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Prophylaxis and Treatment of NSAID-Induced Gastroduodenal Disorders

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Contents

Abstract

A significant percentage of patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) experience some type of adverse gastrointestinal symptoms, lesions of the gastroduodenal tract being clinically the most relevant.

NSAIDs cause gastrointestinal damage by 2 independent mechanisms: a topical effect, which is pH and pKa related, and a systemic effect mediated by cyclo-oxygenase (COX) inhibition with a reduction in prostaglandin synthesis. Using endoscopy, gastroduodenal lesions identified include subepithelial haemorrhages, erosions and ulcers. The prevalence of ulceration in NSAID users has been reported as being between 14 and 31% with a 2-fold higher frequency of gastric ulcers compared with duodenal ulcers.

Among the strategies used to decrease the risk of ulcer development are: (i) the use of analgesics other than NSAIDs; (ii) use of the lowest possible dosage of NSAID; (iii) the use of a COX-2 selective NSAID; (iv) the use of low doses of corticosteroids instead of NSAIDs; (v) avoidance of concomitant use of NSAIDs and corticosteroids; and (vi) use of preventive therapy.

In an attempt to reduce the incidence of NSAID-induced gastrointestinal lesions, the following approaches have been proposed: (i) use of the prostaglandin analogue misoprostol, which is an antiulcer drug which has been proven to be as effective in the prevention of NSAID-induced gastric and duodenal ulcers as in the reduction of serious upper gastrointestinal complications; (ii) histamine H_2 receptor antagonists (H_2 antagonists), e.g. ranitidine, cimetidine and famotidine, which are useful in the prevention of NSAID-induced duodenal ulcers during long term treatment, but not in the prevention of NSAID-induced gastric ulcers; (iii) proton pump inhibitors, e.g omeprazole, and pantoprazole, whose efficacy in preventing NSAID-associated ulcers has been recently demonstrated; and (iv) barrier agents, e.g. sucralfate, which cannot be recommended as prophylactic agents to prevent NSAID-induced gastropathy.

The first step in the treatment of NSAID-associated ulcers lies in a reduction in the dosage of the NSAID or discontinuation of the drug. If NSAID treatment cannot be withdrawn, a proton pump inhibitor appears to be the most effective treatment in healing ulcers, accelerating the slow healing observed with H_2 antagonists.

A significant percentage of patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) experience some type of adverse gastrointestinal symptoms, ranging from dyspepsia to generalised abdominal discomfort. Fortunately, the vast majority of these symptoms are expressions of minor mucosal lesions that are not of major clinical significance, but unfortunately there is poor correlation between dyspeptic symptoms and endoscopic or histological findings.[1]

This means that patients without gastrointestinal lesions may complain of abdominal pain or discomfort during NSAID therapy and conversely, up to 50% of patients with NSAID-induced ulcers or haemorrhagic and erosive lesions in the stomach or in the duodenum may be completely asymptomatic.[2] A life-threatening complication (severe bleeding or perforation) may be the first sign of gastrointestinal damage in asymptomatic NSAID users.[3]

The relative risk of severe complications (massive haemorrhage and perforation) is between 2 to 4 times greater for NSAIDs users than non users.[4] However, the absolute risk (the percentage of patients presenting the complication in the population exposed to NSAIDs) is low: Fries et al.[4] reported a risk of gastrointestinal hospitalisation of 1 to 1.5% per year, with the risk of death being 0.13% per year; Lichtenstein et al.[5] reported an estimated incidence of serious adverse gastrointestinal events at 1 to 2 per 1000 NSAID users per year, with rates ranging from 0.4 per 1000 in the young to 4 per 1000 in the elderly. Finally Champion et al.[2] estimated that the risk of NSAID-related peptic ulcer complications may be low, perhaps 1 in 3000 to 5000 NSAID prescriptions issued in the elderly. Although these seem low risk percentages, due to the great number of NSAID users the final data became numerically relevant. Moreover, the relative and absolute risk rises considerably in elderly patients who are also the patient group who are most exposed to NSAID use.

Although any tract of the small and large intestine may be damaged by NSAID use, the lesions of the gastroduodenal tract (so called 'NSAID gastropathy') are the most frequent and important.

1. Pathogenesis of Nonsteroidal Anti-Inflammatory Drug (NSAID)-Induced Gastrointestinal Lesions

NSAIDs cause gastrointestinal damage by two independent mechanisms: (i) a topical effect, which is pH and pKa related; and (ii) a systemic effect which is mediated by cyclo-oxygenase (COX) inhibition and thus prostaglandin synthesis.[6] Prostaglandins exert different mucosal protective effects, which include increased secretion of bicarbonate and mucous, enhanced resistance of the surface epithelium to injury, mucosal restitution and the preservation of mucosal microvasculature.[7]

The topical effect is due to the nature of weak acid of many NSAIDs. The vast majority of NSAIDs are weak acids with an ionised constant (pKa) in the range of 3 to 5. In the strongly acid environment of gastric juice these drugs are nonionised and freely diffuse across the cell membrane into the cytoplasm of mucosal cells. Once inside the cell, the neutral pH promotes dissociation in the ionised form, that is unable to cross the cell membrane (ion trapping).[6] Because the nonionised form remains in equilibrium across the cell membrane, the total intracellular drug concentration (ionised + nonionised) will be much higher than outside the cell.[8] The accumulation of ionised NSAIDs would mediate an uncoupling of mitochondrial oxidative phosphorylation.[9] However, at neutral intracellular pH, NSAIDs with lower pKa have to be present in a higher concentration to uncouple mitochondrial oxidative respiration. For this reason aspirin (acetylsalicylic acid) [pKA 3.5] freely accumulates into the gastric cells, but requires a higher concentrations to across the mitochondrial membrane to uncouple the oxidative chain, while piroxicam (pKa 6.3) requires lower concentration to induce the same level of uncoupling.[9] The consequent reduction of ATP levels leads to loss of cytoskeletal control over tight junctions and increased mucosal permeability.[9] On the other hand, the inhibition of prostaglandin synthesis (via systemic effect) impairs mucosal repair and microvascular blood flow. Regarding this last aspect, the development of frank ulcers may be predominantly the result of a severe restriction in mucosal blood flow.

The reduction of the mucosal blood flow is preceded by the formation of leucocyte aggregates (white thrombi) adhering to the endothelial cells. Neutrophil adherence to the vascular endothelium and the subsequent activation with release of oxygen-derived free radicals and proteolytic enzymes has been considered a critical event in the pathogenesis of NSAID-induced gastrointestinal ulceration.[10,11] NSAID-induced damage can be prevented by neutropenia or prevention of neutrophil adherence.[10] NSAID administration upregulates the expression of adhesion molecules on the leucocyte cell surface, an effect related to the inhibition of prostaglandin production.[10,12] Furthermore, recent evidence suggests that NSAIDs may delay the healing of a gastric mucosal ulcer, by suppressing hepatocyte growth factor production via inhibition of endogenous prostaglandin production.[13]

The topical and systemic effects together facilitate the development of a tissue reaction that can determine gastrointestinal inflammation and ulcer development.

The NSAIDs that are not weak organic acids (e.g. nabumetone), and drugs that are enteric coated (thereby bypassing a local effect on the upper gastrointestinal mucosa), might theoretically have less topical effect on the gastroduodenal mucosa.[14] Although enteric-coated aspirin preparations reduce the superficial gastroduodenal mucosal injury, the risk of ulcer development may not be reduced. Instead, the enteric coated drugs exert a toxic effect lower in the colon or small bowel. Here, however, the higher pH reduces the amount of drug that penetrates the mucosal layer.[15] In addition, various NSAIDs (e.g. indomethacin, naproxen, diclofenac, piroxicam) are secreted in the bile and having an enteropathic recirculation can once again produce topical damage.[16] Uncoupling of oxidative phosphorylation only occurs within the intestinal epithelium following ingestion or from the biliary excretion phase. This is because of the micromolar concentrations that are

required to uncouple. This uncoupling is not achieved in other cells since over 99% of the drug is protein bound following absorption. As a consequence, an effective free concentration of the drug is only in the picomolar range (sufficient to inhibit COX).[17]

2. NSAID-Induced Gastropathy

The gastroduodenal endoscopically visible lesions induced by NSAIDs use may be labelled 'NSAID gastropathy' and range from erythema through diffuse erosions and microbleeding to ulcers. An ulcer is a defect that penetrates the muscolaris mucosae into the submucosa, or deeper among large vessels. Erosion and subepithelial haemorrhages are breaks that remain confined to the mucosa.[18]

For this reason, only an ulcer may be responsible for massive haemorrhages when it erodes into arteries below the mucosa. Haemorrhagic or erosive gastropathy has been considered the cause of serious bleeding in only 3% of cases, and virtually never leads to life-threatening haemorrhage or large transfusion requirements[19] in the absence of major coagulation defects.

