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WORKING PARTY REPORT: NSAID

Non-steroidal anti-inflammatory drug toxicity in the upper gastrointestinal tract

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Abstract Non-steroidal anti-inflammatory drug (NSAID) toxicity in the upper gastrointestinal tract is the most common serious drug-induced toxicity reported to drug regulatory authorities. In the last two decades, the rediscovery of *H. pylori*, development of potent ulcer-healing drugs and specific Cox-II inhibitors have opened new horizons in the management of NSAID toxicity. A Working Party composed of gastroenterologists and rheumatologists in the Asia-Pacific region met in Cairns, Australia, in 1999 to review the literature and develop appropriate guidelines. Recommendations were made based on the latest existing evidence. The importance of clinical events as study endpoints was emphasized. While differences exist between NSAIDs and aspirin, most studies have shown that advanced age, history of peptic ulcer disease, serious concomitant illnesses and coprescription of NSAID/aspirin with anticoagulants and steroids are high risk factors. These patients should be considered for prophylactic anti-ulcer therapy. *Helicobacter pylori* infection may aggravate the toxicity of NSAIDs and, in selected cases, should be treated before NSAID/aspirin is prescribed. Proton pump inhibitors and misoprostol are the most promising agents in preventing gastric and duodenal ulcers. When NSAID/aspirin needs to be continued in patients who develop an NSAID-related ulcer, proton pump inhibitors offer the best healing effect. With the discovery of cyclo-oxygenase isoforms (Cox-I and Cox-II), preferential and specific Cox-II inhibitors have been developed. While early clinical data have suggested promising anti-inflammatory effects and improved safety profile in the gastrointestinal tract, several key issues on long-term safety remain unresolved. The use of potent anti-ulcer therapy, treatment of *H. pylori* infection and the development of Cox-II inhibitor will change the scenario of NSAID/aspirin-related gastrointestinal toxicity in the next millennium.

Key words: aspirin, cyclo-oxygenase inhibitors, *Helicobacter pylori*, non-steroidal anti-inflammatory drugs, ulcer.

INTRODUCTION

The last decade has witnessed astounding progress in the understanding of peptic ulcer disease related to the use of non-steroidal anti-inflammatory drugs (NSAIDs). The rapidly increasing consumption of NSAIDs and associated adverse events, the rediscovery of *H. pylori* and its possible interactions with NSAIDs in producing peptic ulcers, the development of potent acid-suppressive agents and prostaglandin analogues in the treatment and prevention of ulcers and the discovery of cyclo-oxygenase (COX) isoforms (Fig. 1) and subsequent development of Cox-2 inhibitors have important impacts on family doctors, rheumatologists, orthopaedic surgeons, gastroenterologists and patients. Laboratory data and clinical studies are accumulating rapidly and, in some areas, yield conflicting results. It is important for clinicians as well as scientists to keep abreast of the latest developments in this important area.

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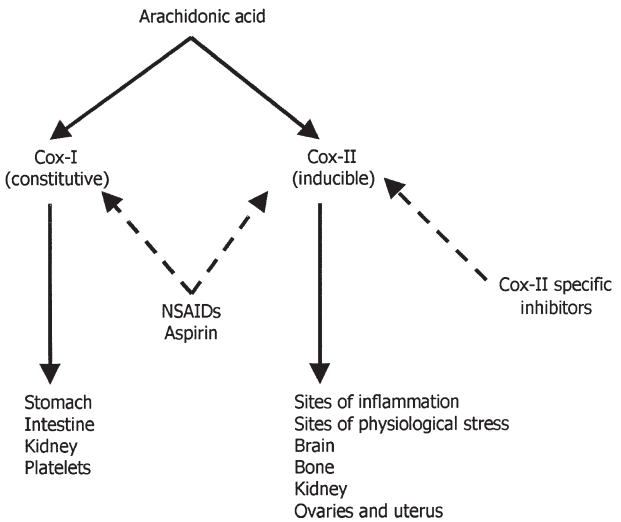

Figure 1 Cyclo-oxygenase (Cox) I and II isoforms. NSAIDs, non-steroidal anti-inflammatory drugs.

A Working Party convened in early 1999 to address the issue of NSAID gastrointestinal (GI) toxicity. The Working Party was composed primarily of clinicians and research workers from the Asia-Pacific region, but international experts from North America, Europe and South Africa were also invited. Members of the Party included gastroenterologists and rheumatologists in the ratio of 3:1. They were divided into four groups to review published data in the English literature on: (i) epidemiology of NSAID-GI toxicity; (ii) interactions between *H. pylori* and NSAIDs; (iii) treatment and prevention of NSAID-related ulcers; and (iv) COX-II-specific inhibitors. Input from pharmaceutical industries was limited to suggestions of published literature for review. After group discussion on these separate issues, the Working Party developed consensus and recommendations that are presented in the present Working Party Report.

