6 months for NSAID users with healed ulcers randomised to famotidine was 26% compared with 53.5% for those randomised to placebo (p < 0.05).

5.2.3 Treatment of Upper GI Symptoms

H_2 receptor antagonists have also shown activity against upper GI symptoms in NSAID users. In an open-label study, patients with NSAID-related dyspeptic symptoms and/or peptic ulcer disease received ranitidine 150mg twice daily or placebo for 4 weeks, with continued NSAID therapy.[92] Among patients who had dyspeptic symptoms but not peptic ulcer disease, these symptoms were resolved in 26% of patients receiving ranitidine, compared with 6% of patients receiving placebo (p < 0.02).

5.2.4 Conclusions

At standard doses, H_2 receptor antagonists are effective at preventing duodenal ulcers but not the more commonly occurring gastric ulcers, possibly because they do not adequately suppress acid secretion. For healing of gastroduodenal ulcers, these drugs appear to be more effective in patients who have ceased NSAID therapy. It is likely that in the long term, efficacy of cotherapies in the prevention and treatment of NSAID-associated upper GI toxicities will depend on sustained control of intragastric pH. However, it has been demonstrated that the

effect of ranitidine on acid suppression is reduced following long-term therapy.[93]

5.3 Proton Pump Inhibitors

PPIs provide more effective gastric acid control than H_2 receptor antagonists.[88] PPIs would, therefore, be expected to be effective cotherapies for preventing NSAID-associated upper GI toxicity.

5.3.1 Prevention of Ulcers

In a 6-month study, 169 patients were randomised to receive either omeprazole 20mg or placebo, in addition to continued NSAID therapy.[94] The probability of remaining free of gastroduodenal ulcers, multiple gastroduodenal erosions and moderate or severe dyspeptic symptoms was significantly higher in the omeprazole group (0.78) than the placebo group (0.53; $p = 0.004$). At the end of the study, 14 patients (16.5%) in the placebo group had gastroduodenal ulcers, compared with 3 patients (3.6%) in the omeprazole group. Other studies have shown that omeprazole 20mg is superior to both misoprostol[95] and ranitidine[96] in the prevention of gastroduodenal ulceration. A further study assessed the efficacy of lansoprazole 15mg and 30mg and misoprostol 200μg four times daily versus placebo in the prevention of NSAID-associated ulcers. After 4, 8 and 12 weeks of treatment, the percentage of ulcer-free patients was significantly higher in the misoprostol and lansoprazole groups than in the placebo group.[97] There was no significant difference between the active treatments in this study.

Two identically-designed, placebo-controlled studies comprising a total of 1429 patients were carried out to determine the efficacy of esomeprazole 20mg or 40mg in the prevention of gastroduodenal ulcers in patients on long-term NSAID therapy.[98] Patients recruited to these studies were required to be at increased risk of developing NSAID-associated ulcers, either because of advanced age (≥60 years) or because of a history of ulcers in the previous 5 years. Both doses of esomeprazole were significantly more effective than placebo at preventing gastroduodenal ulcers; this was true for the overall population and also for subsets of this population that were taking either non-selective NSAIDs or coxibs. For patients taking any kind of NSAID, the life table estimated cumulative proportion of patients without ulcers at 6 months was 94.8% for esomeprazole 20mg, 95.4% for esomeprazole 40mg and 83.0% for placebo ($p < 0.0001$ for both esomeprazole doses vs placebo). In a retrospective analysis, the number needed to treat to prevent a gastric or duodenal ulcer occurring within 6 months in one patient was calculated as nine and eight for esomeprazole 20mg and 40mg, respectively.[99]