The endoscopic distinction between ulcer and erosion is made on the size and shape rather than on depth, as depth is a parameter that is difficult to evaluate. The chance of a lesion being an ulcer increases with lesion size: small lesions (<3mm) are more likely to be shallow lesions, whereas larger lesions (>5mm) are more likely to be deeper ulcers. In spite of its great importance, the specific size cut-off point to define ulcers is arbitrarily selected on the basis of speculation. Studies on drug efficacy and ulcer prevalence generally use size as the only criterion for an ulcer, so the selected cut-off size may greatly influence the results.

The prevalence of ulceration in NSAID users has been reported to be between 14 and 31%[20-22] with a frequency of gastric ulcer 2-fold that of duodenal ulcer but with a similar risk of bleeding.[23] Various meta-analysis studies have concluded that risk factors for adverse ulcer complications are: (i) age >60 years; (ii) history of previous gastrointestinal events; (iii) concomitant use of corticosteroids; (iv) increasing dose of NSAID; and (v) <1 month of NSAID use.[24-26] This last factor may be due to gastric adaptation which occurs with prolonged use of NSAIDs,[27] a still much debated issue.[28] This and other defence mechanisms become stronger with time, making the mucosa more resistant to the noxious agents. It is conceivable that either the lack of or the overcoming of these defence mechanisms determines the onset of the ulcer and the consequent complications. Unfortunately, little is known about the adaptation of the mucosa towards the damaging stimuli, but it is probable that local growth factors (i.e. epidermal growth factor) and products of metabolism such as nitric oxide (NO) may occur.[29]

Other risk factors for adverse ulcer complications include: (i) the use of two or more NSAIDs; (ii) the use of anticoagulant therapy; and (iii) the presence of concomitant disease (such as rheumatoid arthritis or cardiovascular disease). Other potential variables such as smoking, the ingestion of caffeine and alcohol (ethanol) have been considered as potential risk factors but the data are neither conclusive or clear.[30]

Two distinct types of NSAID-associated ulcers have been distinguished: 'virgin' ulcers occurring *de novo* in persons with a normal mucosa, and ulcers exacerbated by such drug use in persons with an underlying ulcer diathesis. Since the typical NSAID-associated ulcer is a gastric ulcer, while peptic ulcers are mostly duodenal, it is probable that a significant number of duodenal ulcers in NSAID-treated patients, are exacerbated ulcers.[20]

Histologically, a non-NSAID–associated gastric ulcer is surrounded by a wide field of non-erosive inflammatory gastritis often associated with *Helicobacter pylori* infection. NSAID-associated ulcers are often without associated gastritis, but definitive data on the histological aspect of NSAID gastropathy is not fully known.[31] Recent data suggests that the so called chemical gastritis is more frequent in NSAID users.[32] This term conveys an image of chemical injury and highlights the non-infectious nature of this entity. The typical fea-

tures of chemical gastritis are a paucity of inflammatory cells, oedema, telangiectasia and increased numbers of smooth muscle fibres in the lamina propria and foveolar hyperplasia. However, the sensitivity and specificity of these features are reported to be low, not allowing a comparison among different studies.[33]

3. *Helicobacter pylori* Infection and NSAID Use

H. pylori and NSAIDs are the 2 most common exogenous factors in the pathogenesis of peptic ulcer disease. The mechanisms involved in mucosal damage are totally different. NSAIDs cause ulcers by interfering with mucosal defence via direct toxic effects in concert with COX-1 inhibition and consequent depletion of endogenous prostaglandins. *H. pylori* resides in the mucous layer of the gastric cells without invasion and directly produces an increase in gastrin levels with a consequent increase in acid level both directly and via a variety of toxins and enzymes. This is believed to be the explanation for the development of gastric-metaplasia in the duodenum, thus allowing *H. pylori* to infect the duodenum and cause inflammation with subsequent ulcer formation.[16] These pathogenetical differences are highlighted by the different histological picture. In fact, an *H. pylori* ulcer is always surrounded by a wide field of inflammatory cells (chronic active gastritis) while an NSAID-associated ulcer often occurs without associated active gastritis.

Nevertheless, the presence of these 2 factors at the same time is quite frequent, especially in elderly patients in whom *H. pylori* infection is more frequent as is NSAID use.[33] The relationships between NSAID use, *H. pylori* infection and gastric damage are not well understood. It is well established that the susceptibility to *H. pylori* infection is not increased by NSAID use of brief or long duration.[34] Our experience suggests that NSAIDs might impair the development of *H. pylori* infection without having any effect on the infection when it is already established.[35] Nevertheless, a mucosa already damaged by *H. pylori* infection might be more susceptible to the toxic effects of NSAIDs.

A recent study[36] has established that eradication of *H. pylori* infection before starting NSAID therapy reduces the occurrence of gastroduodenal ulcers in patients not previously taking NSAIDs. However, other studies do not support the concept that *H. pylori* infection predisposes to or worsens NSAID-induced gastric injury.[37,38] For example, a recent study investigated the effects of *H. pylori* eradication in patients with current or previous NSAID-effects (ulcers or dyspepsia or both) who continued to use NSAIDs.[39] Patients were given omeprazole with either anti–*H. pylori* therapy (amoxicillin plus clarithromycin for 1 week) or placebo. They then took omeprazole until their ulcer was healed or the dyspepsia resolved, after which they continued NSAID treatment, with follow up assessment of ulcers and symptoms at 1, 3, and 6 months. The only difference between *H. pylori* eradicative therapy and omeprazole alone was that gastric ulcers healed faster if *H. pylori* was not treated. Duodenal ulcers healed within the same time frame in both groups. Thus, *H. pylori* eradication did not alter the outcome in terms of recurrence of ulcers or dyspepsia.

This data is substantially in agreement with 2 other recent studies,[40,41] comparing the efficacy of omeprazole versus misoprostol and ranitidine respectively, in healing and preventing ulcers associated with NSAIDs. Higher rates of success were found in *H. pylori* positive patients than in those who were negative. The better prognosis in infected patients may be due to the stimulatory effect on the mucosal prostaglandin synthesis operated by *H. pylori* (an effect, however, easily overcome by NSAIDs) so partly reversing the defect in the gastric mucosa caused by NSAID and improving healing of NSAID ulcers.[42,43]

In peptic ulcers related to *H. pylori* infection, eradication of the infection leads to a fundamental change in the natural history of the disease: eliminating recurrence and curing the illness. Eradication of *H. pylori* infection in individuals without ulcers is not recommended. However, if an in-

fected individual has to take NSAIDs chronically, eradication of *H. pylori* might be a practical option. If *H. pylori* is present in a patient who develops an ulcer whilst taking NSAID, it remains unclear whether it is beneficial to eradicate the infection or not, but this seems advisable in case the ulcer is due to the infection in that particular patient.[44] Further studies need to be done on the fundamental process behind such ulcers so that the degree of mucosal defect by NSAIDs or *H. pylori* or both can be assessed in an individual. Hence therapy can be customised.