EPIDEMIOLOGY OF NSAID GASTROPATHY

Gastrointestinal pathology associated with the use of NSAIDs is increasingly recognized as the most prevalent serious drug toxicity worldwide. It has been estimated that over 30 million people consume NSAIDs worldwide and the per capita consumption averages 278 prescriptions per 1000 patient.[1] Non-steroidal anti-inflammatory drugs are prescribed for musculoskeletal pain and other painful conditions, whereas aspirin has been increasingly used for the prevention of coronary artery disease, stroke and colorectal cancers. With the increasing treatment of *H. pylori* infection, in many countries NSAIDs have become the most important cause of gastroduodenal ulcers. Non-steroidal anti-inflammatory drug-induced ulcers are known to be large and multiple, more commonly found in the stomach than duodenum and, perhaps related to the potent analgesic effects of NSAIDs, often 'painless'.

In studying the epidemiology of NSAID-induced gastrointestinal toxicity, the Working Party agreed that the preferred end-points are clinical events (including dyspepsia, gastrointestinal bleeding or perforation, hospitalization and death) rather than endoscopic lesions. This choice is based on three reasons: (i) endoscopic monitoring often lacks a comparable control group; (ii) endoscopic diagnosis of ulcer and erosion are prone to observer bias; and (iii) the significance of endoscopic lesions without associated clinical events is unclear. There is also ample evidence to suggest that non-aspirin NSAID and aspirin gastropathies are not the same. In the present report, non-aspirin NSAIDs and aspirin will be discussed separately and emphasis will be given to clinical outcome studies.

How much bleeding, perforation, hospitalization and mortality is attributable to NSAIDs?

Most studies showed that NSAIDs cause a three to four fold increase in peptic ulcers with higher risk of developing gastric than duodenal ulcers. Pooled data from case control studies showed an average relative risk of bleeding of 3.09 and perforation of 5.93.[2] The relative risk of death from ulcers or their complications of NSAIDs is 7.62.[2] Results from large-scale cohort studies, such as the Arthritis, Rheumatism, and Ageing Medical Information System (ARAMIS)[3] and the Tennessee Medicaid Program,[4] indicate that the usage of NSAIDs is associated with hospitalization rates of 0.66–1.46% of patients per year, gastrointestinal bleeding of 0.3%, perforation of 0.03% and mortality of 0.22%. The ARAMIS study has also compared patients with rheumatoid arthritis and osteoarthritis and has shown a lower complication rate in the latter.[3] This was, however, attributed to the milder disease and hence requirement of a lower dose of NSAIDs.

The risk of prophylactic use of aspirin has been carefully examined in several case-control studies from UK. The clinical events of aspirin users have been compared with both hospital and community controls. The relative risk of bleeding ranges from 2.3 to 6.4 with the dose of 75 mg to 1200 mg of aspirin per day.[5,6] The relative risks of hospitalization also increase with the rising dose of aspirin from 3.6 (with 300 mg) to 8.7 (with 1200 mg).[6] The UK-Transient Ischemic Attack (TIA) trial has also indicated that the risk of bleeding from duodenal ulcers is higher than that from gastric ulcers and occasionally, bleeding may arise from the lower GI tract. These figures have been compatible with an earlier meta-analysis by Hawkey.[2] Data on gastrointestinal perforation is scant. Lanas *et al*. have reported that the risk of perforation is increased by at least sixfold compared with non-users.[7] In their study, which comprised both aspirin and non-aspirin NSAID users, the risk of the latter for perforation was estimated to be twice that of aspirin users. Combined use of aspirin and non-aspirin NSAID almost doubles the risk of bleeding, as shown by two independent case-control studies, but the dose of aspirin may have some influence.[5,8]

Which patients are more likely to be affected?

There is little evidence to suggest that NSAID-related gastrointestinal toxicity has any sex predilection. However, almost all studies have demonstrated that GI toxicity related to NSAIDs and aspirin is more common in the elderly patients. In the ARAMIS study, the incidence of hospitalization or death from acute gastrointestinal adverse events increased from three per 1000 person years in those below 63 years to 19 per 1000 in those aged 63–75 and to 42 per 1000 in those above 75 years.[3] The age-related risk is confirmed by many other studies from Europe, Australia and North America.[4,8–12] The excess risk is particularly high in those above the age of 75 years.[12] The only exceptional finding comes from Solomon and Gurwitz, who do not support the notion that age, by itself, is an independent risk factor for GI toxicity.[13] They argue that comorbidity and comedication, which are more common in the elderly patients, increase the risk of GI toxicity instead of the age-related physiological changes.

