NON STEROIDAL ANTI-INFLAMMATORY DRUGS AND THE STOMACH – A REVIEW

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Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are standard prescription drugs in the treatment of rheumatic disease, but it is also well known that they carry a high risk of adverse events, particularly in the gastro-intestinal tract. Studies have indicated that the prevalence of GI symptoms among patients taking these agents is in the region of 30% to 40% (1,2) with symptoms ranging in severity from the occasional heartburn or indigestion to severe dyspepsia. Gastric erosions are seen in one third or more of patients who use NSAIDs (3) and continued NSAIDs therapy produces ulcers in 10-20% of patients with gastric ulcers being more common more than duodenal ulcers. Serious and life threatening gastroduodenal complications such as bleeding and ulcer perforation which is the major concern of all doctors, have been reported to occur in about 1-2 % patients during 3-6 months of NSAID therapy or 4-6% of patients treated for a year (4).

It is estimated that worldwide, more than 30 million people consume NSAIDs daily (5). In United Kingdom, about 1.5 million people aged over 60 years take NSAIDs at any one time. Patients who take NSAIDs have a 4-6 fold increased risk of developing peptic ulcers (6). Every year, about 12,000 ulcer complications and 1,200 deaths occur as a result of NSAID therapy (7). In the United States, more than 75,000 hospitalizations and more than 7,500 death occur annually in the elderly directly related to NSAID use (8). Documented NSAID ingestion in Malaysia appears to be low (9). In a cross-sectional survey of 1060 consecutive patients with dyspepsia undergoing endoscopy at the University Hospital, Kuala Lumpur, the prevalence rate of NSAID ingestion was only 0.6% (63/1060) (9). This figure is likely to be an underestimation as many patients do not report nor recognize ingesting NSAIDs taken in the form of herbal or traditional medications. Nonetheless, compared to Western populations, the prevalence of rheumatic diseases is low in Malaysia and the prescribing habits of medical practitioners may be different and as a result, the amount of NSAIDs prescribed may in fact be low as well. The majority of prescriptions for NSAIDs is probably aspirin prescribed as prophylactic therapy for coronary artery disease.

This review article addresses the following issues: mechanisms in maintaining normal gastroduodenal defenses, types of NSAID and mechanisms of NSAID induced gastroduodenal lesions, risk factors for gastroduodenal ulcer complications with NSAID therapy, interaction with *Helicobacter pylori* infection, treatment and prevention of NSAID gastroduodenal lesions.

Mechanisms Involved in Maintaining Gastroduodenal Mucosal Defenses

There are three mechanisms involved in maintaining mucosal integrity: in the normal stomach:

1. Pre-epithelial: Secretion of mucus and bicarbonate from surface epithelial cells to increase pH at the apical mucosal surface.

2. Epithelial: Epithelial cells account for at least a component of the "gastric barrier" (10). Evidence suggests that the apical surface of the epithelial cells directly resists back diffusion of acid and tight junctions on the epithelial surface can withstand acidification. There is also a process called 'restitution', whereby there is migration of existing epithelial cells along the basement membrane to fill in the defects created by the sloughed off cells. Active extrusion of back diffused H^+ via the Na^+/H^+ antiport or Cl^-/HCO^3 exchangers also takes place.

3. Post-epithelial: Mucosal blood flow is critical for delivery of HCO_3^-, O_2^- and nutrients to cells and disposing of back diffused H^+. Lamina propria is also filled with nerves, inflammatory cells and mesenchymal cells that participate in wound healing. The ability of blood vessels to form in granulation tissues may be an important step in the healing process.

Type of NSAIDs and Mechanisms of NSAIDs Induced Gastropathy

NSAIDs are inhibitors of both cyclo-oxygenase (COX) isoenzymes (COX I and COX II) though they vary in degree of inhibition of each enzyme. This results in variable potency in anti-inflammatory, analgesic and antipyretic activity and as well as in their potential of

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causing gastrointestinal complications. NSAIDs produce gastric damage by two independent mechanisms: a) Irritative topical effects b) Systemic effects.

