Aliment Pharmacol Ther 1999; 13: 1273–1285.

Review article: nonsteroidal anti-inflammatory drug-associated gastrointestinal complications—guidelines for prevention and treatment

P. SCHOENFELD*, M. B. KIMMEY†, J. SCHEIMAN‡, D. BJORKMAN§, L. LAINE¶

**Assistant Professor of Medicine, Division of Gastroenterology, Uniformed Services University of Health Sciences, Bethesda, Maryland, USA; †Professor of Medicine and Director of Endoscopy, Division of Gastroenterology, University of Washington, Seattle, Washington, USA; ‡Associate Professor of Medicine, Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, Michigan, USA; §Associate Professor of Medicine, Division of Gastroenterology, University of Utah Medical Center, Salt Lake City, Utah, USA; ¶Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California, USA*

Accepted for publication 14 May 1999

SUMMARY

Chronic ingestion of NSAIDs increases the risk for gastrointestinal complications, which range from dyspepsia to gastrointestinal bleeding, obstruction, and perforation. Among patients using NSAIDs, 0.1 to 2.0% per year suffer serious gastrointestinal complications. Patients who require analgesic therapy should be carefully assessed for the lowest possible dosage and shortest duration of NSAID use and for the potential of treatment with a non-NSAID pain reliever. These patients should also be assessed for factors that increase their risk of gastrointestinal complications, including increased age, concomitant anticoagulant or corticosteroid use, and past history of NSAID-associated gastrointestinal complications.

The exact association between *Helicobacter pylori* infection and NSAID-related ulcer disease is unclear, and the routine testing and treatment of all NSAID using patients for *H. pylori* infection is not recommended at this time. NSAID-using patients who suffer from dyspepsia should have NSAIDs discontinued, the dosage changed, or be changed to a different class of NSAID. If NSAIDs cannot be discontinued, then an antisecretory agent should be initiated. Misoprostol prevents NSAID-associated gastrointestinal complications. Proton pump inhibitors are the most effective at healing NSAID-associated ulcers among patients who cannot discontinue NSAID therapy.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used groups of pharmacologic agents. In 1991, the year that naproxen and ketoprofen became available without a prescription, an estimated 14 million Americans ingested NSAIDs on a daily basis.[1] Additionally, the use of daily aspirin for vascular prophylaxis has added to the vast numbers of the public exposed to NSAIDs. More than 70 000 hospitalizations and 10 000–20 000 deaths annually in the United States can be attributed to NSAID use.[2] When less easily measured factors are considered, such as the impact of missed work or decreased productivity, the costs of NSAID-associated gastrointestinal compli-

Correspondence to: Dr P. Schoenfeld, Division of Gastroenterology, National Naval Medical Center, 8901 Wisconsin Avenue, Bethesda, Maryland, 20889, USA.
E-mail: pssmd@aolcom

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy, the Department of Defense, or the US Government.

cations exceed 4 billion dollars. However, the public appears to greatly underestimate the risks associated with NSAID use.[3]

A complete discussion of the pathogenesis of NSAID-associated dyspepsia, erosions, and ulcers is beyond the scope of this article, but is available in other sources.[4] NSAIDs may cause gastrointestinal injury in two ways: topically due to a direct injury to the gastrointestinal mucosa and systemically due to decreased prostaglandin production. Topical injuries may occur because most NSAIDs are weak organic acids with ionization constants in the range of 3–5, the drugs are non-ionized and freely diffuse across cell membranes into mucosal cells in the environment of highly acidic (pH < 2.5) gastric juice. In the neutral pH within the cells, ion trapping occurs, leading to an intracellular NSAID concentration which is much higher than outside the cell. Some investigators have postulated that when NSAIDs are concentrated in the mucosa, they may alter local immune responses that direct leucocytes against the gastric mucosa.[5]

The systemic effect (i.e. depletion of prostaglandins) of NSAIDs is felt to be the primary cause of important gastrointestinal injury and complications. This depletion occurs as a result of NSAIDs' inhibitory effect on cyclooxygenase (COX) enzymes, which are required for conversion of arachidonic acid to prostaglandins. The two isoforms of COX, COX-1 and COX-2 have contrasting functions: COX-1 is responsible for the maintenance of normal gastrointestinal function while COX-2 is induced in areas of inflammation.[6] Although there are individual differences in the effects of current NSAIDs on COX-1 and COX-2, all NSAIDs marketed until very recently inhibit both functions and may induce serious gastrointestinal complications.[7] Data on the gastrointestinal complications of COX-2 specific NSAIDs remain largely unavailable. Discussion of their role in the prevention of NSAID-associated gastrointestinal complications awaits publication of recent trials.

The following discussion considers several aspects of NSAID-associated gastrointestinal complications: (1) the magnitude of risk for serious gastrointestinal complications (i.e. bleeding, perforation, obstruction, hospitalization for intractable pain); (2) factors which increase the risk of these complications; (3) the effect of *Helicobacter pylori* on the development and healing of NSAID-associated ulcers; (4) healing of NSAID-associated ulcers; (5) treatment and prevention of dyspepsia in patients using NSAIDs; and, (6) prevention of NSAID-associated ulcers and gastrointestinal complications. Expert panel recommendations about these issues are included in the summary of this article.

RISKS OF NSAID-ASSOCIATED GASTROINTESTINAL COMPLICATIONS

What is the risk of serious gastrointestinal complications associated with NSAID use?

Aspirin. Results from two placebo-controlled, randomized trials[8, 9] provide the strongest data that aspirin significantly increases the risk of serious gastrointestinal complications. The UK-TIA trial[8] demonstrated a statistically significant increase in the occurrence of haematemesis or melena in patients taking 300 mg of aspirin or 1200 mg of aspirin daily for 1–7 years compared to patients receiving placebo. Less than 1% of patients [0.6% (5 out of 814)] receiving placebo had upper gastrointestinal bleeding compared to 2.0% (16 out of 806) of patients receiving 300 mg of aspirin and 3.8% (31 out of 815) of patients receiving 1200 mg of aspirin ($P < 0.01$). The odds ratios demonstrated a non-statistically significant trend for increased upper gastrointestinal bleeding with increased dose of aspirin: odds ratio 3.3 (95% CI: 1.2–9.0) for 300 mg of aspirin and 6.4 (95% CI: 2.5–16.5) for 1200 mg of aspirin. However, only 50% of these patients were hospitalized for their bleeding episodes, and 42% of patients did not have a diagnosis established for their bleeding episodes, which may lessen the accuracy of these data. The Aspirin Myocardial Infarction Study provides stronger evidence[9]. This study compared patients receiving 500 mg of aspirin twice daily or placebo with a minimum of 3 years of follow-up, and examined hospitalizations for serious upper gastrointestinal complications. Among patients receiving placebo, 0.2% (4 out of 2257) were hospitalized for ulcers compared to 1.5% (33 out of 2267) of aspirin patients ($P < 0.01$), producing an odds ratio of 8.3 (95% CI: 2.8–27.7).