Past history of peptic ulcer increases the risk of adverse GI events. Studies have shown that NSAID users with a history of dyspepsia, uncomplicated peptic ulcers or bleeding ulcers are associated with a higher risk (adjusted relative risks are 2.9, 6.1 and 13.5, respectively, according to Garcia Rodriguez and Jick) of recurrent ulcer complications when they are given NSAID or aspirin.[3,4,10] The ARAMIS study has also confirmed that reusing NSAIDs in those who have a history of NSAID-related side-effects carries a significantly higher risk of complications.[3] It is reasonable to speculate that previous ulcers not related to NSAIDs are most likely caused by *H. pylori* and these ulcers are also prone to recur on exposure to aspirin and NSAID. In a study from Glasgow, *H. pylori*-associated gastritis has been identified as a risk factor for gastroduodenal ulcers.[14]

The incidence of ulcer bleeding and perforation is further increased if NSAIDs are coprescribed with corticosteroids.[3,9] Concurrent use of anticoagulants has also been found to increase the risk of gastrointestinal complications, by 6-fold according to one report.[10] In the Scandinavian cohort, however, the increased risks of concurrent usage of steroid and anticoagulants were not substantiated.[12]

There are data suggesting that smoking or drinking will increase the risk of NSAID-related upper gastrointestinal complications. Lanas *et al*. and Langman *et al*. have reported that both smoking and alcohol increase the risk of gastrointestinal perforation, but not bleeding, in patients receiving aspirin or non-aspirin NSAIDs.[15,16] In another study, alcohol consumption of five or more standard drinks has been found to increase the risk of gastrointestinal complications with both aspirin and non-aspirin NSAIDs.[17] Based on existing evidence, however, the increased risk of smoking and alcohol is modest.

The high-risk patients who require prophylaxis against NSAID gastropathy are summarized in Table 1.

Table 1 Situations for which prophylactic cotherapy with anti-ulcer drugs is recommended

Past history of peptic ulcer, especially while on NSAIDs and especially if complicated
Older patients (e.g. > 65 years)
Patients requiring high dose NSAIDs (including combination of low-dose aspirin with a non-aspirin NSAID)
Concomitant corticosteroid treatment
Concomitant anticoagulant treatment (NSAIDs should be avoided in this situation unless the need is exceptional)
Serious comorbid disease (e.g. cardiovascular or respiratory) such that the patient would be at increased risk of mortality from an ulcer complication

NSAID, non-steroidal anti-inflammatory drug.

Are all NSAIDs and aspirin the same?

The estimated risk of individual NSAIDs varies widely. Most comparative studies indicate that ibuprofen and diclofenac are relatively safe, whereas piroxicam, ketoprofen and azapropazone are more harmful to the upper gastrointestinal tract.[4,10,11,16,17] Other NSAIDs, such as sulindac, naproxen and indomethacin, hold the middle ranking in their toxicity. The relative risks of different NSAIDs at the two ends of the spectrum could differ 10-fold. Besides the nature of the drug itself, toxicity of NSAIDs has also been found to be dose-related.[4,10,16] Some workers believe that the relative safety of ibuprofen could be attributed to the usual low dose prescribed, because this drug is often used in patients with milder diseases.[17,18] The advantage of 'low-risk' drugs may be lost when they are used at high dosages. Prescribing multiple NSAIDs and combining NSAIDs with aspirin will further increase the risk of gastrointestinal complications.

Kelly *et al*. have compared the risk of gastrointestinal bleeding using plain, enteric-coated and buffered aspirin and have found no significant difference between these preparations (relative risks are 2.6, 2.7 and 3.1, respectively).[19] Their finding does not confirm the relative safety claimed by enteric-coated aspirin over soluble aspirin and buffered aspirin in an earlier study.[5] As with non-aspirin NSAID, toxicity of aspirin also increases with dose. The issue of dose-related toxicity was addressed in the UK-TIA Trial, which studied doses ranging from 300 mg to 1200 mg,[6] as well as by Weil *et al*. at the lower range of 75 mg to 300 mg daily.[5] In both studies, dose-dependent toxicity and gastrointestinal complication were demonstrated.

What is the most dangerous exposure time for developing gastrointestinal complications?

Several studies have indicated that patients with a shorter duration of exposure to NSAIDs have an in-

creased risk for the development of gastrointestinal toxicity.[4,9,16] The first month of treatment appears to be the most dangerous period. Intermittent users of NSAIDs are not spared from the adverse effects.[4] Early gastrointestinal bleeding has also been reported in aspirin users irrespective of dose prescribed.[5,6] This increased risk associated with short-term use may be explained by the fact that those who develop gastrointestinal symptoms or complications have discontinued the medication early. There is also evidence suggesting gastric mucosal adaptation to these drugs, thereby reducing the risk in chronic users. One study from Scotland does not agree. In this cohort study by MacDonald *et al.*, the risk of upper gastrointestinal bleeding and perforation was constant during continuous NSAID exposure.[20] Furthermore, the risk of gastrointestinal complications appeared to carry over for some time after discontinuation of the medications. However, the possibility of self-medication with leftover or non-prescribed NSAIDs by the patients cannot be excluded.

INTERACTIONS OF NSAIDS AND *HELICOBACTER PYLORI*

The interactions of NSAIDs and *H. pylori* in the pathogenesis of gastroduodenal ulcers has generated tremendous controversy in recent years. The Working Party addressed this issue by examining the existing evidence on pathophysiological mechanisms and then on clinical studies in the literature.