5.3.2 Healing of Ulcers

Two large, randomised studies involving 1476 patients with NSAID-associated ulceration showed that the PPI omeprazole can achieve superior healing when compared with prostaglandin analogues and H_2 receptor antagonists.[95,96] The larger of these studies[95] randomly assigned 935 patients with an ulcer and on continuous NSAID therapy to either omeprazole 20mg or 40mg once daily or misoprostol 200μg four times daily for 4 weeks, or in the absence of healing, 8 weeks. Successfully healed patients were then randomly reassigned to receive 6 months' maintenance therapy with one of the two acid suppressive agents. The authors found that the rate of ulcer healing was significantly higher in the omeprazole group than in the misoprostol group. In addition, a greater proportion of patients on omeprazole maintenance therapy remained in remission than in the misoprostol group. Identical inclusion criteria were used for the second study,[96] but in this study patients received either omeprazole 20mg or 40mg once daily or ranitidine 150mg twice daily. The authors found that the rate of healing for all lesion types was higher with omeprazole than with ranitidine. In addition, following maintenance therapy, the estimated proportion of omeprazole patients in remission was 72%, compared with 59% for ranitidine.

Similar studies have also been conducted that compared lansoprazole with ranitidine and misoprostol for the healing of ulcers. A large multicentre trial assessed lansoprazole 15mg and 30mg once daily and ranitidine 150mg twice daily for the healing of ulcers in patients continuing to take NSAIDs.[100] After 8 weeks the percentage of healed patients was significantly higher in both lansoprazole groups compared with ranitidine.

5.3.3 Treatment of Upper GI Symptoms

Two identically-designed studies have demonstrated that cotherapy with a PPI provides effective symptom relief and improved health-related quality of life in ulcer-free patients with NSAID-associated upper GI symptoms.[101,102] These studies are the first with the primary objective of studying upper GI symptoms in users of NSAIDs, including coxibs, who are without a current or previously diagnosed ulcer and without a history of gastroesophageal reflux disease (GERD). Patients who were ulcer free with a chronic condition requiring continuous daily NSAIDs and consequently suffering from moderate-to-severe upper GI symptoms of pain, burning or discomfort in the upper abdomen were randomised to esomeprazole 40mg, esomeprazole 20mg or placebo once daily for 4 weeks. The authors found that both doses of esomeprazole were significantly more effective than placebo in relieving upper GI symptoms, which was the primary endpoint of the studies.

Additionally, in the study by Hawkey et al.,[101] health-related quality of life and symptom assessments were made using the Quality of Life in Reflux and Dyspepsia (QOLRAD) instrument, the Gastrointestinal Symptom Rating Scale (GSRS) and the Short Form-36 (SF-36). The authors found that the study population scored significantly lower on all dimensions of the SF-36 than reference populations of healthy individuals or patients with GERD. Esomeprazole significantly improved health-related quality of life and upper GI symptoms on QOLRAD and GSRS dimensions, respectively, and both doses of esomeprazole produced greater improvements compared with placebo in the QOLRAD dimensions 'vitality' and 'physical/social functioning'.

5.3.4 Conclusions

PPIs are effective in the prevention and healing of gastroduodenal ulcers, and also as treatments for upper GI symptoms in patients receiving NSAID therapy.

The weight of evidence supporting PPI use in NSAID-associated ulceration has prompted contributors to the Sardinia Expert Statement to recommend that "on the basis of effectiveness and tolerance, a PPI is the treatment of choice for healing NSAID-associated ulcers, particularly gastric ulcers".[103] The statement also recommends that "prophylactic use should be on a basis of risk assessment, that all patients who have had previous proven peptic ulceration should have prophylactic co-therapy while taking NSAIDs, and that all patients with two risk factors other than past history should have prophylactic co-therapy if they use non-selective NSAIDs".[103] The statement concludes that "it is the level of acid suppression achieved, rather than a class-specific action that underlies the effectiveness of PPIs, and for patients with NSAID-associated dyspepsia, ulcer complications should be treated with a PPI because this provides ulcer protection as well as symptom relief".[103]

6. Conclusion

The usefulness of NSAID therapy is compromised by adverse GI and cardiovascular effects. Given the association between gastric acid and NSAID-associated upper GI adverse effects, effective acid control with concomitant therapy may be necessary. PPIs provide effective acid suppression and can, therefore, substantially reduce morbidity and mortality in NSAID users. Physicians should be aware of the risk factors for upper GI adverse effects in patients taking NSAIDs, and the efficacy and tolerability profiles of treatments. This will allow preventative acid suppressive therapy to be initiated in appropriate patients.