Non-aspirin NSAIDs. Helpful data about non-aspirin NSAIDs come from a recent randomized controlled trial[10] comparing non-aspirin NSAIDs plus misoprostol to non-aspirin NSAIDs plus placebo in patients with rheumatoid arthritis. This study demonstrated that 0.74% of patients using non-aspirin NSAIDs plus placebo developed serious gastrointestinal complications with confirmed ulcers within 6 months as compared to

0.36% of patients using NSAIDs plus misoprostol. A meta-analysis[11] of cohort studies calculated a 0.1% 1-year prevalence of serious gastrointestinal complications among all NSAID users, with a 0.32% 1-year prevalence among NSAID users aged 65 years and older and a 0.039% 1-year prevalence among NSAID users less than 65 years of age. The disparity between these study results is most likely due to differences in NSAID dosages and concurrent medications. Rheumatoid arthritis patients[10] used higher dosages of NSAIDs with good compliance, while the compliance and dosage of NSAIDs was probably much less in the population of all NSAID-using patients examined in the meta-analysis.[11] Also, there was concurrent corticosteroid use in 42% of rheumatoid arthritis patients in the first trial.[10] Importantly, the individual studies[12–14] from the meta-analysis utilized data primarily from pharmacy records which frequently produce a biased underestimation of the incidence of events.

Another recent meta-analysis,[15] which met multiple criteria for a valid meta-analysis,[16] assessed the effect of different types and dosages of NSAIDs on serious gastrointestinal complications and used ibuprofen as the reference standard. NSAIDs with increasing inhibitory COX-1 activity were associated with increasing risks of serious gastrointestinal complications (Table 1). Furthermore, when data about dosage were extracted from the 12 studies included in the meta-analysis, the relative risk increased twofold with high-dose vs. low-dose NSAID therapy. Considering the overlapping 95% CIs (Table 1), these data indicate a non-statistically significant trend for ibuprofen being less likely to cause serious gastrointestinal complications than naproxen or indomethacin when the confounding effect of NSAID dosages is controlled for in the analysis. This meta-analysis also concluded that the low occurrence of serious gastrointestinal complications associated with ibuprofen in previous individual studies is due to the low dosages of ibuprofen frequently used.

Table 1. Comparison of comparative toxicity of drugs with use of ibuprofen as reference for calculating relative risks

Comparator	No. of studies	95% confidence: Pooled relative risk	95% confidence: Interval for pooled relative risk	*P*-value (heterogeneity)
Ibuprofen	—	1.0*	—	—
Fenoprofen	2	1.6	1.0–2.5	0.310
Aspirin	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	0.585
Diflunisal	2	2.2	1.2–4.1	0.351
Naproxen	10	2.2	1.7–2.9	0.131
Indomethacin	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

*Reference category for calculating relative risk.
Reproduced with permission from Reference 15.

An earlier meta-analysis combined data from nine case-control and seven cohort studies published between 1975 and 1990,[11] and calculated overall odds ratios for serious gastrointestinal complications for all NSAIDs, individual NSAIDs, and duration of NSAID use. The overall odds ratio for serious gastrointestinal complications with NSAIDs was 2.74 (95% CI: 2.54–2.97). Summary odds ratios for serious gastrointestinal complications for individual NSAIDs included: piroxicam = 11.2 (95% CI: 6.2–20.2), indomethacin = 4.69 (95% CI: 3.0–7.4), aspirin = 3.4 (95% CI: 2.3–5.0), naproxen = 2.8 (95% CI: 1.7–4.8), and ibuprofen = 2.3 (95% CI: 1.9–2.8). The summary odds ratio for serious gastrointestinal complications with duration of NSAID use were: (i) less than 1 month = 8.00 (95% CI: 6.37–10.06); (ii) for 1–3 months = 3.31 (95% CI: 2.27–4.82); and (iii) for longer than 3 months = 1.92 (95% CI: 1.19–3.13). However, the test of heterogeneity for this meta-analysis was statistically significant, suggesting important heterogeneity between studies based on study design, population, or intervention utilized in the various studies. Thus, the generalizability of the results to the entire population of patients using NSAIDs is limited.

WHAT IS THE RISK OF ENDOSCOPIC ULCERS WITH NSAID USE?

A recent meta-analysis summarized the occurrence of endoscopic ulcers in NSAID-using patients from 11 randomized controlled trials comparing H_2-receptor antagonists (H_2RAs) to placebo and 13 randomized controlled trials comparing misoprostol to placebo.[17] The cohort of patients receiving only aspirin or another NSAID had an 8.5% incidence of endoscopic gastric ulcers and a 3% incidence of endoscopic duodenal ulcers after 2 weeks or less of NSAID use, and a 9.1% incidence of endoscopic gastric ulcers and 4% incidence

of endoscopic duodenal ulcers with more than 4 weeks of NSAID use. The results from the largest individual randomized controlled trial (638 patients randomized) in this meta-analysis demonstrated that 11.5% of arthritis patients using NSAIDs developed endoscopic gastroduodenal ulcers after 12 weeks of NSAID treatment.[18] Another large randomized controlled trial (420 patients) demonstrated that 12.2% of arthritis patients developed gastric ulcers of at least 0.5 cm in diameter after 12 weeks of NSAID treatments.[19] The methodologic weaknesses of these studies include no assessment of serious gastrointestinal complications (e.g. bleeding, perforation, hospitalization, death) and no information about the dosages of NSAIDs used. However, these studies included many patients with rheumatoid arthritis, who may have been using higher doses of NSAIDs than the average NSAID-using patient.

Several randomized controlled trials have compared agents that bypass gastric absorption (e.g. nabumetone) or agents that more selectively inhibit COX-2 (e.g. flosulide, etodolac, nabumetone) to placebo, commonly used NSAIDs, or aspirin.[20–27] These trials demonstrated a statistically significant reduction in endoscopic gastric ulcers and erosions with salsalate,[20, 21, 26] etodolac,[23–25] nabumetone,[27] and flosulide.[22] The incidence of gastric erosions and ulcers observed with salsalate[26] and etodolac[23, 24] were comparable to placebo. However, the results of these studies should be interpreted cautiously. Previous studies have demonstrated that the assessment of NSAID-associated gastric erosions and ulcers is quite variable.[28] More importantly, no published randomized controlled trial has demonstrated that more COX-2 selective NSAIDs or NSAIDs that bypass gastric absorption produce statistically fewer serious gastrointestinal complications (e.g. bleeding, perforation, hospitalization, or death) when compared to commonly used NSAIDs or aspirin.

WHO IS AT RISK?

Patients with a history of ulcer complications, concomitant anticoagulant therapy, and advanced age have the highest risk of developing NSAID-associated serious gastrointestinal complications. Moderate risk factors include concomitant corticosteroid use, chronic major organ impairment, the use of high dose or multiple NSAIDs, and severe rheumatoid arthritis. Gender and symptoms do not appear to predict increased risk of serious gastrointestinal complications.