In populations among whom peptic ulcer disease induced by *H. pylori* is common, the patients will probably benefit more from *H. pylori* eradication than from other antiulcer measures, irrespective of NSAID use. Conversely, among patients with asymptomatic *H. pylori* infection, ulcers in patients taking NSAIDs may benefit more from acid reduction or prostaglandin therapy alone, without eradication of *H. pylori*.[45] In the future, typing of the *H. pylori* infection as cytoxin-associated gene A (CagA) positive or negative (which reflects cytotoxin production)[46] will help in therapeutic decision-making in western countries, where these virulence factors are important in the induction of duodenal ulcer disease. In developing countries, where CagA positive isolates predominate, typing of the *H. pylori* will be irrelevant[47]

4. Prevention of NSAID-Associated Gastropathy

There are many strategies that can theoretically decrease the risk of ulcer development and its complications (see table I).

4.1 Use of Non-NSAID Analgesics

Use of non-NSAID analgesics, such as paracetamol (acetaminophen) or tramadol instead of an NSAID can be investigated. In chronic inflammatory articular diseases, such as rheumatoid arthritis, these drugs are not very effective. However, as a support to an NSAID, their use can permit the reduction of NSAID dosage.[48] According to the American College of Rheumatology, non-NSAID analgesics are considered as first line therapy in osteoarthritis of the knee or hip.[49,50]

4.2 Use of the Lowest Possible Dose of NSAID

The incidence of untoward events and the degree of anti-inflammatory activity are both dose related.[51] The dose-response curves for anti-inflammatory activity and for analgesia can differ. For example ibuprofen 200mg has no anti-inflammatory activity but does have an analgesic effect.[52] Low doses of ibuprofen (≤1200mg) are reported to be the best tolerated in comparison to other NSAIDs in most studies but higher doses lose this advantage.[53] Aspirin 650mg has no anti-inflammatory activity either.[51] Many studies have reported that decreasing the daily dose of aspirin also decreases the risk of gastrointestinal complications, but nevertheless any dose of aspirin still has the potential to induce gastric lesions and gastrointestinal complications.[54-56] Due to considerable interpatient variation in the response to NSAIDs, low doses of a given drug may be effec-

Table I. Prevention and therapy of nonsteroidal anti-inflammatory drug (NSAID)–induced gastropathy

Measures to prevent NSAID-induced gastropathy
Preventive measures:
use a non-NSAID analgesic instead of an NSAID
use the lowest dose of NSAID
use low doses of a corticosteroid instead of an NSAID
Identify patient at risk. Risk factors are:
age >60 years
history of previous gastrointestinal events
concomitant use of corticosteroids
increasing dose of NSAID
use of 2 or more NSAIDs
use of anticoagulant therapy
presence of concomitant chronic disease (i.e. rheumatoid arthritis)
In patients with risk factors consider preventive therapy with:
misoprostol
omeprazole
Therapy of NSAID-induced ulcer
If NSAID can be discontinued: any conventional 'antiulcer' therapy is effective
If NSAID can not be discontinued: omeprazole seems the most effective therapy

tive in an individual with a chronic inflammatory rheumatic disease. In this respect, the average aspirin dose taken by patients with rheumatoid arthritis was reported to be only 2665 mg/day.[57] Low doses of any NSAID might also facilitate the mechanisms of mucosal adaptation (see section 2).

4.3 Use of NSAIDs with Improved Gastrointestinal Adverse Effects Profiles

4.3.1 Cyclo-Oxygenase-2 Selective NSAIDs

It is now recognised that there are at least 2 isoforms of COX often abbreviated as COX-1 and COX-2.[58,59] COX-1 is a constitutive enzyme that is present in virtually almost all tissues under basal conditions, performing a 'housekeeping' function to synthesise prostanoids that regulate normal activity.[60] For example, COX-1 plays a key role in regulating gastrointestinal mucosal protection, vascular homeostasis and renal functions. COX-2 is an inducible enzyme, whose expression is increased during states of acute inflammation or experimentally in response to mitogenic stimuli and cytokines and decreased by the administration of glucocorticoids.[56,61] COX-2 is, however, present under basal conditions in the brain, spinal cord and renal cortex.[62]

All the currently available NSAIDs inhibit both COX-1 and COX-2 to varying degrees. Inhibition of the constitutive COX-1 is believed to be the primary cause of the many toxic effects associated with NSAIDs, particularly gastroduodenal mucosal damage, whereas COX-2 inhibition explains the therapeutic utility of NSAIDs.[61] The availability of NSAIDs which specifically inhibit COX-2 should maximise anti-inflammatory activity while minimising adverse effects. In contrast, NSAID exhibiting preferential activity for COX-1 would be expected to be less effective and to be associated with additional adverse effects.

Enzyme inhibitors are described according to their efficiency in inhibiting enzyme activity. The most common variable is the IC_{50}, which is the concentration need to produce 50% inhibition of COX activity. Drugs with a high IC_{50} are less potent than drugs with a low one. The different potency against COX-1 and COX-2 can be expressed as a ratio of the IC_{50} values so that the COX-2/COX-1 ratios <1 indicate a more potent inhibition of COX-2. However, to completely inhibit COX-2 without affecting COX-1, a specific COX-2 inhibitor NSAID would need to be at least 100 times more potent against COX-2 than against COX-1.[62] This corresponds to a COX-2/COX-1 ratio of 0.01 or lower.

Unfortunately, there is great variability in the IC_{50} values obtained for individual NSAIDs in different studies, due to the different *in vitro* methods for assessing the relative affinity and selectivity of the NSAID for COX-1 and COX-2 activity (homogenate or recombinant enzymes, whole cell systems, substrate concentration, incubation and preincubation time, etc.). Hence, at the moment, many difficulties exist in interpreting[63-65] *in vitro* results, which should be considered only guidelines for *in vivo* situation. For example, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furan (DFU), a novel, orally active and highly selective COX-2 inhibitor, has been found to be 1000 fold more selective for COX-2 than COX-1 in Chinese hamster ovary cells stably transfected with human COX enzymes, but this compound shows a time dependent and reversible weak inhibition of COX-1 using other sensitive assays.[66] These results indicate that using different assays, COX-1 inhibitory effects can be also detected in compounds that are considered to be highly selective COX-2 inhibitors.

Many 'old' NSAID are mainly COX-1 selective (e.g. aspirin, ketoprofen, indomethacin, piroxicam, sulindac), others are considered slightly selective for COX-1 (e.g. ibuprofen, naproxen, diclofenac), others may be considered slightly selective for COX-2 (e.g. nimesulide, etodolac, nabumetone, meloxicam). None of the available NSAIDs is wholly COX-2 specific.

Moreover, with the currently available NSAIDs, no differences in clinical efficacy are evident between NSAIDs that exhibit preferential activity for either COX-1 or COX-2. NSAIDs representing the extremes in terms of selectivity for

COX-1 or COX-2 do exhibit some differences with respect to gastric safety; those exhibiting preferential COX-2 selectivity are generally less toxic than those exhibiting a preferential COX-1 selectivity.[67,68] Because a strict correlation does not exist between COX selectivity and gastric safety, it is possible that both the safety and the efficacy of NSAID may result from mechanisms distinct from prostaglandins inhibition.[69]

This conclusion has however to be re-evaluated with new specific COX-2 inhibitor NSAIDs, such as celecoxib (recently launched in the US, Mexico, Brazil, Argentina and Switzerland), flosulide or DFU.[66,69] These might be a true specific NSAIDs[70,71] but COX-2 inhibition does not address other mechanisms of gastrointestinal damage, e.g. the topical mucosal toxicity. However, the long term effects and adverse effects of these new NSAIDs must be carefully scrutinised before they become widely used.

The possible roles of COX-2 in the physiological process and the consequences of its inhibition are largely unknown. It is likely that COX-2 expression increases after salt restriction and also it is likely that COX-2 plays a critical role in the development of the kidney since the lack of COX-2 gene (COX-2 knockout mice) is associated with severe congenital renal abnormalities.[72,73] COX-2 may play an important role in the healing of gastric ulcers. In rats, the healing of gastric ulcers is delayed by NS-398 (a COX-2 selective inhibitor). The expression of COX-2 mRNA was only detected in the ulcerated tissue in which the COX-2 enzyme was found in fibroblasts, macrophages/monocytes and granulocytes. The delay in ulcer healing after NS-398 administration was related to the inhibition of prostaglandin E_2 in the ulcerated tissue.[74] Similar results have been detected with L-745337 another selective COX-2 inhibitor.[75] At the moment the possible adverse effects of the highest therapeutic doses of specific COX-2 NSAIDs are unknown.