Acid, mucus, bicarbonate and mucosal blood flow

There are no strong data in the literature to suggest that NSAIDs or aspirin increase gastric acid. In susceptible subjects with antral predominant gastritis, *H. pylori* infection increases gastric acid secretion. Non-steroidal anti-inflammatory drugs and aspirin are well known to reduce the effectiveness of the protection provided by the mucus–bicarbonate barrier as a result of suppressing prostaglandin production. Similarly, *H. pylori* has been shown to reduce the viscosity of gastric mucus.[21] Because both NSAIDs and *H. pylori* appear to adversely affect the integrity of the mucus–bicarbonate layer, together they may further damage the mucosal barrier. Adequate blood flow is essential in mucosal defence and recovery after initial damage. Both NSAIDs and aspirin reduce mucosal blood flow.[22] There are, however, controversial data regarding the effect of *H. pylori* on mucosal blood flow. Two studies using the technique of laser Doppler flowmetry, which is a reasonably good but technically difficult way of measuring blood flow, have provided conflicting data. Taha *et al*.[23] have reported that blood flow may be reduced by *H. pylori* infection and, in contrast, Konturek *et al*.[24] have described an increased mucosal blood flow.

Neutrophil infiltration and inflammatory cytokines

Neutrophils are important in the mediation of NSAID-induced gastrointestinal injury.[25] The association of *H. pylori* with neutrophil infiltration has been widely reported and neutrophils have been suggested as a possible link between NSAIDs and *H. pylori* in the pathogenesis of peptic ulcers.[26] Recent work by Taha *et al*. has shown that of patients who were *H. pylori*-negative, 17% had significant mucosal neutrophil infiltration, whereas in those who were *H. pylori*-positive, 93% had neutrophil infiltration ($P < 0.001$).[27] The cumulative incidence of peptic ulcers in long-term NSAID users was increased in the presence of neutrophil infiltration in the mucosa and most of these inflammatory cells were found in patients who were *H. pylori*-positive. *CagA*-positive strains of *H. pylori* attract more neutrophils and may further aggravate the toxicity of NSAIDs and aspirin.

Inflammatory mediators have received much attention recently. There may be an association between NSAID damage, *H. pylori* infection and cytokines (tumour necrosis factor (TNF)-α and interleukins (IL), notably IL-8).[28] More data are still required on these complex interrelationships.

Prostaglandin production and mucosal adaptation

Non-steroidal anti-inflammatory drugs and aspirin are well known to suppress mucosal prostaglandin production. *Helicobacter pylori* may be associated with an increase of prostaglandin.[24,29] Both studies also looked at the concomitant effect of *Helicobacter pylori* together with NSAIDs. Laine *et al*. have shown that *H. pylori*, together with NSAIDs, causes a marked fall in prostaglandin synthesis,[29] while Konturek *et al*. have reported a similar phenomenon with aspirin.[24] Thus, the stimulatory effect of prostaglandin production by *H. pylori* is insignificant in the presence of NSAIDs or aspirin.

The ability or efficiency of the mucosa to adapt to NSAIDs or aspirin is an intriguing but poorly understood concept. Lipscomb *et al*. have studied adaptation to naproxen in normal volunteers in the presence or absence of *H. pylori*.[30] They found after a 4 week assessment of adaptation by endoscopy that, in *H. pylori*-positive subjects, gastric adaptation was achieved in only 53%, but in *H. pylori*-negative subjects adaptation occurred in 81% ($P = 0.04$). Konturek *et al*. have also found, in volunteers given repeated doses of aspirin and assessed by endoscopy after 2 weeks, that mucosal adaptation is impaired in the presence of *H. pylori*, but is restored after *H. pylori* is eradicated.[24]

In many ways, NSAIDs and *H. pylori* have similar adverse effects on mucosal protective mechanisms and may therefore produce an additive damaging effect when both are present. Evidence from studies on neutrophils and mucosal adaptation also suggest an interrelationship between these factors, which may allow

damage to occur more readily when NSAIDs are taken in the presence of *H. pylori* infection.

Case-control and cohort studies on interactions between *Helicobacter pylori* and NSAIDs

Most of the early reports were based on cross-sectional studies of chronic NSAID users with different background histories and thus generated conflicting results. The confusion arises from variable study design and outcome measurements. Some studies have assessed the prevalence of *H. pylori* in NSAID users with or without mucosal damage whereas others have compared mucosal damage in NSAID users with or without *H. pylori* infection. In a recent meta-analysis of 12 studies, comprising 1901 patients, it has been found that *H. pylori* infection significantly increases the risk of ulcer in NSAID users compared to non-NSAID users and significantly more ulcers are found in *H. pylori*-infected NSAID users than in non-infected NSAID users.[31]

There are six long-term cohort studies in the literature investigating the interactions between *H. pylori* and NSAID usage in the development of peptic ulcers.[27,32–36] Among them, three studies were specifically designed to address this issue[27,32,33] and the others were originally designed to test the efficacy of proton pump inhibitors in NSAID gastropathy.[34–36] All studies showing a positive association between *H. pylori* and NSAIDs were based on patients without acid-suppressive therapy.[27,32,34] The notable exception was the study by Kim and Graham, which failed to demonstrate an increased rate of gastroduodenal ulceration in *H. pylori*-infected NSAID users.[33] However, the study of Kim and Graham excluded patients with erosions at baseline endoscopy and the diagnosis of *H. pylori* infection was based on serology instead of histology. These discrepant findings suggest that selective recruitment of low-risk subjects may have distorted the role of *H. pylori* in NSAID-induced ulcer. In contrast, the negative association reported by the OMNIUM and the ASTRONAUT studies were derived from patients on maintenance acid suppression.[35,36] *Helicobacter pylori*-infected patients were found to fare better in the maintenance phase of the two studies. However, this advantage from *H. pylori*-positivity was not found in the patients who received placebo or misoprostol.