Topical effects

Only aspirin and other salicylic acid subtypes of NSAIDs cause these direct toxic effects. The lipoprotein membrane of the surface of epithelial cells forms a barrier to water-soluble molecules but not to fat-soluble compounds. At pH of 2.5, 91% of salicylic acid is non-ionized but fat soluble and is rapidly absorbed from gastric lumen into gastric mucosal cells, where the aspirin encounters a pH of about 7.0 and ionisation occurs. This results in a high concentration gradient of non-ionized salicylic acid across the mucosal surface. As a consequence, absorption is enhanced, with tendency for aspirin to accumulate within the cells in high concentration (10). It is postulated that aspirin disrupts the lipid-protein layer on the surface of cells causing desquamation by breaking the tight junction between cells (11). Davenport (10) concluded that salicylate opens the gates of the mucosal barrier and lead to acid pouring through the breached defence destroys capillaries and venules. Vasodilatation and increased capillary permeability resulting from release of histamine within the damaged mucosa aggravate the later action.

Systemic effects

All NSAIDs inhibit the activity of cyclo-oxygenase, the enzyme that catalyses the synthesis of cyclic endoperoxides from arachidonic acid to form prostalglandins from precursor membrane fatty acids and thereby reducing the production of prostaglandins. They also have other effects such as the generation of O_2 free radicals and products of lipoxygenase pathway.

COX I is a constitutive enzyme expressed in most tissues, including blood platelets and gastric mucosa and also cell to cell signaling. COX II is induced in inflammatory cells when they are activated and is believed to be the enzyme that produces the prostanoid mediators of inflammation. Hence, clearly anti-inflammatory action is related to COX II inhibition and probably their unwanted effects are due to COX I inhibition. NSAIDs have three major actions; all of which are mainly due to the inhibition of arachidonic acid cyclooxygenase in inflammatory cells (COX II) and the resultant reduction in prostanoid synthesis. They are: anti-inflammatory action: the decrease in vasodilator prostaglandin's (PGE_2 / PGI_2) means less vasodilation and indirectly less edema but accumulation of inflammatory cells is not reduced; analgesic effect: decreased prostaglandins generations means less sensitisation of nocioeptic nerve endings to inflammatory mediators e.g. bradykinins and 5HT. Relief of headache is probably is due to reduced prostaglandins mediated vasodilatation; and antipyretic effect: due to reduced prostaglandins mediator, which is generated in response to the inflammatory pyrogens.

It is now known that several principal physiological mechanisms which are compromised through COX I inhibition are (12): mucosal blood flow, secretion of mucus, secretion of bicarbonate, cytoprotection effect, maintenance of hydrophobic mucosal surface and reduced basal and maximally stimulated gastric acid secretion.

NSAIDs are also found to be associated with reduced epithelial proliferation and diminished angiogenesis (7) which are important in ulcer healing.

Risk Factors for NSAIDs Induced Peptic Ulcer Complications

Who amongst those taking NSAIDs are most prone to develop GI complications?

In a large case control study by Rodriguez and Jick (13) the overall risk of UGIB was 4.7 in NSAIDs users. The study comprised of 1457 cases of UGIB and 10000 control subjects identified from general practitioner's computerised records in UK. Previous UGIB was identified as the single most important predictor of UGIB with a relative risk of 13.5 (10.3-17.7). The risk was higher with higher doses of NSAIDs than with lower doses (7.0 (5.2-9.6) vs 2.6 (1.8-8.3)). Increasing age, male sex, smoking and a history of peptic ulcer were also identified as independent risk factors. Other risk factors such as concurrent use of warfarin (6.4 (2.8-14.6)) and steroid (2.2 (1.4-3.5)) were also identified

Are some NSAIDs more ulcerogenic than others ?

The relative risk varied widely with different agents, with azapropazone and piroxicam having the highest risks and ibuprofen and naproxen the lowest risks. In a review of the literature, ibuprofen followed by diclofenac has consistently been associated with the lowest risk of complications (13,14,15). Henry *et al* (15) in his review suggested that some of the differences between different drugs may be because of differential doses and the advantage of "low risk drugs may be lost once their dose is increased.

Aspirin and Gastroduodenal Complications

Aspirin: How low is low dose?

Aspirin has been increasingly used as an anti-thrombotic agent in the past 25 years, since the discovery of its ability to inhibit platelet function. Its cardiovascular and neurovascular protective role has been confirmed by

several large studies (16) and its use is now widespread for these indications. As with other NSAIDs, the risk of complications with aspirin is dose-related (17,18) and it is therefore reassuring to note that lower doses of aspirin of 75-325mg daily are now recommended for anti-platelet activity (19). However, even with lower doses, patients are still at risk for ulcer complications. Weil *et al.* reported an odds ratio for UGIB of 2.3 (1.2-4.4) with aspirin 75 mg daily, 3.2 (1.7-6.5) with 150 mg daily and 3.9 (2.5-6.3) with 300mg daily (18).