Meta-analysis of 16 studies performed between 1975 and 1990 found the overall odds ratio for an adverse gastrointestinal event associated with NSAID use to be 2.74 (95% CI: 2.54–2.97).[11] Patients who experienced one NSAID-associated gastrointestinal event were at increased risk of a subsequent event (relative risk 4.76; 95% CI: 4.05–5.59).[11] Not surprisingly, the concomitant use of NSAIDs and anticoagulants exacerbates the risk of gastrointestinal bleeding (odds ratio = 2.2; 95% CI: 1.6–3.1).[11, 29]

The relationship between corticosteroids and peptic ulcer disease has been a source of debate within the literature, but recent data demonstrate that corticosteroids do not appear to increase the risk of peptic ulcer disease when used alone.[30] However, the use of corticosteroids with NSAIDs leads to nearly a twofold increase (odds ratio = 1.83; 95% CI: 1.20–2.78) in the risk of serious gastrointestinal complications and a greater than 10-fold risk of death when compared to the use of an NSAID alone.[11, 31]

Increasing age is an independent predictor of an NSAID-associated gastrointestinal complication. Meta-analysis[11] confirmed that NSAID users greater than the age of 60 years had a largely increased risk of experiencing a gastrointestinal complication (5.52; 95% CI: 4.63–6.60) compared to non-users of NSAIDs. However, NSAID users under the age of 60 only had a small increased risk of gastrointestinal complications (odds ratio = 1.65; 95% CI: 1.08–2.53) compared to non-users. Elderly individuals taking NSAIDs were 10 times more likely to develop an ulcer complication requiring surgery than young individuals that did not use NSAIDs. Chronic major organ impairment, particularly cardiovascular disease, has also been identified as an independent risk factor: patients with a history of heart disease were found to have a significantly increased risk of serious gastrointestinal complications due to NSAID therapy (odds ratio = 1.84; 95% CI: 1.07–3.15).[10, 32] Groups of patients receiving high dose NSAIDs or multiple NSAIDs often include those with severe rheumatoid arthritis since these patients are more difficult to control and are often using multiple drug therapies. Data collected from five ARAMIS data bank centres suggest an increased risk for NSAID-associated gastrointestinal complications in patients receiving multiple NSAIDs or high dose NSAIDs (odds ratio = 1.4; 95% CI: 0.87–2.11).[33]

Symptoms, or the lack thereof, are not good predictors of NSAID complications. Up to 40% of patients with erosive disease are asymptomatic, and as many as 58%

of patients admitted with an NSAID complication had no antecedent gastrointestinal symptoms.[34] Conversely, many NSAID-using patients with epigastric complaints (e.g. dyspepsia, nausea) have normal endoscopic examinations.

WHAT IS THE RELATIONSHIP OF *H. PYLORI* TO NSAID-INDUCED ULCERS?

H. pylori infection has been hypothesized to increase the development of NSAID-associated ulcers. However, the pathophysiology for NSAID-associated ulcers and *H. pylori*-associated ulcers appears to be different. NSAID-associated ulcers occur in the absence of histological evidence of gastritis, while *H. pylori* ulcers occur in the setting of diffuse inflammation of the gastric mucosa. NSAIDs decrease prostaglandin synthesis, and *H. pylori* increases the synthesis of prostaglandins.[35] Most importantly, patients with gastric ulcers using NSAIDs have a significantly ($P = 0.01$) lower prevalence of *H. pylori* infection (53%) than ulcer patients not taking NSAIDs (83%) suggesting two independent mechanisms of ulcer pathogenesis.[36] Finally, data from multiple epidemiologic trials confirm that *H. pylori* infection is not a required cofactor for NSAID-associated ulcers.[36–40]

Evidence that *H. pylori* eradication may reduce the incidence of NSAID-associated endoscopic ulcers is relatively limited. Chan and colleagues[41] randomized 100 NSAID-naive patients (i.e. patients who had not previously used NSAIDs) with *H. pylori* infection to receive either naproxen alone (750 mg o.d.) or naproxen plus bismuth-based triple therapy for *H. pylori*. Ninety-two patients completed the trial: 47 patients in the naproxen group and 45 patients in the naproxen plus *H. pylori* eradication group. After 8 weeks of NSAID therapy, 26% naproxen-treated patients developed ulcers, while only 7% of patients in the *H. pylori* eradication group developed ulcers ($P = 0.01$). Hence, eradication of *H. pylori* in NSAID-na patients might reduce the occurrence of NSAID-associated endoscopic ulcers.

H. pylori infection may play a different role in ulcer formation among chronic NSAID users. Here the prevalence of *H. pylori* infection appears to be similar in those with or without ulcers.[38, 42] Lai and colleagues[43] studied *H. pylori*-positive patients receiving long-term NSAID therapy, who were proven to be ulcer free by endoscopy. Patients were randomized to receive 2 weeks of anti-*H. pylori* treatment ($n = 16$) or no treatment ($n = 23$). Endoscopy performed at 12 weeks revealed a comparable and low rate of peptic ulcers in both treatment groups: 6% in the eradication group developed an ulcer vs. 9% in the no treatment group ($P > 0.05$), and no clinical evidence of gastrointestinal bleeding occurred in any patients during the trial.[43]

Concurrent use of omeprazole may further limit any beneficial effect of *H. pylori* eradication on the occurrence of NSAID-associated ulcers. Hawkey and colleagues[44] evaluated 285 established NSAID users found to be *H. pylori*-positive by serology and urease testing. Patients were randomized to receive either omeprazole with antibiotic placebos for 1 week or omeprazole with clarithromycin and amoxycillin for 1 week. Both treatments were followed by omeprazole o.d. for 3 weeks prior to further endoscopy. New ulcers developed in five patients who received the anti-*H. pylori* regimen and in one patient in the omeprazole monotherapy group.[44]

Several large endoscopic studies[45, 46] suggest that *H. pylori* infection does not effect NSAID-ulcer healing rates or NSAID-ulcer recurrence rates. One of these trials[45] compared omeprazole vs. rantitidine among patients who continued NSAID therapy during treatment and subsequent prophylaxis of gastroduodenal ulcers or erosions, and the second trial[46] assessed a similar population of patients while comparing omeprazole vs. misoprostol. *H. pylori* infection status was assessed in both trials. Logistic regression analysis documented *H. pylori*-positive status as a good prognostic factor for higher healing rates and lower recurrence rates of duodenal and gastric ulcers, for omeprazole and ranitidine.[45, 46] No significant effect on patients taking misoprostol or placebo was identified.[45, 46] These results were supported by another recent study[47] comparing lansoprazole 15 mg o.d., lansoprazole 30 mg o.d., and ranitidine 150 mg b.d. for 8 weeks in NSAID-using patients with gastric ulcers ≥ 5 mm. Again, *H. pylori* status did not influence the ulcer healing rate in this trial.