Interventional studies on interaction between *Helicobacter pylori* and NSAIDs

Whether or not eradicating *H. pylori* would affect the incidence of ulcer in patients taking NSAIDs is the key question in the whole issue. Chan *et al*. have assessed the efficacy of prophylactic eradication of *H. pylori* in preventing the subsequent occurrence of ulcers in NSAID naïve subjects (median age over 60) who were about to start NSAIDs.[37] It was found that pretreatment with antihelicobacter therapy markedly reduced the 8 week incidence of ulcers from 26% to 7%. Two studies have evaluated, by endoscopy, the effect of *H. pylori* eradication on ulcer healing and relapse in subjects already on long-term NSAIDs. Bianchi Porro *et al*. have randomized *H. pylori*-positive NSAID users with uncomplicated ulcer to either omeprazole alone or proton pump inhibitor (PPI)-dual therapy for ulcer healing.[38] After ulcer healing, patients resumed NSAIDs for 6 months and ulcer recurrence was monitored. The authors found that eradication of *H. pylori* did not influence the rate of ulcer healing and there was a numerical trend towards a higher rate of ulcer relapse in *H. pylori*-positive patients, but the difference failed to reach statistical significance. In this study, however, the *H. pylori* eradication rate of the antihelicobacter regimen used was very low, at just 56%, and the result was further limited by the small number of patients studied. In a much larger scale study, Hawkey *et al*. have found that curing *H. pylori* infection does not reduce the rate of ulcer relapse in long-term NSAID users.[39] Furthermore, in a subgroup of 41 patients with gastric ulcers detected at baseline endoscopy, eradication of *H. pylori* was associated with delayed ulcer healing. In another prospective randomized study from Hong Kong recruiting 195 patients with *H. pylori* infection and NSAID-associated bleeding ulcers, eradication of *H. pylori* did not impair the healing of either gastric or duodenal ulcers.[40] There is not a good explanation for these divergent findings at the present time. Finally, an ongoing prospective randomized clinical outcome trial comparing *H. pylori* eradication alone versus long-term omeprazole for the prevention of recurrent ulcer haemorrhage in high-risk users of aspirin or non-aspirin NSAIDs has been conducted.[41] Preliminary data has suggested that antihelicobacter therapy alone cannot prevent recurrent ulcer bleeding associated with non-aspirin NSAIDs, whereas curing *H. pylori* alone appears as effective as maintenance omeprazole in preventing recurrent bleeding induced by low-dose aspirin.

Should *Helicobacter pylori* infection be treated in NSAID or aspirin users?

Helicobacter pylori interacts with NSAIDs in different ways. Whether an ulcer will be produced is influenced by factors such as previous exposure to NSAIDs, past or coexisting *H. pylori*-associated ulcers, mucosal neutrophil infiltration, gastric acid output and the use of acid suppressive therapy. Preliminary data suggest that low-dose aspirin and non-aspirin NSAIDs may have different interactions with *H. pylori* in terms of the risk of peptic ulcer haemorrhage. Based on the existing evidence, several recommendations on *H. pylori* eradication are proposed for the prevention of NSAID-induced ulcers (Table 2). For NSAID naïve subjects who also have also high-risk factor(s) for developing NSAID gastropathy (e.g. old age, previous ulcer history), the policy of test-and-treat for *H. pylori* before initiating NSAID therapy is advisable. Testing for *H. pylori* infection would not be necessary for patients who had already been receiving NSAID or aspirin for some time without

Table 2 Recommendations for *Helicobacter pylori*-infected NSAID users

Previous use of NSAIDs	History of ulcer and complications	Known *H. pylori* status	Recommendation
No	No	Negative	Do nothing
	No (with risk factor)		Test and Rx Hp
No	No	Positive	Rx Hp
No	Yes	Positive	Rx Hp + ?
Yes	Yes	Positive	Rx Hp + PPI
			Rx Hp (with ASA)
Yes	No	Positive/negative	Do nothing

NSAID, non-steroidal anti-inflammatory drug; Rx, treatment; Hp, *Helicobacter pylori*; PPI, proton pump inhibitor; ASA, aspirin.

developing adverse events. For those with a past history of NSAID-related ulcers, acid-suppressive agents or misoprostol are indicated even after eradication of *H. pylori*. Although preliminary results suggest that curing *H. pylori* infection alone may be adequate for some patients with ulcer complications associated with low-dose aspirin, more data will be needed.