4.3.2 Future NSAIDs

Over the next few years new NSAIDs, other than COX-2 specific inhibitors, showing reduced adverse effects, particularly in the gastrointestinal tract, will probably be available as valid therapeutic alternatives. Examples of these new drugs are the nitric oxide-releasing NSAIDs (NO-NSAIDs) such as NO-naproxen, NO-aspirin, etc. In experimental models NO-aspirin, although it inhibits both COX-1 and COX-2 activity, had no deleterious effects on the gastric ulcerogenic and healing process. It shows, nevertheless, an anti-inflammatory effect that is equipotent with that of NS-398, a COX-2 specific inhibitor.[76] The topical administration of an NO–releasing derivative of aspirin, NCX-4016, caused a marked increase in mucosal blood flow (probably by releasing NO) with no effect on potential transmural difference and Ph.[77] This effect may be in part due to inhibition of neutrophil adherence, operated by NO.[78]

Many NSAIDs are marketed as racemic mixtures, composed of *(R)*- and *(S)*-enantiomers. Racemic NSAIDs are potent COX inhibitors only through the action of the *(S)*-enantiomers, as the *(R)*-enantiomers do not exhibit COX inhibition but rather have potent analgesic activity with minimal ulcerogenic potential.[79] Of many NSAIDs currently available in racemic form, such as ketoprofen, flurbiprofen, ibuprofen and ketorolac, it is now possible to use only the *(R)*-enantiomer to obtain an analgesic effect without causing important adverse effects. Preliminary premarketing data confirmed the efficacy and safety of such drugs in humans.[80]

4.4 Use of Corticosteroids as an Alternative to NSAIDs

The corticosteroids have demonstrated less gastrointestinal adverse effects compared with NSAIDs. The relative risk of ulcer in patients taking corticosteroids is only 1.1 but this increases to 4.4 if NSAIDs are given concomitantly (see section 4.5).

4.5 Avoid Use of Concomitant Corticosteroids

A strong interaction between NSAID and corticosteroids has been noted, with an increased risk

of ulcers in corticosteroid users confined only to those who concomitantly take an NSAID. In such patients, the risk of peptic ulcer disease is 15 times greater than in nonusers of either drug and the estimated relative risk for upper gastrointestinal haemorrhage is 10.6.[81] In a recent meta-analysis, significant risk factors for serious gastrointestinal complication included: age >60, previous history of gastrointestinal complications and concomitant corticosteroid use, with relative risk ratios of 5.4, 4.8, and 1.8 respectively.[24]

4.6 Use of Preventive Therapy

In high risk patients preventive therapy should be considered. The presence of a risk factor elevates the risk of gastrointestinal complications but the concomitant presence of more than one risk factor is even more deleterious. In the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial 4 risk factors were identified: age >75 years, history of gastrointestinal bleeding, history of previous peptic ulcer and history of cardiovascular disease.[82] After 6 months' NSAID therapy, patients with none of the 4 factors were found to have a risk of NSAID-induced gastrointestinal complications of only 0.4%. In patients with any single factor, the risk was approximately 1% and in patients with all 4 risk factors, the risk would be around 9%. These data correspond to risk incidence rates per year of 0.8% (no risk factor), 1.7% (1 risk factor), and 18.5% (4 risk factors).[82,83]

However, preventive therapy cannot be recommended for all patients who take an NSAID. The cost-effectiveness ratio would be unfavourable. From our experience, we agree with the conclusions of the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) study, performed in patients with rheumatoid arthritis. The study identified 5 major risk factors for gastrointestinal complications: age >60 years; degree of disability due to rheumatoid arthritis; previous NSAID-related gastrointestinal events; daily dose of NSAID and concomitant corticosteroid administration.[20] We consider these patients to be at high risk of experiencing NSAID-induced gastroduodenal effects and therefore, in need of preventative treatment.

5. Preventive Therapy

Various agents have been used in attempts to reduce the incidence of NSAID-induced gastrointestinal lesions. The most frequently used drugs are:

- prostaglandin analogues (misoprostol)
- histamine H_2 receptor antagonists (ranitidine, cimetidine, famotidine, nicotidine)
- proton pump inhibitors (omeprazole, lansoprazole, pantoprazole)
- barrier agents (sucralfate).

Methodological problems do exist in evaluating pharmacological mucosal protection afforded by these agents because the reported improvements achieved by the use of cytoprotective and/or antisecretory drugs are based on the reduction in the degree of the endoscopical score and this may be of questionable significance.[6]

5.1 Misoprostol

An extensive evaluation of the literature shows that the antiulcer agent misoprostol, a synthetic prostaglandin E_1 analogue, has proven to be effective in the prevention of NSAID-induced gastric and duodenal ulcers as well as in the reduction of serious upper gastrointestinal complications. A recent meta analysis[84] concludes that the use of misoprostol, but not of H_2 antagonists, induced a significant reduction in gastric or duodenal lesions (erosions or ulcers) during short term or long term NSAID therapy. In the same study H_2 antagonists were reported to be beneficial only in the reduction of duodenal ulcers during long term NSAID treatment.

The most convincing study, the MUCOSA trial,[82] enrolled 8843 patients and aimed to evaluate the efficacy and safety of misoprostol 200μg 4 times daily *vs* placebo given for 6 months to patients with rheumatoid arthritis aged ≥52 years, for the prevention of NSAID-induced gastrointestinal complications. The study was designed to detect gastrointestinal complications under ordinary clin-

ical conditions without routine endoscopy. At the end of the study the misoprostol group showed a reduction of 40 to 50% in serious gastrointestinal complications, compared with the placebo group.

In a regression analysis of data from the MUCOSA study, Simon et al.[83] defined the specific risk reduction effects of misoprostol therapy in patients with specific risk factors. For example, in patients with a history of peptic ulcer disease there was a 52.4% [95% confidence interval (CI) 23.5 to 70.4] risk reduction with misoprostol cotherapy and a 50% (95% CI 4.2 to 73.9) risk reduction in patients with a history of gastrointestinal bleeding.

This finding suggested that there are good economic as well as medical reasons for identifying patients who are at significantly increased risk of NSAID-induced gastrointestinal adverse events and to provide prophylaxis with misoprostol. The number of patients who need to be treated with misoprostol to prevent 1 gastric or duodenal ulcer has been recently calculated by taking into account the baseline risks of ulcer.[84] For example, for a 3% baseline risk of gastric ulcer the number of patients who need to be preventively treated during short (<2 weeks) or long term (>4 weeks) NSAID therapy would range from 34 to 41 and for a baseline risk of 10% from 10 to 13. Similar data has been calculated for the prevention of 1 duodenal ulcer with misoprostol.

For this study population, averting 1 serious gastrointestinal complication by prescribing misoprostol 200 μg 4 times a day would cost an additional $Can94 766; for patients with previous peptic ulcer disease (medium risk), the cost would be $Can14 943, and for patients with previous peptic ulcer disease and age >75 (high risk), the cost would be $Can4101 (1994 values).[85] However, leading health economists in 6 different countries, evaluating the economic implications of prophylactic treatment with misoprostol to prevent NSAID-induced ulcers, concluded that misoprostol was a cost-effective or a cost-saving approach to the prevention of NSAID-induced ulcers when compared with the costs associated with ulcer treatment or the management of ulcer complications (e.g. hospitalisation, surgery, medical costs).[86] These data further emphasise the need to carefully select which patients to treat.