TREATMENT OF NSAID-ASSOCIATED ULCERS

Histamine$_2$-receptor antagonists

H_2RAs heal almost all NSAID ulcers when the patient discontinues NSAID use. However, the rate of ulcer healing with H_2RA therapy decreases significantly if the patient cannot discontinue NSAID use. Lancaster-Smith[48] evaluated ulcer healing in 190 NSAID-using

patients with endoscopically confirmed ulcers. All patients received rantidine 150 mg b.d., and patients were randomized to continue or discontinue NSAID ingestion. Gastric ulcers healed in significantly more patients who had discontinued NSAIDs: 95% vs. 63% ($P = 0.001$). Duodenal ulcers were also healed in significantly more patients who had discontinued NSAIDs: 100% vs. 84% ($P = 0.006$).[48]

Proton pump inhibitors

Proton pump inhibitors are more effective than histamine$_2$-receptor antagonists at healing ulcers in patients who require continuous NSAID therapy.[45] In a recent double-blind study of 541 patients with endoscopically confirmed ulcers and continuous NSAID use, patients were randomized to receive omeprazole 20 mg or 40 mg o.d. or ranitidine 150 mg b.d.[45] After 8 weeks of treatment, the rates of healing in all types of lesions were higher in those treated with omeprazole as compared to ranitidine. The rates of gastric-ulcer healing during the 8-week period were significantly higher with 20 mg of omeprazole and 40 mg of omeprazole vs. ranitidine (84% vs. 87% vs. 64%, respectively; $P < 0.001$ for both doses of omeprazole vs. rantidine). The rates of healing of duodenal ulcers were significantly improved with 20 mg of omeprazole vs. ranitidine (92% vs. 81%, respectively, $P = 0.03$). Healing of duodenal ulcers was also higher with 40 mg of omeprazole vs. ranitidine (88% vs. 81%), but this improvement was not statistically significant ($P = 0.17$); further evidence supports these findings.[49] Another recent trial compared lansoprazole 15 mg or 30 mg o.d. with ranitidine 150 mg b.d. in the healing of non-malignant NSAID-induced gastric ulcers greater than 5 mm in diameter among patients who continued to use NSAIDs. Patients randomized to 15 mg of lansoprazole and 30 mg of lansoprazole experienced significantly higher ulcer healing rates than patients receiving rantidine (73% vs. 75% vs. 57%, respectively; $P < 0.05$ for comparison of both doses of lansoprazole to rantidine).[49]

Proton pump inhibitors also appear to be more effective than misoprostol at healing endoscopic ulcers among patients who use NSAIDs continuously. Hawkey *et al.*[46] compared misoprostol 200 μg q.d.s. to omeprazole 20 mg or 40 mg o.d. for 8 weeks in patients with NSAID-associated ulcers or erosions. The patients continued NSAID use during the trial. After 8 weeks of treatment, healing of gastric ulcers was significantly more common among patients treated with 20 mg of omeprazole as compared to those given misoprostol (87% vs. 73%, respectively; $P = 0.004$). The healing rate for omeprazole 40 mg was better than misoprostol (80% vs. 73%, respectively), although this difference did not attain statistical significance ($P = 0.14$). The rates of healing of duodenal ulcers were also significantly higher in the groups given omeprazole 20 mg or 40 mg as compared to misoprostol (93%, 89%, and 77%, respectively; $P < 0.001$ for comparison of both doses of omeprazole vs. misoprostol).

PREVENTION AND TREATMENT OF DYSPEPSIA ASSOCIATED WITH NSAID USE

Dyspepsia and heartburn are prevalent symptoms in patients who take NSAIDs, occurring daily in ≈15% of NSAID users.[50, 51] Cross-sectional population based studies indicate that aspirin and non-aspirin NSAIDs are associated with a 2-fold increased risk of dyspepsia.[52, 53] The cause of these symptoms is unknown. Acid secretion is not increased in NSAID-using patients with duodenal ulcers[54] and there is no evidence that NSAIDs affect oesophageal clearance or lower oesophageal sphincter pressure. Also, the presence of endoscopic lesions is not necessarily associated with dyspepsia. Dyspepsia is seen with similar frequency in patients with a normal upper endoscopy (19%), minor endoscopic changes (9%), and in those with ulcers (30%).[55]

Among patients already using H_2RAs, proton pump inhibitors, or misoprostol with NSAIDs, the occurrence of moderate to severe dyspepsia strongly predicts endoscopic ulcers or multiple erosions. In a cimetidine prophylaxis study, NSAID-using patients who had continued dyspepsia despite use of cimetidine 400 mg b.d. had a 31-fold increased probability of ulcers ($P < 0.01$).[56] These data are supported by similar trials that examined the efficacy of ranitidine, omeprazole, and misoprostol. In these endoscopic trials, over 90% of patients that complained of moderate to severe dyspepsia had endoscopic ulcers or multiple erosions.[57] However, similar endoscopic lesions were also found in 15–25% of patients without dyspepsia. Hence, the presence of moderate to severe dyspepsia among patients using NSAIDs and other protective agents (i.e. H_2RAs, proton pump inhibitors or misoprostol) is a strong predictor of endoscopic ulcer, but the absence of these symptoms

does not rule out endoscopic lesions among these patients.

Several approaches are available for the treatment of NSAID-associated dyspepsia. A past history of NSAID-related dyspepsia and higher NSAID doses have been described as risk factors for dyspepsia. Therefore, discontinuing NSAID use or lowering NSAID dose may be associated with resolution or a decrease in dyspepsia symptoms, and anecdotal reports suggest that NSAID-associated dyspepsia may resolve with a different NSAID. However, many patients will not be able to discontinue their current NSAID or lower its dose. For these patients, antisecretory agents may be most appropriate.

The results of controlled trials have shown a reduction in dyspeptic symptoms with omeprazole.[44, 58] Results from uncontrolled studies suggest that sucralfate may reduce dyspeptic symptoms.[59, 60] Misoprostol does not reduce the frequency of dyspepsia.[19, 46] In studies with endoscopic ulcer as the endpoints, acid suppression with traditional-dose histamine$_2$-receptor antagonists did not provide clear cut control of NSAID-induced gastrointestinal symptoms compared to placebo.[61] This is in contrast to assessing symptoms alone which demonstrate efficacy for cimetidine and antacids compared to placebo for the prevention of NSAID-related dyspepsia.[62, 63]

PREVENTION OF NSAID-ASSOCIATED GASTROINTESTINAL COMPLICATIONS AND NSAID-ASSOCIATED ENDOSCOPIC ULCERS

The use of pharmacologic agents to prevent NSAID injury has focused on two approaches: prostaglandin replacement and inhibition of acid secretion. These approaches appear to have varying effectiveness in the prevention of NSAID-associated endoscopic ulcers. However, a reduction in endoscopic lesions cannot automatically be extrapolated to a reduction in serious gastrointestinal complications.

Misoprostol

NSAID use depletes gastric prostaglandin production, which appears to be central to the development of NSAID-ulcers. Thus, replacement therapy with a synthetic prostaglandin should prevent NSAID-associated ulcers. Misoprostol, a synthetic prostaglandin, has well established prophylactic efficacy for the prevention of NSAID-associated endoscopic ulcers[18, 19] and NSAID-associated serious gastrointestinal complications (e.g. bleeding, perforation, obstruction).[10] However, direct comparisons with omeprazole indicate that proton pump inhibitors are more effective than twice daily doses of misoprostol for the prevention of recurrent endoscopic duodenal ulcers in NSAID-using patients.[46]

Multiple trials have demonstrated misoprostol's efficacy at the prevention of NSAID-associated endoscopic ulcers. In a randomized, placebo-controlled trial, Graham *et al.* demonstrated that duodenal ulcers developed in fewer patients using NSAIDs and misoprostol compared to NSAIDs plus placebo (0.6% vs. 4.6%, respectively, $P = 0.002$).[18] Gastric ulcers also developed in fewer patients using NSAIDs and misoprostol compared to NSAIDs plus placebo (1.9% vs. 7.7%, respectively; $P < 0.005$).[18] In an 8-week study of 374 NSAID-using arthritis patients, misoprostol 200 μg q.d.s. was significantly more effective than 150 mg of ranitidine b.d. for the prevention of gastric ulcers (0.58% vs. 5.67%, $P < 0.01$) and was equivalent for the prevention of duodenal ulcers (1.08% vs. 1.10%).[64] However, it should be noted that the number of patients withdrawing from the study due to adverse events was significantly greater in the misoprostol group (13% vs. 6.7%, respectively; $P = 0.014$).[64]