Acknowledgements

Both authors are employees of AstraZeneca. AstraZeneca manufactures the proton pump inhibitors omeprazole and esomeprazole. We thank Cathy Saunders from Adis Communications, who provided medical writing support on behalf of AstraZeneca.

References

1. Singh G, Triadafilopoulos G. Epidemiology of NSAID-induced gastrointestinal complications. J Rheumatol 1999; 26 Suppl. 26: 18-24
2. Cullen DJ, Seager JM, Holmes S, et al. Pharmacoepidemiology of non-steroidal anti-inflammatory drug use in Nottingham general practices. Aliment Pharmacol Ther 2000; 14: 177-85
3. Brooks P. Use and benefits of nonsteroidal anti-inflammatory drugs. Am J Med 1998; 104: 9S-13S
4. Bedson J, Whitehurst T, Lewis M, et al. Factors affecting over-the-counter use of aspirin in the secondary prophylaxis of cardiovascular disease. Br J Gen Pract 2001; 51: 1001-3
5. Jones R. Nonsteroidal anti-inflammatory drug prescribing: past, present, and future. Am J Med 2001; 110 (1A): 4S-7S
6. Czernichow P, Merle V. Epidemiology of digestive complications associated with low-dose aspirin [in French]. Gastroenterol Clin Biol 2004; 28: 37-44