Despite the efficacy of misoprostol in preventing gastroduodenal ulcers, a beneficial effect on dyspepsia symptoms attributable to NSAIDs has not been proven. Moreover, misoprostol itself may provoke symptoms and induce adverse effects, the most frequently reported being diarrhoea. This effect is, at least in part, dose dependent: in the MUCOSA trial, more patients receiving misoprostol (20%) than placebo (15%) withdrew from the study during the first month because of diarrhoea, abdominal pain or flatulance.[82] Overall, significantly more patients in the misoprostol group (42%) than in the placebo group (36%) withdrew from treatment prematurely.

In another trial,[87] a total of 1623 patients receiving NSAIDs were randomised to receive misoprostol 200μg twice daily, misoprostol 200μg 3 times daily, misoprostol 200μg 4 times daily or placebo. The difference in gastric or duodenal ulcer incidence between the placebo group and each of the misoprostol treatment groups was statistically significant. Premature withdrawal from the study due to adverse events occurred in 11% of the placebo group, 12% of patients treated with misoprostol either 200μg twice daily or 200μg 3 times daily and 20% of those treated with misoprostol 200μg 4 times daily. The difference in the withdrawal rate between the misoprostol 200μg 4 times daily group and each of the other 3 treatment groups was statistically significant.

These results indicate that misoprostol 200μg twice daily or 3 times daily can provide significant protection against gastroduodenal ulcer in patients undergoing long term NSAID therapy. Furthermore, at these dosages misoprostol is better tolerated than it is given at a dosage of 200μg 4 times daily. However, for dosages of less than 200μg 4 times daily there is a lack of data definitively demonstrating a preventative effect against the most severe gastroduodenal complications.

In both UK and Canada, misoprostol 200μg twice daily is approved for prophylaxis of NSAID-induced gastric or duodenal ulcers.

5.2 Histamine H_2 Receptors Antagonists

In the great majority of published studies ranitidine has been evaluated in the prevention of NSAID-induced gastrointestinal toxicity. However, other H_2 antagonists, such as cimetidine, famotidine, nizatidine and ebrotidine (a new H_2 receptor antagonist), have also been evaluated in this setting.

A meta-analysis[88] of 6 placebo-controlled studies of at least 4 weeks' duration designed to evaluate the prophylactic use of ranitidine 150mg twice daily has recently been conducted. The studies involved a total 1200 patients with rheumatic disorders who required NSAID therapy who had no, or only minor, gastric or duodenal damage at baseline endoscopy. Overall, 1054 (88%) patients underwent endoscopy after 4 weeks of treatment and ulceration was found in 3.2% of the patients treated with ranitidine and in 7.8% of the patients treated with placebo ($p < 0.005$). However, the difference was especially attributable to the reduced frequency of duodenal ulcers ($p < 0.005$); the frequency of gastric ulcers between the 2 groups was not significantly different.

The results of this analysis demonstrate that the coadministration of full dosage ranitidine protects against NSAID-induced chronic ulcerations but does not produce a significant benefit in the prophylaxis of NSAID-induced gastric ulcerations in patients with rheumatic disorders after 4 weeks of NSAID treatment.

Another meta-analysis,[84] that included 24 placebo-controlled randomised studies investigating the use of H_2 antagonists (ranitidine, cimetidine or nizatidine) or misoprostol, as preventive agents during short term (<2 weeks) or long term (>4 weeks) NSAID treatment, confirmed that the use of H_2 antagonists was beneficial in the prevention of NSAID-induced duodenal ulcers during long term treatment, but not in the prevention of NSAID-induced gastric ulcer. Misoprostol was found to be efficient as preventive agent both in gastric and duodenal NSAID-induced ulceration.

The number of patients who would need to be treated in order to prevent a duodenal ulcer was also calculated, by taking into account different baseline risks of ulcer. For example, for a baseline risk of duodenal ulcer of 3 or 10%, the number of patients who would need to be treated with a H_2 antagonist in order to prevent 1 duodenal ulcer during long term NSAID therapy was 54 and 17, respectively. The cost effectiveness ratio of H_2 antagonists remains controversial even when taking into account the fact that the efficacy of H_2 antagonists seems limited to the prevention of duodenal ulcer only.

However, in a recent study of high dosage famotidine (40mg twice a daily), the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long term (6 months) NSAID therapy was significantly reduced compared with placebo.[89] However, in this study an ulcer was defined as a mucosal break ≥3mm in diameter, a cut-off size that increases the proportion of trivial lesions that are classed as ulcers; a more appropriate diameter to use for a definition of an ulcer is ≥5mm. If this cut-off size is considered, the results could be vastly different. Furthermore, whether ulcer prevention reduces ulcer complications or not is still a matter for discussion

5.3 Omeprazole

Given that acid suppression with a high dosage of a H_2 antagonist may reduce the incidence of NSAID-induced gastric and duodenal ulcers, it follows that other more potent acid inhibitors should be as, or more, effective. Preliminary studies, comparing omeprazole at 20 mg/day with placebo in patients receiving continuous NSAID therapy, reported a significant reduction in the incidence of gastroduodenal ulcers[90,91] and in dyspeptic symptoms[91] in the omeprazole treated group. In the study by Ekstrom et al.,[91] the patients enrolled had a history of peptic ulcer disease or ongoing dyspepsia. Endoscopy was not performed on entry into the study. The peptic ulcer incidence was 4.7%

(4/85 patients) in omeprazole recipients and 16.7% (15/90 patients) in placebo recipients ($p < 0.05$). Ekstrom et al.[91] also stratified for history of previous ulcer and they found that omeprazole significantly reduced the ulcer rate both in patients with previous ulcer and in those without.

In agreement with these studies, there are 3 more recent randomised, double-blind, controlled trials. In the Omeprazole versus Placebo as Prophylaxis of Ulcers and Erosions from NSAID Treatment (OPPULENT) study,[92] patients were randomised to receive 20 mg/day of omeprazole or placebo. The estimated probability of remaining in remission for 6 months while receiving omeprazole was 0.78, compared with 0.53 for placebo. 14 (16.5%) patients receiving placebo developed ulcer, compared with 3 (3.6%) patients receiving omeprazole.

The Omeprazole (20 or 40 mg/day) versus Misoprostol (200μg 4 times daily) for NSAID-Induced Ulcer Management (OMNIUM) study[40] consisted of a healing and a prophylactic phase. At 8 weeks (healing phase) the rates of gastric ulcer healing were significantly higher with omeprazole 20 mg/day (but not omeprazole 40 mg/day) than with misoprostol. Healing rates among patients with duodenal ulcer were higher with both dosages of omeprazole than with misoprostol, whereas healing rates among patients with erosions alone were higher with misoprostol. These ratios were equal for both *H. pylori* positive and negative patients. Patients who successfully completed the healing phase were re-randomised to receive omeprazole 20 mg/day or misoprostol 200μg twice daily or placebo for up to 6 months (prophylactic phase). More patients remained in remission during maintenance treatment with omeprazole (61%) than with misoprostol (48%) [$p = 0.001$] and with either drugs than with placebo (27%) [$p < 0.001$]. In the healing phase, omeprazole was better tolerated than misoprostol.

The ACID Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) study[41] had the same study design as the OMNIUM study with the substitution of misoprostol with ranitidine 150mg twice daily in the healing and prophylactic phases. The rates of healing for all types of lesions were higher with omeprazole than with ranitidine. During maintenance therapy, the estimated proportion of patients in remission at the end of 6 months was 72% in the omeprazole group and 59% in the ranitidine group. The percentages of patients with peptic ulcer relapse were 5.7% for omeprazole and 19.5% for ranitidine. Both medications were well tolerated. This data shows that omeprazole is an effective and well-tolerated agent for both primary and secondary (maintenance) prophylaxis in patients receiving NSAIDs.[92]

5.4 Sucralfate

Sucralfate is an effective antiulcer drug that is thought to provide a physical barrier to acid injury. It has been suggested that sucralfate stimulates mucosal protective factors, such as mucus and bicarbonate secretion, perhaps through increases in prostaglandin E_2 production.