The efficacy of misoprostol appears to be related to the frequency of dosing. In a dose ranging study, gastric ulcers developed more frequently in patients who received twice daily dosing of misoprostol 200 μg: the incidence of gastric ulcers was 8.1% in those receiving misoprostol 200 μg b.d., 3.9% in those given 200 μg t.d.s. ($P = 0.02$ as compared to twice daily dosing), and 4.0% in patients given misoprostol 200 μg q.d.s. ($P < 0.03$ as compared to twice daily dosing).[65] Less frequent dosing of misoprostol was also associated with a trend toward higher incidence of duodenal ulcers: 2.6% vs. 3.3% vs. 1.4%, respectively, for twice daily, thrice daily and four times daily dosing ($P = 0.22$).[65]

The MUCOSA trial[10] provides the strongest evidence that a pharmaceutical agent can prevent serious upper gastrointestinal complications associated with NSAID use. This randomized, double-blind trial of 8849 rheumatoid arthritis patients on chronic NSAIDs gave patients misoprostol 200 μg q.d.s. or placebo. During a 6-month follow-up period, 0.74% of patients receiving placebo developed serious gastrointestinal complications, while 0.36% of patients receiving misoprostol developed serious gastrointestinal complications ($P = 0.049$), producing an $\approx$ 50% relative risk reduc-

tion with misoprostol use. Notably, the reduction in gastrointestinal complications was far less than the reduction in endoscopic lesions, indicating that extrapolating from reduction in endoscopic lesions to reduction of gastrointestinal complications may not be appropriate.

Although misoprostol may effectively reduce the frequency of NSAID-associated upper gastrointestinal complications, it may be cost-effective only in subgroups of high risk patients. The absolute risk reduction in serious upper gastrointestinal complications with misoprostol is only 0.38%. Therefore, the *number needed to treat* (i.e. the inverse of the absolute risk reduction) equals 264. That is, 264 chronic NSAID-using patients would need to be treated with misoprostol for 6 months to prevent one additional upper gastrointestinal complication.[66] However, high-risk subgroups have an increased risk of serious upper gastrointestinal complications, and the use of misoprostol is probably cost-effective and appropriate in these groups.[67, 68] Based on regression analysis of risk factor subgroups from the MUCOSA trial,[68] these high-risk subgroups should include patients with: (i) previous history of gastrointestinal bleed; (ii) previous history of peptic ulcer disease; (iii) significant cardiovascular disease; (iv) significant functional disability; and (v) patients who required concomitant antacid use.[68]

Histamine$_2$-receptor antagonists

Histamine$_2$-receptor antagonists do prevent NSAID-associated duodenal ulcer formation when given in traditional doses, but do not prevent gastric ulcers when given in traditional doses.[61, 69] In a study by Robinson and colleagues,[61] 144 NSAID-using patients with normal endoscopic findings were randomly assigned to treatment with either ranitidine 150 mg b.d. or placebo for 8 weeks. Duodenal ulcers developed in 8% placebo patients vs. 0% in ranitidine patients ($P = 0.02$). No difference was seen in the incidence of gastric ulcers: 10% of ranitidine patients vs. 12% of placebo patients developed gastric ulcers ($P = 0.74$).

Larger than traditional doses of H_2RAs appear to be more effective at preventing NSAID-associated ulcers. In a 6-month study from the UK,[70] 285 NSAID-using arthritis patients were randomized to receive either placebo, or 20 mg or 40 mg of famotidine b.d. The reduction in the incidence of gastric ulcer in these NSAID users was dose-dependent: 20% of the placebo group had gastric ulcers vs. 13% of the famotidine 20 mg twice daily group ($P = 0.24$ as compared to placebo) vs. 8% in the famotidine 40 mg twice daily group ($P = 0.03$ as compared to placebo). With regard to duodenal ulcer, placebo patients suffered significantly more duodenal ulcers compared to patients receiving 20 mg famotidine twice daily or patients receiving 40 mg famotidine twice daily (13% vs. 4% vs. 2%, respectively; $P < 0.04$ for comparison of both doses of famotidine to placebo). However, there are no statistically significant data demonstrating that high dose histamine$_2$-receptor antagonists reduce serious gastrointestinal complications among NSAID-using patients.

Proton pump inhibitors

Proton pump inhibitors appear to be superior to placebo in the prevention of NSAID-associated endoscopic ulcers. A large multicentre randomized controlled trial[71] randomized 168 NSAID-using dyspeptic patients (with no endoscopic ulcer on entry into the trial) to receive 20 mg of omeprazole daily or placebo. After 6 months, more patients in the placebo group had ulcers than patients in the omeprazole group (16.5% vs. 3.6%, respectively; $P = 0.006$).

Proton pump inhibitors appear to be more effective than twice daily doses of misoprostol or H_2RAs at preventing NSAID-associated endoscopic ulcers. Yeomans and colleagues[45] randomized 432 patients with a past history of NSAID-associated endoscopic ulcer to receive ranitidine 150 mg b.d. vs. omeprazole 20 mg o.d. Patients were then followed for 6 months. Gastric ulcers recurred more frequently in the ranitidine group compared to the omeprazole group (16.3% vs. 5.2%, respectively; $P < 0.001$). Duodenal ulcers also recurred more frequently in the ranitidine group compared to the omerpazole group (4.2% vs. 0.5%, respectively; $P = 0.02$). Hawkey *et al.*[46] evaluated 732 NSAID-using patients with a history of NSAID-associated endoscopic ulcer and randomized the patients to receive placebo, omeprazole 20 mg o.d. or misoprostol 200 μg b.d. and followed patients for 6 months. Gastric ulcers occurred most commonly in the placebo group but there was no significant difference between misoprostol and omeprazole patients (32% vs. 10% vs. 13%, respectively; $P < 0.001$ for misprostol or omeprazole vs. placebo). Duodenal ulcers developed least often in omeprazole patients compared to misoprostol patients and placebo patients (3% vs. 10% vs. 12%, respectively; $P < 0.001$ vs. placebo and misoprostol). However, two caveats

should be remembered when applying these trial results. First, the efficacy of misoprostol in the prevention of NSAID-associated ulcers appears to be dose-dependent, and this trial used only twice daily dosing of misoprostol. Second, a recurrence in endoscopic lesions cannot automatically be extrapolated to a reduction in serious gastrointestinal complications. Currently, there are no statistically significant data available to indicate that proton pump inhibitors reduce the frequency of serious upper gastrointestinal complications among NSAIDs users.

SUMMARY AND RECOMMENDATIONS

Figures 1 and 2 offer algorithms designed to guide clinicians in the management of patients who require NSAID therapy and those who develop complications.