7. Bloom BS. Cost of treating arthritis and NSAID-related gastrointestinal side-effects. Aliment Pharmacol Ther 1988; 2 Suppl. 1: 131-8
8. Smalley WE, Griffin MR, Fought RL, et al. Excess costs from gastrointestinal disease associated with NSAIDs. J Gen Intern Med 1996; 11: 461-9
9. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998; 105 (1B): 31S-8S
10. Lanas A. Gastrointestinal injury from NSAID therapy: how to reduce the risk of complications. Postgrad Med 2005; 117 (6): 23-8, 31
11. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature 1971; 231: 232-5
12. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev 2004; 56: 387-437
13. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995; 44: 1-10
14. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu Rev Biochem 2000; 69: 145-82
15. Wallace JL, McKnight W, Reuter BK, et al. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. Gastroenterology 2000; 119: 706-14
16. Takeeda M, Hayashi Y, Yamato M, et al. Roles of endogenous prostaglandins and cyclooxygenase isozymes in mucosal defense of inflamed rat stomach. J Physiol Pharmacol 2004; 55: 193-205
17. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999; 340: 1888-99
18. Singh G, Rosen Ramey D. NSAID-induced gastrointestinal complications: the ARAMIS perspective: 1997. Arthritis, Rheumatism, and Aging Medical Information System. J Rheumatol Suppl 1998; 51: 8-16
19. Straus WL, Ofman JJ, MacLean C, et al. Do NSAIDs cause dyspepsia? A meta-analysis evaluating alternative dyspepsia definitions. Am J Gastroenterol 2002; 97: 1951-8
20. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am 1996; 6: 489-504
21. Brown GJ, Yeomans ND. Prevention of the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: the role of proton pump inhibitors. Drug Saf 1999; 21: 503-12
22. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28: 527-32
23. Larkai EN, Smith JL, Lidsky MD, et al. Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic nonsteroidal anti-inflammatory drug use. Am J Gastroenterol 1987; 82: 1153-8
24. Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. Arch Intern Med 1996; 156: 1530-6
25. Brooks PM, Day RO. Nonsteroidal anti-inflammatory drugs: differences and similarities. N Engl J Med 1991; 324: 1716-25
26. Hardin JG, Longenecker GL. Handbook of drug therapy in rheumatic disease. Pharmacology and clinical aspects. Boston (MA): Little Brown Co., 1992
27. Bjarnason I, Hayllar J, Macpherson AJ, et al. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 1993; 104: 1832-47
28. Aalykke C, Hallas J, Lauritsen JM, et al. Role of NSAID use in inflammatory bowel disease: a 5-year follow-up study [abstract]. Gastroenterology 2000; 118 Suppl. 2: A-869
29. Allen A, Flemstrom G, Garner A, et al. Gastroduodenal mucosal protection. Physiol Rev 1993; 73: 823-57
30. Wallace JL, Whittle BJR. The role of extracellular mucus as a protective cap over gastric mucosal damage. Scand J Gastroenterol 1986; 21 Suppl. 125: 79-84
31. Wallace JL, McKnight GW. The mucoid cap over superficial gastric damage in the rat: a high pH microenvironment dissipated by nonsteroidal anti-inflammatory drugs and endothelin. Gastroenterology 1990; 99: 295-304
32. Levine RA, Schwartzel EH. Effect of indomethacin on basal and histamine-stimulated human gastric acid secretion. Gut 1984; 25: 718-22
33. Savarino V, Mela GS, Zentilin P, et al. Effect of one-month treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) on gastric pH of rheumatoid arthritis patients. Dig Dis Sci 1998; 43: 459-63
34. Feldman M, Colturi TJ. Effect of indomethacin on gastric acid and bicarbonate secretion in humans. Gastroenterology 1984; 87: 1339-43
35. Shiotani A, Yamaoka Y, El-Zimaity HMT, et al. NSAID gastric ulceration: predictive value of gastric pH, mucosal density of polymorphonuclear leukocytes, or levels of IL-8 or nitrite. Dig Dis Sci 2002; 47: 38-43
36. Elliott SL, Ferris RJ, Giraud AS, et al. Indomethacin damage to rat gastric mucosa is markedly dependent on luminal pH. Clin Exp Pharmacol Physiol 1996; 23: 432-4
37. Cheatum DE, Arvanitakis C, Gumpel M, et al. An endoscopic study of gastroduodenal lesions induced by nonsteroidal antiinflammatory drugs. Clin Ther 1999; 21: 992-1003
38. Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs: an overview of the epidemiologic evidence. Drugs 1993; 46 Suppl. 1: 243-8
39. Fries JF, Williams CA, Bloch DA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991; 91: 213-22
40. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991; 115: 787-96
41. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. Gastroenterology 2002; 123: 1006-12
42. Garcia Rodriguez LA, Harnandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001; 52: 563-71
43. Henry D, Lim LL-Y, Garcia Rodriquez LA, et al. Variability in risk of gastrointestinal complications with individual nonsteroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996; 312: 1563-6
44. Richy F, Bruyere O, Ethgen O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. Ann Rheum Dis 2004; 63: 759-66
45. Laine L, Harper S, Simon T, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Gastroenterology 1999; 117: 776-83
46. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999; 282: 1921-8
47. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343: 1520-8
48. Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. Am J Gastroenterol 2000; 95: 1681-90