TREATMENT AND PREVENTION OF NSAID-RELATED ULCERS

Healing of NSAID-related ulcers

The efficacy of ulcer-healing agents for NSAID-related ulcers depends on whether NSAIDs or aspirin can be discontinued during the ulcer-healing phase. There is evidence from animal experiments that NSAIDs retard the healing of gastric ulcers. The same appears to be true with human ulcers. Lancaster-Smith *et al*. have shown that, during treatment with standard dose ranitidine, more than 95% of either gastric or duodenal ulcers were healed in 8 weeks in those who stopped their NSAIDs: approximately 30% more than in those who continued them.[42] Healing rates with a PPI might be expected to be even faster (by analogy with the abundant data on healing of peptic ulcers associated with *H. pylori* infection), but no data are available for NSAID-associated ulcers with NSAIDs stopped. If there is a need for the patient to continue their NSAIDs, there are now several options. Two large studies have now shown faster healing with a PPI than an H_2-blocker or a prostaglandin. The OMNIUM and ASTRONAUT studies have compared omeprazole (20 or 40 mg daily) with ranitidine 150 mg twice per day (b.i.d.) and misoprostol 200 µg four times daily (q.i.d.).[35,36] Proton pump inhibitors healed significantly more ulcers, both gastric and duodenal, than ranitidine or misoprostol. However, there was no extra benefit from using the higher omeprazole dose. Gastric ulcers healed at 8 weeks in 22% and 15% more patients given omeprazole 20 mg daily than ranitidine or misoprostol, respectively. More patients had diarrhea or abdominal pain in the misoprostol group. An earlier, smaller study has also shown that omeprazole heals gastric ulcers much faster than ranitidine.[43]

Prevention of NSAID-related ulcers and erosions

The agents that are proven to reduce the chance of either gastric or duodenal ulceration in patients taking NSAIDs are the same as those described earlier for healing. Cotherapy with one of these agents is not a guarantee that ulceration will not develop, but the protection offered by particularly PPI and misoprostol is quite high.

Histamine H_2-receptor antagonists

A drug from this class has often been prescribed with an NSAID, in the belief it will offer protection against gastroduodenal damage. There is good evidence that these agents reduce the risk of NSAID-associated duodenal ulcers, but the protection against gastric ulcers is much lower. In three large, randomized controlled trials with standard dosage ranitidine or famotidine, the incidence of duodenal ulcers was markedly reduced but there was no significant protection against gastric ulcers.[44–46] The protection conferred by these agents is considered inadequate, because gastric ulcers are the more common outcome of NSAID treatment. However, double-dose famotidine has been found (in one study) to significantly reduce gastric ulcers as well, by approximately 50% in high-risk patients and approximately 65% in those without prior ulcers.[46]

Prostaglandins

There have been many randomized controlled trials using misoprostol as a protective cotherapy. The first published study found a 90% reduction in ulceration compared with placebo over a 3 month period in NSAID users. The misoprostol dose was 200 µg q.i.d. for most patients.[47] Most subsequent studies have used 400–600 µg per day and have found reductions in ulcer incidence in the range 50–75% over 3–12 months.[48,49] The level of protection has generally been similar for both gastric and duodenal ulcers. Misoprostol has also been formulated in a compound tablet containing both diclofenac and misoprostol. This combination has the advantage for some patients that compliance is obligatory. It is not possible to forget the 'antidote' to the

NSAID and neither is there the chance of futilely taking the prostaglandin and forgetting the NSAID.

Proton pump inhibitors

Four randomized controlled trials lasting 3–6 months have now been performed with omeprazole 20 mg daily.[34–36,50] These have shown quite high efficacy for preventing both gastric and duodenal ulcers, with about a 75–80% reduction in ulcers compared with placebo. Two of the studies have compared omeprazole with either ranitidine (150 mg b.i.d.) or misoprostol (200 μg b.i.d.).[35,36] The PPI prevented significantly more ulcers (gastric and duodenal combined) than the H_2 blocker or the prostaglandin, although the efficacy against gastric ulcers was not significantly different between these doses of omeprazole and misoprostol. One smaller study on patients with history of gastric ulcer, but no current peptic ulcer, has reported similar protective effective effects with lansoprazole 15 or 30 mg or misoprostol 800 μg daily.[51]

What is the efficacy of these agents for preventing complicated ulcers?

A large case-control study in the USA has found that patients taking NSAIDs concurrently with an H_2 blocker (most were taking cimetidine) are no less likely to present to hospital with ulcer complications[3] than those not taking cotherapy. Another very large blinded study with misoprostol versus placebo (the 'MUCOSA' study) has found a significant reduction in GI bleeding events (by about 40%) and ulcer perforations (90%).[52] In this study, misoprostol was given at 800 μg daily and 27% of patients withdrew from the therapy because of side-effects (primarily diarrhoea). The PPI has been studied for its efficacy of protecting complicated ulcers in the context of *H. pylori* infection in one study.[41] Significantly less ulcer bleeding has been reported in patients treated by omeprazole 20 mg daily compared with those receiving antihelicobacter therapy without PPI.