Although initial studies using sucralfate for protection against short term aspirin administration were encouraging, longer term studies were generally disappointing. A comparative study with misoprostol demonstrated that sucralfate 1g 4 times daily was ineffective in preventing gastric ulcer.[93] Gastric ulcers occurred during 3 months of prophylactic therapy in only 2 of 122 (1.6%) patients taking misoprostol compared with 21 of 131 (16%) patients taking sucralfate, a rate equivalent to rates in the placebo group in studies of similar design. Thus, sucralfate cannot be recommended as a prophylactic agent to prevent NSAID-induced gastropathy.

6. Conclusions on the Treatment of NSAID-Induced Ulcers

As a first step in therapy for NSAID-associated ulcers, use of these drugs should be reduced as much as possible or they should be discontinued and treatment should be changed to an alternative agent. If this is not feasible, an NSAID with less toxic potential (for example on the basis of a more

favourable COX-2/COX-1 inhibition rate) should be used.

Recent studies have demonstrated that meloxicam (a slightly selective COX-2 inhibitor) exhibits better gastrointestinal tolerability than equi-effective doses of piroxicam and diclofenac.[68,94] However, serious gastrointestinal complications (perforation, ulceration or bleeding) were reported to be less frequent in meloxicam recipients but the differences did not reach statistical significance. In a preliminary study, celecoxib (a specific COX-2 inhibitor) was found to be effective in treating the signs and symptoms of arthritis without showing any evidence of gastroduodenal ulcer and platelet effects.[69]

If NSAIDs are discontinued, the ulcer generally heals in the usual time with any conventional antiulcer therapy. If the NSAID cannot be discontinued, it is mandatory to use an antiulcer agent,[95] controlling endoscopically, if possible, the outcome of the lesion.

For the H_2 antagonists, the available findings, imply that healing is slower if the NSAID is continued. Complete healing may require higher dosages (double the traditional ulcer healing dosages) and/or a prolonged duration (>8 weeks) of therapy. For example,[96] in patients with confirmed ulcers randomly assigned to continue or discontinue NSAID treatment, after 8 weeks the gastric ulcer healing rate was 63% in those still taking an NSAID, compared with 95% in those who had stopped NSAID treatment. For duodenal ulcers, the corresponding healing rates at 8 weeks were 84% in the NSAID group and 100% in those who discontinued NSAID. Extension of ranitidine treatment for an additional 4 weeks improved healing rates among patients who continued to take an NSAID to 79% in those with gastric ulcer, and 92% in those with duodenal ulcer.

In general, taking into account the most significant studies, H_2 antagonists can promote the healing of 40 to 60% of NSAID-induced gastric ulcers within 4 weeks and approximately 90% within 3 months while NSAID therapy is continued.[30] For duodenal ulcer, the healing rates range from 67 to 100% within 3 months.[30]

The initial gastric ulcer diameter is considered an important prognostic factor for ulcer healing. Cimetidine therapy was found to produce a lower ulcer healing rate when the diameter of the ulcer was >5mm.[97] However, cimetidine is the least effective of the H_2 antagonists. However, it has also been demonstrated that using a high dosage of famotidine larger ulcers healed more slowly.[98] In this study, high dosage famotidine (40mg twice daily) was found to be effective in the healing of gastroduodenal ulcers in patients who stopped or continued NSAID treatment. Cumulative ulcer healing rates at 12 weeks were 89% for patients who continued NSAID treatment and 100% for those who stopped, percentages quite similar to those reported with ranitidine treatment. However, famotidine significantly reduced the cumulative incidence of gastroduodenal ulcer recurrence compared with placebo when given as maintenance therapy.[98]

In patients with rheumatoid arthritis who developed peptic ulcer and continued to receive NSAID treatment, treatment with tripotassium dicitrato bismuthate or cimetidine showed similar healing activity.[99]

Profound acid suppression with a proton pump inhibitor such as omeprazole appears to be most effective in healing ulcers during continued NSAID use, accelerating the slow healing observed with H_2 antagonists. In patients who must remain on NSAID therapy, Walan et al.[100] reported 8-week healing rates of 53% with ranitidine 150mg twice a daily, 82 and 95% with omeprazole 20 and 40 mg/day, respectively, indicating substantially improved healing rates with both dosage levels of omeprazole. Furthermore, patients treated with omeprazole who remained on NSAID therapy had healing rates similar to those in ranitidine-treated patients who had discontinued NSAID treatment.

To compare omeprazole, misoprostol and ranitidine in the healing of gastric and duodenal NSAID-induced ulcers and erosions, the relief of

dyspeptic symptoms and the presence of adverse effects, 2 double-blind, controlled studies, OMNIUM[40] and ASTRONAUT,[41] using identical study design but with different treatment arms, have recently been performed (see section 5.3 for study details). Chronic NSAID users with either an ulcer or >10 erosions in the stomach or duodenum were treated for 4 weeks or for 8 weeks until success (defined as no ulcer, <5 erosions at any site and not more than mild dyspeptic symptoms) was achieved.

Yeomans et al.[101] recently conducted a pooled analysis of these 2 studies. Overall, 65% of the patients had ulcers at entry, the remainder had erosions. After 8 week's treatment, omeprazole 20 mg/day resulted significantly superior to ranitidine and misoprostol for overall treatment and ulcer healing. Gastric ulcer healing rates were 83, 82, 64 and 74% for omeprazole 20 mg/day, omeprazole 40 mg/day, ranitidine and misoprostol, respectively; duodenal ulcer healing occurred in 93, 88, 79, and 79%, respectively. Omeprazole was better tolerated than misoprostol which caused more diarrhoea or abdominal pain. Omeprazole 20 mg/day was at least as effective as 40 mg/day.

Patients from OMNIUM[40] and ASTRONAUT[41] whose ulcers healed, but who required continuous NSAID use, were successively recruited to take part in the maintenance studies for the prevention of relapse of NSAID-associated ulcers, using the same drug comparisons with misoprostol reduced to 200μg twice daily and with the addition of a placebo in the OMNIUM maintenance study. Treatment failure was defined as appearance of ulcer, >10 erosions in the stomach or in duodenum, more than mild dyspeptic symptoms or adverse events leading to study discontinuation.

According to the pooled analysis,[101] over a 6-month period, significantly more long term NSAID users receiving omeprazole remained in overall remission than did recipients of ranitidine, misoprostol or placebo. Gastric ulcer relapsing rates were 9.5, 16.3, 10.5, and 32.2% for omeprazole, ranitidine, misoprostol and placebo, respectively. For the duodenal ulcer the relapse rates were 1.7, 4.2, 10.1, and 12.2%, respectively. So omeprazole and misoprostol resulted quite similar in preventing gastric ulcer relapse but omeprazole was better than misoprostol in preventing duodenal ulcer relapse where the efficacy of misoprostol 200μg twice daily was similar to placebo.

Finally, sucralfate seems less effective than omeprazole but similar to ranitidine in the healing of gastric and duodenal NSAID-induced ulcers.[102,103]