49. Goldstein JL, Correa P, Zhao WW, et al. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. Am J Gastroenterol 2001; 96: 1019-27
50. Hawkey C, Laine L, Simon T, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis. Arthritis Rheum 2000; 43: 370-7
51. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284: 1247-55
52. Hawkey CJ, Laine L, Simon T, et al. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003; 52: 820-6
53. Lisse JR, Perlman M, Johansson G, et al. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. Ann Intern Med 2003; 139: 539-46
54. Watson DJ, Harper SE, Zhao PL, et al. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 2000; 160: 2298-3003
55. Goldstein JL, Eisen GM, Burke TA, et al. Dyspepsia tolerability from the patients' perspective: a comparison of celecoxib with diclofenac. Aliment Pharmacol Ther 2002; 16: 809-27
56. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999; 282: 1929-33
57. Tacconelli S, Capone ML, Patrignani P. Clinical pharmacology of novel COX-2 inhibitors. Curr Pharm Des 2004; 10: 589-601
58. Hunt RH, Harper S, Watson DJ, et al. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. Am J Gastroenterol 2003; 98: 1725-33
59. Goldstein JL, Eisen GM, Agrawal N, et al. Reduced incidence of upper gastrointestinal ulcer complications with the COX-2 selective inhibitor, valdecoxib. Aliment Pharmacol Ther 2004; 20: 527-38
60. Harris SI, Stoltz RR, LeComte D, et al. Parecoxib sodium demonstrates gastrointestinal safety comparable to placebo in healthy subjects. J Clin Gastroenterol 2004; 38: 575-80
61. Kivitz AJ, Nayiager S, Schimansky T, et al. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with rheumatoid arthritis. Aliment Pharmacol Ther 2004; 19: 1189-98
62. Schnitzer TJ, Burmester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutics Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised, controlled trial. Lancet 2004; 364: 665-74
63. Watson DJ, Bolognese JA, Yu C, et al. Use of gastroprotective agents and discontinuations due to dyspepsia with the selective cyclooxygenase-2 inhibitor etoricoxib compared with nonselective NSAIDs. Curr Res Med Opin 2004; 20: 1899-908
64. Hawkey CC, Svoboda P, Fiederowicz-Fabrycy IF, et al. Gastroduodenal safety and tolerability of lumiracoxib compared with ibuprofen and celecoxib in patients with osteoarthritis. J Rheumatol 2004; 31: 1804-10
65. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004; 351: 1709-11
66. Furberg CD, Psaty BM, Fitzgerald GA. Parecoxib, valdecoxib, and cardiovascular risk. Circulation 2005; 111: 249
67. Patrono C, Coller B, Dalen JE, et al. Platelet-active drugs: the relationship among dose, effectiveness, and side effects. Chest 2001; 119: 39S-63S
68. Fitzgerald DJ, Roy L, Catella F, et al. Platelet activation in unstable coronary disease. N Engl J Med 1986; 315: 983-9
69. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286: 954-9
70. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352: 1092-102
71. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352: 1071-80
72. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005; 352: 1081-91
73. U.S. Food and Drug Administration [online]. Available from URL: http://www.fda.gov/cder/drug/infopage/cox2/COX2qa.htm [Accessed 2005 Apr 14]
74. Alvaro-Gracia JM. Licofelone: clinical update on a novel LOX/COX inhibitor for the treatment of osteoarthritis. Rheumatology 2004; 43 Suppl. 1: I21-5
75. Bias P, Buchner A, Klesser B, et al. The gastrointestinal tolerability of the LOX/COX inhibitor, licofelone, is similar to placebo and superior to naproxen therapy in healthy volunteers: results from a randomized, controlled trial. Am J Gastroenterol 2004; 99: 611-8
76. Hallas J, Lauritsen J, Villadsen HD, et al. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. Scand J Gastroenterol 1995; 30: 438-44
77. Piper JM, Ray WA, Daugherty JR, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114: 735-40
78. Shorr RI, Ray WA, Daugherty JR, et al. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993; 153: 1665-70
79. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. Lancet 2002; 359: 14-22
80. Hudson N, Balsitis M, Filipowicz F, et al. Effect of *Helicobacter pylori* colonisation on gastric mucosal eicosanoid synthesis in patients taking non-steroidal anti-inflammatory drugs. Gut 1993; 34: 748-51
81. Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract: indigestion and non-steroidal anti-inflammatory drugs. BMJ 2001; 323: 1236-9
82. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995; 123: 241-9
83. Elliott SL, Yeomans ND, Buchanan RRC, et al. Efficacy of 12 months' misoprostol as prophylaxis against NSAID-induced gastric ulcers: a placebo controlled trial. Scand J Gastroenterol 1994; 23: 171-6
84. Raskin JB, White RH, Jackson JE, et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Intern Med 1995; 123: 344-50
85. Robinson MG, Griffin JW, Bowers J, et al. Effect of ranitidine on gastroduodenal damage induced by nonsteroidal antiinflammatory drugs. Dig Dis Sci 1989; 34: 424-8
86. Ehsanullah RS, Page MC, Tildesley G, et al. Prevention of gastroduodenal damage induced by non-steroidal anti-inflam-