Are side-effects a major problem with misoprostol?

Diarrhea and abdominal cramps have been consistently reported as side-effects of misoprostol in controlled trials. The working party concluded that the importance of these is sometimes overstated, especially when the misoprostol dose is lower than 800 μg daily. In most studies, including the MUCOSA study, the incidence of diarrhoea has been in the range of 5–10% more than on placebo. The incidence of withdrawal for adverse effects of misoprostol is significantly lower when a lower dose (400–600 μg daily) is given.[53] In the maintenance phase of the large OMNIUM study (misoprostol dose 400 μg daily), diarrhea was only slightly more common in the misoprostol arm, a mean difference of 0.2 on a 7 point scale ($P = 0.04$).[35] The Working Party concluded that side-effects are usually not a major problem with misoprostol.

How should the risk of gastrointestinal complications from 'low-dose' aspirin be reduced?

No data are available on this situation. By analogy with the trials using full-dose conventional NSAIDs, a PPI or a prostaglandin should give protection, but this is an inference. There is clearly a need for research, especially because the use of vascular-protective aspirin doses is increasing steadily and the relative risk of complications is similar to those with many other NSAIDs.

CYCLO-OXYGENASE-II INHIBITORS

The new millennium marks the second century of aspirin and its role as an anti-inflammatory, analgesic and antithrombotic agent. The discovery in the early 1990s that there was a second and inducible form of cyclo-oxygenase, known as Cox-II,[54,55] led to a target approach by the pharmaceutical industry to develop Cox-II-specific inhibitors. There are differences between Cox-I and Cox-II, indicated by their structures, with Cox-II being highly inducible while Cox-I is constitutively expressed.[56] A variety of *in vitro* and *in vivo* animal studies have shown that specific Cox-II inhibition is both anti-inflammatory and analgesic.[57,58] Interest from the pharmaceutical companies has been significant, because the potential market for NSAIDs is in excess of US$13 billion per annum and drugs that might provide all the activities of the currently available non-selective NSAIDs without having the potential for adverse reactions would be of considerable advantage. At the present time, however, the long-term safety of Cox-II specific inhibitors is still not clear, because studies using clinical outcome as the primary end-point are not yet available. What is clear is that there are differences between currently available and new NSAIDs in their capacity to inhibit Cox-I and Cox-II, although there is variability in the reported results. This variability is due in part to the wide variety of *in vitro* assay systems and parameters used, such as incubation time, the presence of exogenous and endogenous substrate, the use of whole cells or microsomes and the presence or absence of plasma proteins in the medium. This has led to the suggestion that the ideal system for estimation of Cox activity should contain human isoforms of the enzyme, whole-cell endogenous substrate and allow testing of each isoform separately. At the present time, the human whole blood assay, as developed by Patrignani *et al.*, would seem most appropriate as the definitive test for Cox-I and Cox-II activity, because this will provide data on the inhibition of both enzymes in a reproducible fashion.[59] As Hawkey has pointed out, future studies may also involve the non-inhibition of human gastric prostaglandins as part of the assessment

process.[60] However, it must be emphasized that the *in vitro* selectivity of various selective COX-II inhibitors is only of secondary importance. It is the ratio of the therapeutic dose to the toxic dose of the drug that is clinically important.

How should a specific Cox-II inhibitor be defined?

A Cox-II-specific inhibitor should demonstrate anti-inflammatory and analgesic effects and have a significant reduction in the side-effect profile, particularly the gastrointestinal side-effects. To be defined as a Cox-II-specific inhibitor, a drug should be able to demonstrate suppression of Cox-II but no inhibition of Cox-I throughout the plasma concentration range seen at maximum therapeutic dosing. This definition of Cox-II specificity provides a simple way of differentiating agents on pharmacodynamic grounds, but it does not necessarily imply that Cox-II-specific agents have an improved safety profile. The benefits of Cox-II-specific agents need to be demonstrated through randomized clinical trials. Because the NSAIDs are such a well-recognized group of drugs with well-defined therapeutic applications, it is considered that the Cox-specific inhibitors (CSI) should probably become a subcategory of NSAIDs rather than being separated as a different class.

What is the impact of Cox-II inhibition in musculoskeletal diseases?

Some of the preferential Cox-II inhibitors, such as meloxicam and nimesulide, have been shown to be equivalent to non-selective NSAIDs in trials in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[61,62] Data are now becoming available to show that the Cox-II-specific inhibitors celecoxib and rofecoxib are equally effective to non-selective NSAIDs in relieving pain in musculoskeletal diseases. Both demonstrate short-term analgesic effects in the dental pain model following tooth extraction when compared to ibuprofen and placebo[63] or aspirin and placebo.[64] In studies of osteoarthritis of the knee and hip, a 6 week placebo-controlled study has shown rofecoxib at doses of 12.5, 25 and 50 mg to be more effective than placebo as assessed by the WOMAC Pain Index, Stiffness and Disability subscales.[65] Celecoxib, at doses of 40, 100 and 200 mg twice daily, showed a greater decrease in joint pain than placebo in a 2 week study of osteoarthritis of the knee.[66] In rheumatoid arthritis, celecoxib at 200 and 400 mg twice daily was superior to placebo for patient global assessment and tender or painful joints over a 4 week period.[66] Long-term studies are now becoming available with a 1 year trial of rofecoxib at 12.5 and 25 mg daily compared with diclofenac 75 mg twice daily in patients with osteoarthritis of the hip or knee. In this study, rofecoxib has been shown to be no different from diclofenac for all efficacy outcome measures.[67]

In summary, the specific and preferential Cox inhibitors seem to be no different from non-selective, non-steroidal NSAIDs in the management of musculoskeletal pain.