Table 1. Comparison of serious GI complications with different NSAIDs with ibuprofen used as reference for calculating relative risks (adapted with permission from Henry D *et al.*, BMJ 1996 (15))

NSAID	No. studies	Pooled relative risk	95% Confidence interval
Ibuprofen	-	1.0	-
Fenoprofen	2	1.6	1.0-2.5
Aspirin	6	1.6	1.3-2.0
Diclofenac	8	1.8	1.4-2.3
Sulindac	5	2.1	1.6-2.7
Diflunisal	2	2.2	1.2-4.1
Naproxen	10	2.2	1.7-2.9
Indomethacin	11	2.4	1.9-3.1
Tolmetin	2	3.0	1.8-4.9
Piroxicam	10	3.8	2.7-5.2
Ketoprofen	7	4.2	2.7-6.4
Azapropazone	2	9.2	4.0-21.0

Aspirin associated gastrointestinal toxicity: Do different formulations differ?

As aspirin has substantial direct mucosal irritative effect, it would appear reasonable to develop special formulations to bypass the above effect in order to improve its side-effect profile or tolerability without compromising antiplatelet efficacy. For enteric-coated preparation, the tablet is coated with cellulose, silicon or other inactive ingredients that has resistance to disintegration in the stomach; hence, allowing dissolution of the drugs in the more neutral to alkali environment of the duodenum (41). Whereas, in buffered aspirin, buffering agents (Mg oxide, Mg carbonate, calcium carbonate, etc) lower H^+ concentration in the microenvironment of aspirin particles and results in increased gastrointestinal solubility of aspirin and reduced contact time between aspirin particles and the gastric mucosa (20).

To compare the risk of major upper GI bleeding between these formulations with plain aspirin, a large multicentre case-control study was carried out by Judith *et al.* (21). Relative risks of upper gastrointestinal bleed (UGIB) for each type of formulation used regularly were calculated overall, according to dose and site of bleeding, by multiple logistic regression, controlling for age, sex, marital status, education smoking, alcohol and concomitant other NSAID use.

Result showed relative risks of UGIB for plain, enteric-coated and buffered aspirin at average daily doses of 325 mg or less were 2.6, 2.7 and 3.1 respectively. At doses greater than 325 mg, the relative risk was 5.8 for plain and 7.0 for buffered aspirin, and there were insufficient data to evaluate enteric-coated aspirin at this dose level. There were no substantial differences in risk attributable to all three aspirin forms to bleeding site (gastric vs duodenum). A possible explanation is that systemic effects, which are unlikely to differ according to the aspirin preparation used, may overwhelm any differences in local effects on the gastric or duodenal mucosa.

This study did not show any substantial reduction in relative risk for low dose enteric-coated aspirin in UGIB occurrence which is inconsistent with the findings from previous endoscopic studies (20,22) which had reported much less gastric erosion and microbleeding in enteric-coated aspirin users as compared with plain aspirin users. This discrepancy is explained by the fact that mucosal erosion and submucosal haemorrhage detected in the endoscopic studies are actually poor indicators of UGIB (22).

Interaction Between NSAIDs and *H. Pylori*

H. pylori and NSAIDs are the 2 most important etiological factors in gastroduodenal ulceration. It is not entirely clear whether, when present together, they act independently or synergistically in causing ulcers. Both *H. pylori* and NSAID have been shown to interfere with various protective mechanisms in the gastroduodenal mucosa. Several of these pathogenic effects are common to both and include their effects on gastric mucus, mucosal prostaglandins and mucosal blood flow (23). *H. pylori* is known to cause hypergastrinaemia and increased acid secretion in duodenal ulcer patients; NSAIDs are also known to cause an increase in basal and maximally stimulated gastric acid (24).

There are several questions that need to be answered which will help clarify this interaction between NSAID ingestion and *H. pylori*: Are gastroduodenal ulcers more common in patients who ingest NSAIDs and are *H. pylori* infected? Is *H. pylori* more commonly found in NSAID patients with ulcers compared with those without ulcers? Data on this is conflicting. Several cross-sectional studies have shown an increase prevalence of ulcers in NSAID users who were *H. pylori* positive (25,26,27) while other

have not (28,29,30). On the other hand, two studies have reported a higher prevalence of *H. pylori* in patients with ulcers compared to those with a normal gastroduodenal mucosa (31,32).

Two longitudinal follow-up studies have again yielded conflicting results: Kim *et al.* reported no significant increase in the incidence of gastroduodenal ulcers among chronic NSAID users with *H. pylori* infection (33) while Taha *et al.* (34) found that *H. pylori* positive patients with duodenal erosions were more likely to develop ulcers during chronic NSAID treatment.