The following conclusions and recommendations were developed by the expert panel:

- The use of aspirin or NSAIDs increases the risk of serious gastrointestinal complications (i.e. bleeding, perforation, obstruction, and/or hospitalization), and this risk ranges from 0.1 to 2.0% per year. This risk is greatest during the first 3 months of treatment, although the risk continues to increase slowly, but steadily, with continued treatment. Past history of NSAID-associated gastrointestinal complications, advanced age, and concomitant anticoagulant use are the most serious risk factors for NSAID-associated gastrointestinal complications.
- Twelve to 25% of patients using NSAIDs develop endoscopic ulcers within 3 months of continued use. However, the occurrence of endoscopic lesions cannot automatically be extrapolated to the occurrence of serious gastrointestinal complications.

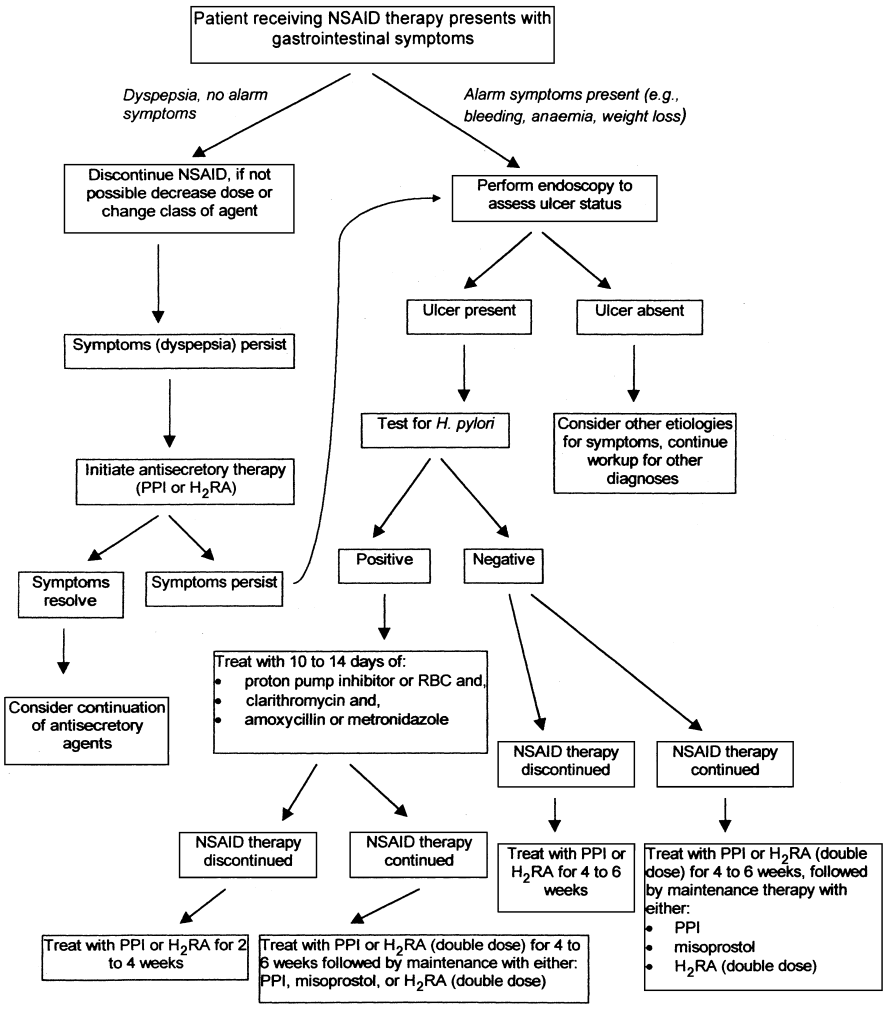

Figure 1. Management of gastrointestinal adverse effects of NSAIDS.

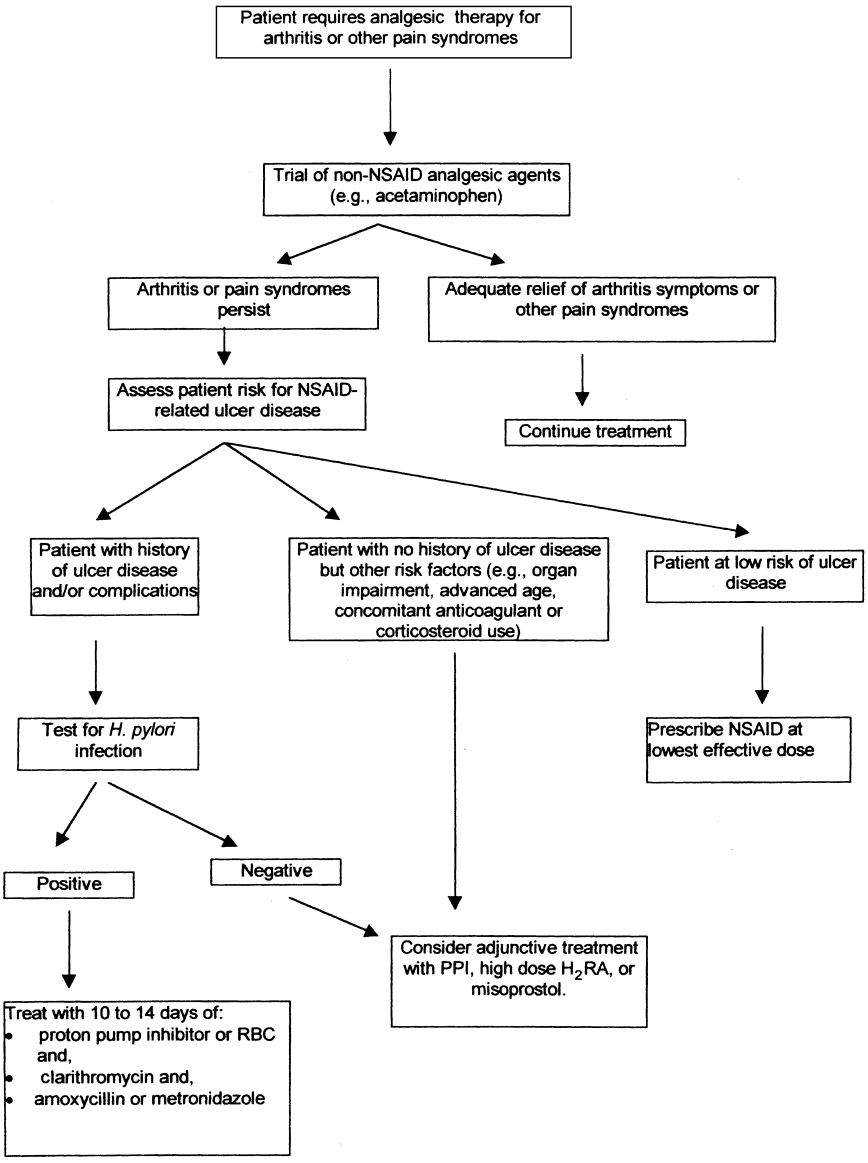

Figure 2. Management of patients who require NSAID therapy.

• The effect of *H. pylori* on NSAID-associated ulcer formation is unclear. Based on currently available information, eradication of *H. pylori* in an NSAID-naïve patient may reduce the frequency of endoscopic ulcers. However, eradication of *H. pylori* does not appear to reduce the frequency of endoscopic ulcers in chronic NSAID users, and the absence of *H. pylori* does not appear to have a beneficial effect on the healing or recurrence of NSAID-associated ulcers. Therefore, the routine testing and treatment of *H. pylori* in all NSAID-using patients cannot be recommended currently. However, as per standard guidelines, all ulcer patients should be tested and treated for *H. pylori*, regardless of NSAID use.