Are Cox-II inhibitors less gastrotoxic than standard NSAIDs?

Data on clinical trials with meloxicam suggest that it may be associated with a slightly lower incidence of drug-related upper GI adverse events compared with placebo and piroxicam.[61] In the larger studies, MELISSA and SELECT, meloxicam has been compared to diclofenac and piroxicam for its gastrointestinal tolerability.[68,69] While most of the GI adverse events (dyspepsia, nausea and vomiting, abdominal pain and diarrhea) are significantly less common with meloxicam, there is no statistically significant difference in the number of patients with upper gastrointestinal bleeding, ulcers or perforations.[70]

Short-term endoscopic studies with both celecoxib and rofecoxib have shown a significant reduction in the incidence of endoscopically proven gastric lesions, but the majority of these studies are of 1–4 weeks' duration. In a study of healthy volunteers receiving 10–20 times the clinically effective dose of rofecoxib, gastrointestinal damage as measured by the Lanza score was no different from placebo and significantly less than with ibuprofen or aspirin.[71] Similar data have been reported with celecoxib, with no gastric or duodenal ulcers developing in patients receiving placebo or celecoxib while nine gastric ulcers have been reported in patients receiving naproxen.[66] Large-scale endoscopic studies of 24 weeks' duration in patients with osteoarthritis and over the age of 50 have demonstrated a lower incidence of endoscopic ulcers in the rofecoxib-treated patients (at 25–50 mg) compared with ibuprofen use.[72] There is no evidence that rofecoxib additionally enhances gastric injury in subgroups of patients with baseline erosions. Pooled clinical data have also shown that both rofecoxib and celecoxib produce less clinically significant upper gastrointestinal events (perforations, ulcers and bleeding) than non-selective NSAIDs with safety profiles equivalent to placebo.[73,74]

There is no evidence that celecoxib or rofecoxib interferes with platelet Cox-I production and prolongs bleeding time.[57,75] Although early studies suggested that Cox-II was only induced at sites of inflammation or uncontrolled cellular proliferation, Cox-II is also expressed constitutively in the kidney. Studies on healthy volunteers have shown that Cox-II-specific inhibitors cause acute sodium retention but do not reduce the glomerular filtrate rate.[76] The renal safety of Cox-II-specific inhibitors in at-risk patients would require further investigation. The role of Cox-I inhibition on cardiovascular protection is an important one, because the Cox-II-specific inhibitors would not have this effect. It may well be necessary to continue some Cox-I inhibition in the form of low-dose aspirin to reduce the current epidemic of coronary heart disease and this may negate some of the reduced GI toxicity seen with Cox-II-specific inhibitors.

Currently available data suggest that Cox-II-specific inhibitors are less gastrotoxic than standard NSAIDs, but the data are still limited, particularly in the at-risk groups of those patients who are elderly, have had a previous history of GI complications and are on corticosteroids.

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APPENDIX I

Attendees at the Asia Pacific Working Party on NSAID and GI Toxicity: Epidemiology and New Developments

Prof. Peter Brooks, Royal Brisbane Hospital, Herston, Qld and Prof. Neville D Yeomans, The University of Melbourne Department of Medicine, Western Hospital, Footscray, Vic., Australia; Prof. Chen Shun-Le, Department Rheumatology, Ren-Ji Hospital and Prof. SD Xiao, Shanghai Institute of Digestive Diseases, Shanghai, China; Dr Francis KL Chan, Department of Medicine, Prince of Wales Hospital and Prof. Joseph Sung (Co-Chairman), Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Dr Lau Chak-sing, Division of Rheumatology & Immunology, Department of Medicine, Queen Mary Hospital, Hong Kong; Prof. Ken Kimura, Department of Endoscopy, Jichi Medical School, Tochigi, Japan; Prof. KL Goh, Division of Gastroenterology and Hepatology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia; Prof. Jose Sollano, Department of Gastroenterology, University Santo Thomas Hospital, Manilla, Philippines; Prof. KM Fock, Division of Gastroenterology, Department of Medicine, New Changi Hospital, Singapore; Prof. Pinit Kullavanijaya, Gastroenterology Unit, Department of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand; Prof. Japie Louw, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; Prof. Robin Russell, Bearsden, Glasgow, Scotland; Prof. George Triadafilopoulos, Stanford University, Palo Alto, California, USA.