matory drugs: controlled trial of ranitidine. BMJ 1988; 297: 1017-21

87. Battler NY, Abuksis G, Gal E, et al. Endoscopy in asymptomatic minidose aspirin consumers. Dig Dis Sci 2005; 50: 78-80
88. Walt RP, Gomes MD, Wood EC, et al. Effect of daily oral omeprazole on 24 hour intragastric acidity. BMJ 1983; 287: 12-4
89. Taha AS, Hudson N, Hawkey CJ, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 1996; 334: 1435-9
90. Lancaster-Smith MJ, Jaderberg ME, Jackson DA. Ranitidine in the treatment of non-steroidal anti-inflammatory drug associated gastric and duodenal ulcers. Gut 1991; 32: 252-5
91. Hudson N, Taha AS, Russell RI, et al. Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology 1997; 112: 1817-22
92. Van Groenendael JHLM, Markusses HM, Dijkmans BAC, et al. The effect of ranitidine in NSAID-related dyspeptic symptoms with and without peptic ulcer disease of patients with rheumatoid arthritis and osteoarthritis. Clin Rheumatol 1996; 15: 450-6
93. Prichard PJ, Jones DB, Yeomans ND, et al. The effectiveness of ranitidine in reducing gastric-acid secretion decreases with continued therapy. Br J Clin Pharmacol 1986; 22: 663-8
94. Cullen D, Bardhan KD, Eisner M, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. Aliment Pharmacol Ther 1998; 12: 135-40
95. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338: 727-34
96. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338: 719-26
97. Rose P, Huang B, Lukasik N, et al. Evidence that lansoprazole is effective in preventing NSAID induced ulcers [abstract]. Gastroenterology 1999; 116: A295
98. Scheiman JM, Vakil N, Hawkey CJ, et al. Esomeprazole prevents gastric and duodenal ulcers in at-risk patients on continuous non-selective or COX-2-selective NSAID therapy [abstract no. 638]. Gastroenterology 2004; 126 Suppl. 2: A-82
99. Yeomans N, Scheiman JM, Hawkey CJ, et al. An evidence-based analysis of esomeprazole therapy versus placebo for the prevention of gastric or duodenal ulcers in at-risk continuous NSAID users [abstract no. W1278]. Gastroenterology 2004; 126 Suppl. 2: A-604
100. Agrawal NM, Campbell DR, Safdi MA, et al. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. Arch Intern Med 2000; 160: 1455-61
101. Hawkey CJ, Yeomans ND, Jones R, et al. Esomeprazole improves quality of life in patients with upper GI symptoms associated with long-term NSAID therapy [abstract]. Gastroenterology 2003; 124 (4 Suppl. 1): A-107
102. Yeomans ND, Hawkey CJ, Jones R, et al. Esomeprazole provides effective control of NSAID-associated upper GI symptoms in patients continuing to take NSAIDs [abstract]. Gastroenterology 2003; 124 (4 Suppl. 1): A-107
103. Hawkey CJ, Lanas AI. Doubt and certainty about nonsteroidal anti-inflammatory drugs in the year 2000: a multidisciplinary expert statement. Am J Med 2001; 110: 79S-100S

Correspondence and offprints: Dr *Jørgen Næsdal*, AstraZeneca R&D, Mölndal, S-431 83, Sweden.
E-mail: jorgen.naesdal@AstraZeneca.com