• NSAID-using patients with dyspepsia should discontinue NSAIDs. If patients cannot discontinue this medication, both histamine$_2$-receptor antagonists (H_2RAs) and proton pump inhibitors may improve dyspepsia. Direct comparison of H_2RAs and proton pump inhibitors in the treatment of NSAID-associated dyspepsia has not been performed.

• The treatment of NSAID-associated ulcers should be guided by the continued need for NSAIDs. Among patients who can discontinue NSAIDs, H_2RAs, proton pump inhibitors and misoprostol will heal ulcers. Among patients who cannot discontinue NSAIDs, proton pump inhibitors are most effective at healing endoscopic ulcers.

• Misoprostol is the only agent demonstrated to reduce the frequency of NSAID-associated serious gastrointestinal complications. Proton pump inhibitors are more effective than standard dose histamine$_2$-receptor antagonists at the prevention of endoscopic gastric and duodenal ulcers. Proton pump inhibitors are more effective than twice daily dosing of misoprostol at preventing NSAID-associated endoscopic duodenal ulcers.

ACKNOWLEDGEMENTS

This project was supported by an unrestricted educational grant from TAP Pharmaceuticals, Inc.

REFERENCES

1 Antiarthritis medication usage, United States, 1991. Stat Bull Metrop Ins Co 1992; (73): 25–34.
2 Fries JF. NSAID gastropathy: The second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol 1991; 18(Suppl. 28): 6–10.
3 Goldstein JL. Public misunderstanding of nonsteroidal antiinflammatory drug (NSAID)—mediated gastrointestinal complications toxicity: a serious potential health threat. Gastroenterology 1998; 114: G0555.
4 Scheiman JM. NSAIDs, cytoprotection, and gastrointestinal injury. Gastroenterol Clinics North Am 1996; 25: 279–98.
5 Lanza FL, Karlin DA, Yee JP. A double-blind, placebo-controlled endoscopic study comparing the mucosal injury seen with orally and parenterally administered nonsteroidal analgesic ketorolac tromethamine at therapeutic and supratherapeutic doses. Am J Gastroenterol 1987; 82: 939.
6 Vane JR, Mitchell JA, Appelton I, *et al.* Inducible isoforms of cyclooxygenase and nitric acid synthase in inflammation. Proc Natl Acad Sci USA 1994; 91: 2046–50.
7 Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med 1998; 104: 413–21.
8 Slattery J, Warlow CP, Shorrock CJ, Langman MJS. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin-analysis of gastrointestinal bleeding during the UK-TIA trial. Gut 1995; 37: 509–11.
9 Kurata JH, Abbey DE. The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. J Clin Gastroenterol 1990; 12(3): 260–6.
10 Silverstein F, Graham D, Senior J, *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.
11 Gabriel S, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of NSAIDs. A Meta-Anal Ann Intern Med 1991; 115: 787–96.
12 Beard K, Walker AM, Perera DR, Jick H. Nonsteroidal anti-inflammatory drugs and hospitalizations for gastroesophageal bleeding in the elderly. Arch Intern Med 1987; 147: 1621–3.
13 Guess HA, West R, Strand LM, Helston D, *et al.* Fatal upper gastrointestinal hemorrhage or perforation among users and nonusers of nonsteroidal anti-inflammatory drugs with upper gastrointestinal drugs in Saskatchewan, Canada 1983. J Clin Epidemiol 1988; 41: 35–45.
14 Jick H, Feld AD, Perera DR. Certain nonsteroidal anti-inflammatory drugs and hospitalization for upper gastrointestinal bleeding. Pharmacotherapy 1985; 5: 280–4.
15 Henry D, Lim L, Garcia Rodriguez L, *et al.* Variability in risk of gastrointestinal complications with individual NSAIDs: results of a collaborative meta-analysis. Br Med J 1996; 312: 1563–6.
16 Oxman AD, Cook DJ, Guyatt G. Users' guides to the medical literature. How to use an overview. J Am Med Assoc 1994; 272: 1367–71.
17 Koch M, Dezi A, Ferrario F, Capurso L. Prevention of NSAID-induced gastrointestinal mucosal injury. Arch Intern Med 1996; 156: 2321–32.
18 Graham D, White R, Moreland L, *et al.* Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Ann Intern Med 1993; 119: 257–62.
19 Graham D, Agrawal N, Roth S. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet 1988; 2: 1277–80.
20 Scheiman JM, Elta GH. Gastroduodenal mucosal damage with salsalate versus aspirin: results of experimental models and endoscopic studies in humans. Semin Arthritis Rheum 1990; 20: 121–7.
21 Roth S, Bennett R, Caldron P, *et al.* Reduced risk of NSAID gastropathy (GI mucosal toxicity) with nonacetylated salicylate (salsalate): an endoscopic study. Semin Arthritis Rheum 1990; 19(Suppl. 2): 11–9.
22 Bjaranason I, Macpherson A, Rotman H, *et al.* A randomized, double-blind, crossover comparative endoscopy study on the gastroduodenal tolerability of a highly specific cyclooxygenase-2 inhibitor, flosulide, and naproxen. Scand J Gastroenterol 1997; 32: 126–30.
23 Laine L, Sloane R, Ferretti M, Cominelli F. A randomized, double-blind comparison of placebo, etodolac, and naproxen on gastrointestinal injury and prostaglandin production. Gastrointest Endosc 1995; 42: 428–33.
24 Lanza F, Rack MR, Lynn M, Wolf J, Sanda M. An endoscopic comparison of the effects of etodolac, indomethacin, ibuprofen, naproxen, and placebo on gastrointestinal mucosa. J Rheumatol 1987; 14: 338–41.
25 Bianchi Porro G, Caruso I, Petrillo M, Montrone F, Ardizzone S. A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. J Intern Med 1991; 97: 1400–5.
26 Cryer B, Goldschmiedt M, Redfern JS, Feldman M. Comparison of salsalate and aspirin on mucosal injury and gastroduodenal mucosal prostaglandins. Gastroenterology 1990; 99: 1616–21.
27 Roth SH, Tindall EA, Jain AD, *et al.* A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen

plus misoprostol on the upper gastrointestinal mucosa. Arch Intern Med 1993; 153: 2565–71.
28 Hudson N, Everitt S, Hawkey CJ. Interobserver variation in assessment of gastroduodenal lesions associated with non-steroidal anti-inflammatory drugs. Gut 1994; 35: 1030–2.
29 Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anti-coagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993; 153: 1665–70.
30 Conn HO, Poynard Y. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994; 236: 619–32.
31 Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: Role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114: 735–40.
32 Maetzel A, Ferraz MB, Bombardier C. The cost effectiveness of misoprostol in preventing serious gastrointestinal events associated with the use of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1998; 41: 16–25.
33 Fries JF, Williams CA, Bloch DA. Nonsteroidal anti-inflammatory drug-associated gastropathy: Incidence and risk factor models. Am J Med 1991; 91: 213–22.
34 Armstrong CP, Blower Al. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28: 527–32.
35 Laine L, Marin-Sorensen M, Weinstein WM. The histology of gastric erosions in patients taking nonsteroidal anti-inflammatory drugs: a prospective study. Gastroenterology 1987; 94: A247(Abstract).
36 Laine L, Marin-Sorensen M, Weinstein WM. Nonsteroidal anti-inflammatory drug-associated gastric ulcers do not require *Helicobacter pylori* for their development. Am J Gastroenterol 1992; 87: 1398–402.
37 Laine L, Cominelli F, Sloane R, Casini-Raggi L, Marin-Sorensen M, Weinstein WM. Interaction of NSAIDs and *Helicobacter pylori* on gastrointestinal injury and prostaglandin production: a controlled double-blind trial. Aliment Pharmacol Ther 1995; 9: 127–35.
38 Kim JG, Graham DY. *Helicobacter pylori* infection and development of gastric or duodenal ulcer in arthritic patients receiving chronic NSAID therapy. Am J Gastroenterol 1994; 89: 203–7.
39 Gubbins GP, Schubert TT, Attanasio F, Lubetsky M, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* seroprevalence in patients with rheumatoid arthritis: effect of nonsteroidal anti-inflammatory drugs and gold compounds. Am J Med 1992; 93: 412–8.
40 Graham DY, Lidsky MD, Cox AM, *et al.* Long-term nonsteroidal anti-inflammatory drug use and Helicobacter infection. Gastroenterology 1991; 100: 1653–7.
41 Chan FKL, Sung JY, Chung SCS, *et al.* Randomized trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997; 350: 975–9.
42 Konturek JW, Fuchs W, Elbert J, Domschke W. The prevalence of *Helicobacter pylori* infection in long-term users of nonsteroidal antiinflammatory drugs. Gastroenterology 1998; 114: G0762.
43 Lai KC, Lam SK, Hui WM, *et al.* Can eradication of *Helicobacter pylori* prevent future development of peptic ulcers in patients receiving long-term continuous non-steroidal anti-inflammatory drugs. Gastroenterology 1998; 114: A192(Abstract).
44 Hawkey CJ, Tullassay Z, Szcepanski L, *et al.* Failure of *Helicobacter pylori* eradication to influence site-specific relapse in high risk NSAID users: Results of a large six month double blind randomised controlled clinical trial. Gastroenterology 1998; 114: G0594.
45 Yeomans ND, Zsolt T, 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.
46 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.
47 Campbell DR, Shah N, Winston B, Karvois D, Greski-Rose P, Effect of *H. pylori* status on healing of gastric ulcer in patients continuing to take NSAIDs and treated with lansoprazole or ranitidine. Gastroenterology 1998; 114: G0339.
48 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.
49 Agrawal N, Farmington CT, Safdi M, *et al.* Effectiveness of lansoprazole in the healing of NSAID-induced gastric ulcer in patients continuing to take NSAIDs. Gastroenterology 1998; 114: G0213.
50 Coles LS, Fries JF, Kraines RG, *et al.* From experiment to experience: side effects of nonsteroidal anti-inflammatory drugs. Am J Med 1983; 74: 820–8.
51 Larkai EN, Smith JL, Lidsky MD, Sessoms SL, Graham DY. Dyspepsia in NSAID users: the size of the problem. J Clin Gastroenterol 1989; 11: 158–62.
52 Talley NJ, Zinsmeister AR, Scleck CD, Melton LJ. Smoking, alcohol, and analgesics in dyspepsia and among dyspepsia subgroups: lack of association in a community. Gut 1994; 35: 619–24.
53 Talley NJ, Evans JM, Fleming KC, *et al.* Nonsteroidal antiinflammatory drugs and dyspepsia in the elderly. Dig Dis Sci 1995; 40: 1345–50.
54 Collen MJ, Abdulian JD. Do nonsteroidal anti-inflammatory drugs cause duodenal ulcer? Evaluation of basal output and ulcer complications. J Gastroenterol Hepatol 1996; 11: 520–3.
55 Larkai EN, Smith JL, Lidsky MD, Graham DY. Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic nonsteroidal anti-inflammatory drug use. Am J Gastroenterol 1987; 82: 1153–8.
56 Wallin BA, Grier CE, Fox MJ, *et al.* Prevention of NSAID-induced ulcers with cimetidine: results of a double-blind, placebo-controlled trial. Gastroenterology 1990; 98: A146(Abstract).
57 Hawkey CJ, Langstrom G, Naesdal J, Yeomans N. Significance of symptoms during healing and maintenance of NSAID-associated gastroduodenal lesions with omeprazole, misoprostol, and ranitidine. Gastroenterology 1997; 112: A144(Abstract).

58 Ekstrom P, Carling L, Wetterhus S, *et al.* Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. Scand J Gastroenterol 1996; 31: 753–8.
59 Caldwell JR, Roth SH, Wu WC, *et al.* Sucralfate treatment of nonsteroidal anti-inflammatory drug-induced gastrointestinal symptoms and mucosal damage. Am J Med 1987; 83(Suppl. 3B): 74–82.
60 Miller K. Effect of gastric mucosal protection in nonrheumatoid patients with short-term nonsteroidal antiinflammatory drug therapy: a prospective randomized multicenter study. Hepatogastroenterol 1997; 44: 872–9.
61 Robinson MG, Griffin JW Jr, Bowers J, *et al.* Effect of ranitidine on gastroduodenal mucosal damage induced by nonsteroidal anti-inflammatory drugs. Dig Dis Sci 1989; 34: 424–8.
62 Rugstad HE, Giersky KE, Husby G, Holme I. Effect of cimetidine on gastrointestinal symptoms in patients taking non-steroidal anti-inflammatory drugs. Scand J Rheumatol 1994; 23: 177–82.
63 Bijlsma JW. Treatment of endoscopy-negative NSAID-induced upper gastrointestinal symptoms with cimetidine: an international multicentre collaborative study. Aliment Pharmacol Ther 1988; 2(Suppl. 2): 75–84.
64 Raskin JB, White R, Jaszewski R, *et al.* Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double blind, multicenter study. Am J Gastroenterol 1996; 91: 223–7.
65 Raskin JB, White RH, Jackson JE. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Int Med 1995; 123: 344–50.
66 Scheiman JM. Commentary on 'Meta analysis: Misoprostol reduced NSAID-induced gastrointestinal injury'. ACP J Club 1997; 124: 36.
67 Stucki G, Johannesson M, Liang MH. Is misoprostol cost-effective in the prevention of nonsteroidal anti-inflammatory drug-induced gastropathy in patients with chronic arthritis? A review of conflicting economic evaluations. Arch Intern Med 1994; 154: 2020–5.
68 Simon LS, Hatoum HT, Bittman RM, *et al.* Risk factors for serious nonsteoidal-induced gastrointestinal complicaitons: regression analysis of the MUCOSA trial. Fam Med 1996; 28: 204–10.
69 Ehsanullah RSB, Page MC, Rildesley G, *et al.* Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: Controlled trial of ranitidine. Br Med J 1988; 297: 1017–21.
70 Taha AS, Hudson N, Hawkey CJ, *et al.* Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal anti-inflammatory drugs. N Engl J Med 1996; 334: 1435–9.
71 Cullen D, Bardhan KD, Eisner M, *et al.* Primary gastroduodenal prophylaxis with omeprazole for NSAID users. Gastroenterology 1996; 110: A86(Abstract).