Can we prevent the development of NSAID ulcers by eradicating H. pylori (when present))?

A recent study form Hong Kong (35) addressed this question and convincingly demonstrated that it was indeed worthwhile to eradicate *H. pylori* before commencing on NSAID therapy. Twelve of 47 patients (26%) develop ulcers in the group that did not receive *H. pylori* eradication therapy compared to 1 of 45 (7%) patients who had received such therapy before commencement of NSAIDs (p=0.01). The implications of this study may be important, as it would support a strategy of testing for *H. pylori* routinely in patients undergoing NSAID treatment.

Is healing of ulcers retarded in H. pylori positive patients?

It seems intuitive to assume that ulcer healing would be impaired in patients who are *H. pylori* positive. On the contrary, in the large ASTRONAUT study (36) comparing the effect of omeprazole vs ranitidine in the treatment of NSAID associated ulcers, consistently higher healing rates were achieved for duodenal and gastric ulcers in those who were *H. pylori* positive.

Does eradication of H. pylori affect ulcer healing and ulcer relapse in NSAID users?

Seppala *et al.* (37) have shown a reduction in gastric ulcer recurrence in patients who had their *H. pylori* eradicated. In another study, Bianchi *et al.* (38), showed a trend towards lower recurrence rate with a dual amoxicillin-omeprazole therapy.

In an on-going study (HELP) (39), no difference was seen between *H. pylori* eradicated and not eradicated patients in terms of ulcer healing and ulcer relapse.

Treatment of NSAID Induced Gastroduodenal Ulcers

Almost all NSAIDs induced ulcers heal after cessation of NSAID therapy. Continued NSAID use delays healing despite standard anti-ulcer treatment. Thus, if the patient can be managed reasonably well without NSAIDs, it should be stopped.

Acid-suppression therapy is the cornerstone of treatment. In general compared to non-NSAID associated ulcers, healing appears to take a longer time when NSAID therapy is continued. Early studies using H_2 antagonists showed gastric and duodenal ulcer healing in 8-12 weeks in 80-90% ulcers despite the continued use of NSAIDs (40). Sucralfate, a surface coating agent was shown to heal duodenal but not gastric ulcers. In a review of the earlier studies (41), duodenal ulcers seem to heal more easily compared to gastric ulcers and large gastric ulcers were found to be slow and difficult to heal with treatment.

The first reported use of proton pump inhibitors in NSAID ulcers was by Walan *et al.* (42) who in a randomized controlled trial comparing the effect of omeprazole vs ranitidine in the healing of gastric ulcers, demonstrated the superiority of more potent acid suppression in the healing of NSAID ulcers (95% vs 53%). More recent studies specifically designed to look at the effect of omeprazole on the healing and maintenance of NSAID induced ulcers have been carried out and preliminary results have again shown the clear superiority of this drug compared to the prostaglandin analogue, misoprostol and ranitidine (43,36). A recent study using high doses of famotidine 40mg twice daily achieved a comparable ulcer healing rate with a longer duration of treatment of 12 weeks (44) again underlining the importance of acid suppression in the healing of NSAID ulcers.

Prevention of NSAID Induced Ulcers and Complications

The most widely studied drug for prophylaxis against NSAID ulcers or maintenance of healing has been the prostaglandin E_1 analogue, misoprostol. In placebo controlled studies, misoprostol was shown to significantly reduce the incidence of gastric and duodenal ulcers in NSAID patients (45,47). In the latter study, Graham *et al.* (47), showed that misoprostol reduced the incidence of endosopically detected gastric ulcers by 75% and duodenal ulcers by 87%. In a more recent large scale practice-based study (MUCOSA), Silverstein *et al.* (48) showed a 40% difference in incidence of serious gastrointestinal complications in patients taking misoprostol compared to placebo. In comparative studies with ranitidine and sucralfate, misoprostol has been shown to be more effective in preventing gastroduodenal lesions (48,49). Side-effects have limited the use of misoprostol; with doses of 200 µg qid, up to 1 % of patients have been reported to have diarrhoea. Lower doses of misoprostol have been used to reduce the side-effects without lowering the efficacy of the drug (50). Abdominal cramps is another frequent complain

of patients and because of the effect on the uterus is contraindicated in pregnant women.