References

1. McCarthy DM. Nonsteroidal anti-inflammatory drugs: the clinical dilemmas. Scand J Gastroenterol 1992; 27 Suppl.: 9-16
2. Champion GD, Feng PH, Azuma T, et al. NSAID-induced gastrointestinal damage: epidemiology, risk and prevention, with an evaluation of the role of misoprostol: an Asia-Pacific perspective and consensus. Drugs 1997; 53: 6-19
3. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulcerations. Gut 1987; 28: 527-32
4. Fries JF, Miller SR, Spits PW, et al. Toward an epidemiology of gastropathy associated with non steroidal anti-inflammatory drug use. Gastroenterology 1989; 96: 647-55
5. Lichtenstein DR, Syngal S, Wolfe MM. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Arthritis Rheum 1995; 38: 5-18
6. Shoen RT, Vender RJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced damage. Am J Med 1979; 86: 449-58
7. Levi S, Shaw-Smith C. Non-steroidal anti-inflammatory drugs: how do they damage the gut? Br J Rheumatol 1994; 33: 605-12
8. Brune K, Rainsford KD, Schweitzer A. Biodistribution of mild analgesics. Br J Pharmacol 1980: 10 Suppl.: 279S-84S
9. Mahmud T, Rafi S, Scott DL, et al. Nonsteroidal antiinflammatory drugs and uncoupling of mitochondrial oxidative phosphorylation. Arthritis Rheum 1996: 39; 1998-2003
10. Wallace JL. Gastric ulceration: critical events at the neutrophil-endothelium interface. Can J Physiol Pharmacol 1993; 71: 98-102
11. Pihan G, Regillo C, Szabo S. Free radicals and lipid peroxidation in ethanol- or aspirin-induced gastric injury. Dig Dis Sci 1987; 32: 1395-401
12. McCafferty DM, Granger DN, Wallace JL. Indomethacin-induced gastric injury and leukocyte adherence in arthritic versus healthy rats. Gastroenterology 1995; 109: 1173-80
13. Bamba H, Ota S, Kato A, et al. Nonsteroidal anti-inflammatory drugs may delay the repair of gastric mucosa by suppressing prostaglandin-mediated increase of hepatocyte growth factor production. Biochem Biophys Res Commun 1998; 24: 567-71
14. Lister BJ, Poland M, DeLapp RE. Efficacy of nabumetone versus diclofenac, naproxen, ibuprofen, and piroxicam in osteoarthritis and rheumatoid arthritis. Am J Med 1993; 95 Suppl.: 2S-9S
15. Day TK. Intestinal perforation associated with osmotic slow release indomethacin capsules. BMJ 1983; 287: 1671-2

16. Scheiman JM. Management of peptic ulcer disease. Proceedings of the American College of Rheumatology 61st National Scientific Meeting; 1997 Nov 8-12; Washington DC
17. Bjarnason I, Hayllar J. Early pathogenic events in NSAID-induced gastrointestinal damage. Ital J Gastroenterol 1996; 28 Suppl.: 19-22
18. Laine L, Weinstein WM. Subepithelial hemorrhages and erosions of human stomach. Dig Dis Sci 1988: 33; 490-503
19. Laine L. Upper gastrointestinal hemorrhage. West J Med 1991; 155: 274
20. Soll AH, Weinstein WM, Kurata J, et al. Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. Ann Intern Med 1991; 114: 307-19
21. Geis GS, Stead H, Wallemark CB, et al. Prevalence of mucosal lesions in the stomach and duodenum due to chronic use of NSAIDs in patients with RA or OA, and interim report on prevention by misoprostol of diclofenac-associated lesions. J Rheumatol 1991; 18 Suppl. 28: 11-4
22. Nobunaga M. NSAID-induced GI damage: a serious problem [abstract]? In: Nasution AR, Darmawan J, editors. Proceedings of the 7th APLAR Congress of Rheumatology; 1992 Sep 13-18; Bali, Tokio: Churchill Livingstone, 1991; 319
23. Zeidler H. Epidemiology and economics of NSAID-induced gastropathy. Scan J Rheumatol 1991; Suppl. 92: 3-8
24. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to the use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991; 115: 787-96
25. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991; 114: 257-63
26. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998; 105 (1B): 31S-8S
27. Graham DY, Smith JL, Dobbs SM. Gastric adaptation occurs with aspirin administration in man. Dig Dis Sci 1983; 28: 1-6
28. Fenn GC. Review article: controversies in NSAID-induced gastroduodenal damage – do they matter? Aliment Pharmacol Ther 1994; 8: 15-26
29. Wallace JL, Bell CJ. Gastroduodenal mucosal defence. Curr Opin Gastroenterol 1994; 10: 589-94
30. Hollander D. Gastrointestinal complications of nonsteroidal anti-inflammatory drugs: prophylactic and therapeutic strategies. Am J Med 1994; 96: 274-81
31. McDonald WC. Correlation of mucosal histology and aspirin intake in chronic gastric ulcer. Gastroenterology 1973; 84: 1268-72
32. El-Zimaity HMT, Genta RM, Graham DY. Histological features do not define NSAID-induced gastritis. Hum Pathol 1996; 27: 1348-54
33. Graham DY, Klein PD, Opekun AR, et al. Effect of age on the frequency of active Campylobacter pylori infection diagnosed by the (13C) urea breath test in normal subjects and patients with peptic ulcer disease. J Infect Dis 1988; 157: 777-80
34. McCarthy DM. Helicobacter pylori infection and gastroduodenal injury by nosteroidal antiinflammatory drugs. Scand J Gastroenterol 1991; 26 Suppl.: 91-7
35. Caselli M, Pazzi P, La Corte R, et al. Campylobacter-like organism, non-steroidal anti-inflammatory drugs and gastric lesions in patients with rheumatoid arthritis. Digestion 1989; 44: 101-4
36. Chan FKL, Sung JJY, Chung Scs, et al. Randomised trial of eradication of Helicobacter pylori before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997; 350: 975-9
37. Labenz J, Borsch G. Role of Helicobacter pylori eradication in the prevention of peptic ulcer bleeding relapse. Digestion 1994; 55: 19-23
38. Cullen DJE, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs. Gut 1997; 41: 459-62
39. Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of Helicobacter pylori eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Lancet 1998; 352: 1016-21
40. Hawkey CJ, Karrasch JA, Szczepanski L, et al. For the Omeprazole versus Misoprostol for NSAID-induced ulcer management (OMNIUM) study group. N Engl J Med 1998; 338: 727-34
41. Yeomans NV, Tulassay Z, Juhasz L, et al. For the acid suppression trial: ranitidine versus omeprazole for NSAID-associated ulcer treatment (ASTRONAUT) study group. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338: 719-26
42. Hudson N, Balsitis M, Filipowicz F, et al. Effects of Helicobacter pylori colonisation on gastric mucosal eicosanoid synthesis in patients taking non-steroidal anti-inflammatory drugs. Gut 1993; 34: 459-62
43. Konturek JW, Dembinski A, Konturek SJ, et al. Infection of Helicobacter pylori in gastric adaptation to continued administration of aspirin in humans. Gastroenterology 1998; 114: 245-55
44. Calam J. Clinical science of Helicobacter pylori infection: ulcers and NSAIDs. Br Med Bull 1998; 54: 55-62
45. Marshall B. NSAIDs and Helicobacter pylori: therapeutic options. Lancet 1998: 352: 1001-3
46. Blaser MJ. Role of vacA and cagA locus of Helicobacter pylori in human disease. Aliment Pharmacol Ther 1996; 10 Suppl. 1: 73-7
47. Pan ZJ, van der Hulst RW, Feller M, et al. Equally prevalences of infection with cagA-positive Helicobacter pylori in Chinese patients with peptic ulcer disease and those with chronic gastritis-associated dyspepsia. J Clin Microbiol 1997; 35: 1344-7
48. Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. Br J Rheumatol 1993; 32: 1077-82
49. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis: pt 1: osteoarthritis of the hip. Arthritis Rheum 1995; 38: 1535-40
50. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis: pt 1: osteoarthritis of the knee. Arthritis Rheum 1995; 38: 1541-6
51. Graham DY. Nonsteroidal anti-inflammatory drugs, helicobacter pylori, and ulcers: where we stand. Am J Gastroenterol 1996; 91: 2080-6
52. Cooper SA. New peripherally acting oral analgesic agents. Ann Rev Pharmacol Toxicol 1983; 23: 617-47
53. Henry D, Lim LLY, Garcia-Rodriguez LA, et al. Variability in the risk of major gastrointestinal complications from single nonsteroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996; 312: 1563-66
54. The SALT Collaborative Group: Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular events. Lancet 1991; 338: 1345-9

55. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991; 325: 1261-6
56. Silagy CA, McNeil JJ, Donnan GA, et al. Adverse effects of low-dose aspirin in a healthy elderly population. J Clin Pharmacol Ther 1993; 54: 84-9
57. Fries JF, Eamey DR, Singh G, et al. A reevalutation of aspirin therapy in rheumatoid arthritis. Arch Intern Med 1993; 153: 2465-71
58. Fu J, Masferrer J, Seibert K, et al. The induction and suppression of prostaglandin H2 synthase (cycloxygenase) in human monocytes. J Clin Invest 1990; 86: 1375-9
59. Xie W, Chipman JG, Robertson DL, et al. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci U S A 1991; 88: 2692-6
60. Smith WL, DeWitt DL. Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and -2. Adv Immunol 1996; 62; 167-215
61. Jones DA, Carlton DP, McIntyre TM, et al. Molecular cloning of human prostaglandin endoperoxide synthase type II and demonstration of expression in response to cytokines. J Biol Chem 1993; 268: 9049-54
62. Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. J Rheumatol 1997; 24 Suppl.: 15-9
63. Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. Scand J Rheumatol 1996; 25 Suppl.: 9-21
64. de Brum-Fernandes AJ. New perspective for nonsteroidal antiinflammatory therapy. J Rheumatol 1997; 24: 246-8
65. Battistini B. COX-1 and COX-2: toward the development of more selective NSAIDs. Drug News Perspect 1994; 7: 501-12
66. Riendeau D, Percival MD, Boyce S, et al. Biochemical and pharmacological profile of a tetrasubstituted furanone as highly selective COX-2 inhibitor. Br J Pharmacol 1997; 121: 105-17
67. Spangler RS. Cyclooxygenase 1 and 2 in rheumatic disease: implications for nonsteroidal anti-inflammatory drug therapy. Semin Arthritis Rheum 1996; 26: 435-46
68. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-3 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of the COX-inhibiting therapies (select) trial in osteoarthritis. Br J Rheum 1998; 37: 946-51
69. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum 1998; 41: 1591-602
70. Lipsky PE. Isakson PC. Outcome of specific COX-2 inhibition in rheumatoid arthritis. J Rheumatol 1997; 24 Suppl.: 9-13
71. Hayllar J, Bjarnason I. Gastroduodenal tolerability of highly specific cyclo-oxygenase-2 inhibitor. Ital J Gastroenterol 1996; 28 Suppl.: 30-2
72. Dinchuck JE, Car BD, Focht RJ, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. Nature 1995; 378: 406-9
73. Morham SG, Langenbach R, Loftin CD, et al. Prostaglandin synthase 2 gene disruption causes severe renal pathology in the mouse. Cell 1995; 83: 473-82
74. Shigeta J, Takahashi S, Okabe S. Role of cyclooxygenase-2 in the healing of gastric ulcers in rats. J Pharmacol Exp Ther 1998; 286: 1383-90
75. Schmassmann A, Peskar BM, Stettler C, et al. Effects of inhibition of prostaglandin endoperoxide synthase-2 in chronic gastro-intestinal ulcer models in rats. Br J Pharmacol 1998; 123: 795-804
76. Ukawa H, Yamakuni H, Kato S, et al. Effects of cyclooxygenase-2 selective and nitric oxide-releasing nonsteroidal anti-inflammatory drugs on mucosal ulcerogenic and healing responses of the stomach. Dig Dis Sci 1998; 43: 2003-11
77. Takeuchi K, Ukawa H, Konaka A, et al. Effect of nitric oxide-releasing aspirin derivate on gastric functional and ulcerogenic responses in rats: comparison with plain aspirin. J Pharmacol Exp Ther 1998; 286: 115-21
78. Wallace JL, McKnight W, Wilson TL, et al. Reduction of shock-induced gastric damage by a nitric oxide-releasing aspirin derivate: role of neutrophils. Am J Physiol 1997; 273: G1246-51
79. Handley DA, Cervoni P, McCray JE, et al. Preclinical enantioselective pharmacology of (R)- and (S)- ketorolac. J Clin Pharmacol 1998; 38: 25S-35S
80. Jerussi TP, Caubet JF, McCray JE, et al. Clinical endoscopic evaluation of the gastrointestinal tolerance to (R)-ketoprofen, (R)-furbiprofen, racemic ketoprofen, and paracetamol: a randomised, single-blind, placebo-controlled trial. J Clin Pharmacol 1998; 38: 19S-24S
81. Piper JM, Ray WA, Daugherty JR, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal antiinflammatory drugs. Ann Intern Med 1991; 114: 735-40
82. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995; 123: 241-9
83. Simon LS, Hatoum HT, Bittman RM, et al. Risk factors for serious nonsteroidal-induced gastrointestinal complications. regression analysis of the MUCOSA trial. Fam Med 1996; 28: 204-10
84. Koch M, Dezi A, Ferrario F, et al. Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury. Arch Intern Med 1996; 156: 2321-32
85. Maetzel A Bosi, Ferraz M, 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
86. Dajani EZ, Agrawal NM. Prevention of nonsteroidal anti-inflammatory drug-induced gastroduodenal ulcers: role of mucosal protective and gastric antisecretory drugs. Dig Dis 1995; 13 Suppl.: 48-61
87. Raskin JB, White RH, Jakson JE, et al. Misoprostol dosage in the prevention of NSAID-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Intern Med 1995; 123: 344-50
88. French PC, Darekar BS, Mills JG, et al. Ranitidine in the prevention of nonsteroidal antiinflammatory drug-associated gastric and duodenal ulceration in arthritic patients. Eur J Gastroenterol Hepatol 1994; 6: 1141-7
89. Taha AS, Hudson N, Hawkey CJ, et al. Prevention of NSAID related gastric and duodenal ulcers by famotidine: a placebo controlled blind study. N Engl J Med 1996; 334: 1435-9
90. Bianchi Porro G, Santalucia F, Petrillo M, et al. Omeprazole vs Placebo in the prevention of NSAIDs-induced gastroduodenal lesions [abstract]. Gastroenterology 1994; 106 : A51

91. Ekstrom P, Carling L, Wetterhus S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous nonsteroidal antiinflammatory drug therapy. Scand J Gastroenterol 1996; 31: 753-8
92. Hawkey CJ. Progress in prophylaxis against nonsteroidal anti-inflammatory drug-associated ulcers and erosions. Omeprazole NSAID Steering Committee. Am J Med 1998; 104 (3A): 67S-74S; discussion 79S-80S
93. Agrawal NM, Roth S, Graham D, et al. Misoprostol compared with sucralfate in the prevention of non-steroidal anti-inflammatory drug-induced gastric ulcer. Ann Intern Med 1991; 115: 195-200
94. Hawkey C, Kahan A, Steinbruk, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheum 1998; 37: 937-45
95. La Corte R, Caselli M, Ruina M, et al. Therapy of NSAIDs-induced gastropathy. Ital J Gastroenterol 1996; 28 Suppl.: 37-41
96. Lancaster-Smith MJ, Jaderberg ME, Jackson DA. Ranitidine in the treatment of nonsteroidal anti-inflammatory drug-associated gastric and duodenal ulcers. Gut 1991; 32: 252-5
97. O'Laughin JC, Silvoso GK, Ivey KJ. Resistance to medical therapy of gastric ulcers in rheumatic patients. Dig Dis 1982; 27: 976-80
98. Hudson N, Taha AS, Russel RI, et al. Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology 1997; 112: 1817-22
99. Bianchi Porro G, Lazzaroni M, Petrillo M, et al. Peptic ulcer therapy with cimetidine versus tripotassium dicitrato bismuthate in rheumatoid arthritis patients undergoing chronic NSAID treatment. Aliment Pharmacol Ther 1998; 12: 343-7
100. Walan A, Bader JP, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989: 320; 69-75
101. Yeomans ND, Omeprazole NSAID Steering Committee. New data on healing of nonsteroidal anti-inflammatory drug-associated ulcers and erosions. Am J Med 1998; 104 (Suppl. 3A): 56-61
102. Bianchi-Porro G, Lazzaroni M, Manzionna G, et al. Omeprazole and sucralfate in the treatment of NSAID-induced gastric and duodenal ulcer. Aliment Pharmacol Ther 1998; 12: 335-60
103. Manniche C, Malchow-Moller A, Andersen JR, et al. Randomised study of the influence of non-steroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatic disease. Gut 1987; 28: 226-9

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