What about H_2 antagonists? In 2 well-conducted placebo-controlled studies (51,52), ranitidine was shown to be effective in preventing duodenal but not gastric ulcers. However, recent study by Hudson N *et al.* (44) demonstrated that with a higher dose of famotidine 40 mg bid the relapse rate of gastroduodenal ulcer could be reduced from 53% to 26% at the end of 6 months. There have been few reports on sucralfate. Several small studies have produced conflicting results (53,54,55).

In recent years, large trials using the proton pump inhibitor, omperazole have been carried out. In the OMNIUM study (43), following healing of ulcers in the acute treatment phase patients were entered into a prophylactic maintenance phase. Omeprazole at a dose of 20 mg daily was again shown to be superior to misoprostol and placebo in the prevention of recurrence of ulcers. Only 32% of placebo treated patient remained in remission after 6 months whereas 64% and 51% sustained remission being achieved by omeprazole and misoprostol (200 µg bid) respectively. Similarly, in the ASTRONAUT study (36), omperazole at a dose of 20 mg daily was shown to be superior to ranitidine in keeping patients in remission. After 6 months of maintenance treatment, 80 % omeprazole treated patients remained in remission as compared with 66 % of those receiving ranitidine.

In 2 further studies, the SCUR (56) and OPPULENT (57) studies, omeprazole was again shown to be superior to placebo in preventing the occurrence of new ulcers. SCUR showed 74% remission rate in omeprazole group as compared to only 48% in the placebo group at the end of 3 months. Consistent findings have also been shown in the OPPULENT study where after 6 months of treatment, 78% of patients ($p<0.01$) remained in remission compared with 53% of those on placebo ($p<0.01$).

Conclusion

NSAIDs are perhaps one of the most widely prescribed drugs in the world today. They are valuable therapeutic agents for a broad range of rheumatic diseases. Aspirin is now widely prescribed for prevention of vaso-occlusive disorders. There are however, major side-effects associated with its use. These are mainly in the upper gastrointestinal tract where serious complications such as bleeding and ulcer perforation can occur. Risk factors include older age group, concomitant serious medical illness, higher dose of and use of multiple NSAIDs.

The association with *H. pylori* is an intriguing one. There is persuasive evidence that eradicating the bacteria results in lower incidence of gastroduodenal ulcers. On the other hand, data from on-going studies suggest that NSAID ulcers heal less well when *H. pylori* is eradicated. It seem logical and even intuitive that a second ulcerogenic factor should be eliminated and this has prompted the European Consensus to categorize as "advisable", eradication of *H. pylori* in patients embarking on long term NSAID therapy (58). The controversy is however reflected in the Asian Pacific Consensus statements (59) where, routine screening for *H. pylori* was not recommended prior to initiating NSAID therapy. However, patients with dyspepsia and starting on long term NSAID therapy were advised to seek investigations for their dyspepsia. Dyspepsia has been demonstrated to have high specificity but extremely low sensitivity in predicting the presence of gastroduodenal lesions (60) in patients taking NSAIDs.

Although NSAID ulcers in general heal less well than non-NSAID ulcers, effective treatment can be achieved with acid-suppressing agents, in particular, the proton pump inhibitors. Prevention of gastroduodenal damage by NSAIDs can be achieved with the prostaglandin analogues although recent data shows again the superiority of potent acid suppression with proton pump inhibitors.

What then are the practical recommendations?

NSAIDs should be used judiciously. The lowest doses of NSAID should be used and should be stopped when no longer required. It appears that some NSAIDs are less toxic than others and these should be chosen wherever possible. Newer NSAIDs including selective COX II inhibitors or NO-NSAIDs that incorporate a nitroxybutyl moiety may have lower toxicity. However their predicted lower toxicity has to be proven in wider clinical usage.

How should NSAID associated ulcers be treated?

Stopping NSAIDs helps with healing. Non NSAIDs alternatives such as paracetamol could be substituted for pain relief. Omeprazole at a dose of 20 mg om is recommended for treatment. Where detected *H. pylori*, on the balance of present evidence, should be eradicated.

Should every patient on NSAIDs receive prophylactic therapy?

The consensus at the present time, taking into consideration costs and magnitude of NSAID use is to offer prophylaxis to only the high-risk groups of patients: elderly patients, patients with history of peptic ulcers and /or gastrointestinal bleed and those with concomitant serious medical illness. Recommended prophylaxis treatment includes omeprazole 20 mg om.

Newer proton pump inhibitors (lansoprazole, pantoprazole) are available and are likely to be equally effective but to date there are no published data in support of their efficacy in preventing NSAID complications. Misoprostol is also effective in prophylaxis at a dose of 200 µg qid.

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