REVIEW ARTICLE

NSAID Gastropathy

A New Understanding

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Nonsteroidal anti-inflammatory drug (NSAID) gastropathy is associated with substantial morbidity and mortality, which result in high costs to both the patient and society. The subset of patients who are at greatest risk for developing NSAID gastropathy continues to be better defined, but various risk factors, such as age and previous gastrointestinal tract disease, have been identified. In patients receiving older NSAIDs, the choice of NSAID should be based on differences in formulations at the lowest effective dose. Gastroprotective cotherapy should be instituted if treatment with older NSAIDs is continued in at-risk patients; misoprostol is currently the only agent approved for this indication. The impact of misoprostol on clinical gastrointestinal tract end points has recently been documented. Newer NSAIDs may have an improved safety profile over older NSAIDs; some have a clinically documented reduction in the incidence of adverse gastrointestinal tract effects. An understanding of these issues should enable the informed clinician to choose an NSAID on the basis of risk-benefit and cost-benefit considerations.

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By the turn of the century, aspirin had become the most frequently used drug in the world. As an effective anti-inflammatory agent, aspirin was used to treat rheumatic disorders but was frequently associated with adverse effects, such as "gastric irritation" and tinnitus.[1] By the 1950s, nonsteroidal anti-inflammatory drugs (NSAIDs) had been developed to provide alternatives to aspirin, primarily because of the perceived gastrotoxic effects of aspirin.[2] To date, more than 100 NSAIDs have been tested; at least 18 have been marketed in the United States and many more are marketed in other countries. There are 70 million to 100 million prescriptions for NSAIDs per year, and approximately 15 million patients in the United States require long-term NSAID therapy.[1] In addition, the over-the-counter availability of NSAIDs is reported to exceed prescription NSAID use by 7-fold.[3]

The term *NSAID gastropathy* was first introduced into the medical literature in 1986 in an effort to differentiate between classic peptic ulcer disease and the unique range of gastric mucosal lesions associated with long-term NSAID therapy.[4,5] Symptoms of NSAID gastropathy range from dyspepsia and pain to the serious, silent, and potentially deadly consequences of perforations, ulcers, and hemorrhages. Gastropathy from NSAIDs usually occurs within the first few weeks of treatment[6,7] but also seems to be associated with long-term NSAID use.[8]

Gastropathy from NSAIDs differs from classic peptic ulcer disease in several aspects. Classic peptic ulcers are usually duodenal and symptomatic and are seen most frequently in younger men. In contrast, NSAID gastropathy includes mucosal lesions of the upper gastrointestinal (GI) tract and usually affects the elderly.[5] In addition, there are important differences that are evident endoscopically. Gastropathy caused by NSAIDs is characterized by lesions ranging from erythema through diffuse erosions and microbleeding to gastric crater ulcer.[5] However, the subset of patients who take NSAIDs for a long period and develop serious ulcer complications because of failure of normal mucosal adaptation remains to be identified.[9]

Gastropathy from NSAIDs is recognized as the most frequent serious complication from medication therapy.[10,11] Such complications as hemorrhage and perforation require hospitalization and/or

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surgery, and up to 10% of these complications can be fatal.[12] An analysis of data from the Medicaid Management Information System of Pennsylvania in 1985 suggested that the hospitalization of patients for the treatment of NSAID gastropathy costs $2000 for a 3-month period, compared with an average cost of $27 for outpatient treatment of NSAID-related GI tract effects.[13] The annual cost of GI tract complications is estimated at $3.9 billion, with at least 2600 deaths and up to 20 000 hospitalizations per year.[11,14]

This article reviews new understandings in the epidemiology, pathogenesis, treatment, and prophylaxis of NSAID gastropathy (**Table 1**).

Table 1. A New Understanding of NSAID Gastropathy*

Issues	Answers
Significant morbidity and mortality	Results in high costs to patient and society
Identify those at greatest risk	Age, sex, medical history, endoscopy
Choose safest NSAID	Based on pharmacological formulation differences at lowest effective dose for older NSAIDs; newer NSAIDs such as nabumetone appear to be gastroprotective
Institute gastroprotective cotherapy if continuing therapy with older NSAIDs	Misoprostol is only approved agent for this indication
Cost-effectiveness	Misoprostol demonstrated cost-effective; nabumetone demonstrated cost-effective compared with fixed-combination misoprostol and NSAID

*NSAID indicates nonsteroidal anti-inflammatory drug.

PATHOGENESIS OF NSAID GASTROPATHY

Defensive gastric mechanisms in the face of the hostile acid pepsin environment of the gastric lumen are now well understood. The phospholipid interface over a semipermeable mucin barrier, reinforced with bicarbonate ions in an unstirred water layer, forms a neutral pH interface between mucosal epithelial cells and the acid lumen. Critical microcirculatory substrata reinforce the resilience of those mucosal cells.[15]

Under normal circumstances, the gastric mucosa adapts to compensate for adverse conditions.[16] In 1986, Graham and Smith[8] defined the resiliency of the gastric mucosa under NSAID attack. They reported that continuing NSAID use ultimately produced an "invisible callus" that was seemingly resistant to NSAID insult. However, it appears that this resiliency fails in "at-risk" populations who are receiving long-term NSAID therapy, ie, there is a compromise of adaptive mucosal responses.[9]

Adaptive mechanisms, so critical to organisms on a system-by-system basis, can indeed fail before aging and disease processes.[17] More recent investigations indicating the possible amplification of ulcer complication rates with NSAIDs require further study.[18] Yet understanding the basis for that failure, and recognizing those mechanisms most likely to fail, provides the rationale for therapeutic response.

The basis of gastrotoxic effects is multifactorial. The NSAIDs compromise both platelet and coagulation mechanisms. The generic description of cytoprotection must now include issues of restitution and regenerative repair as part of adaptation and include new understandings of the relevance of growth factors.[16] Superimposed on preexisting risk factors are interactions with aging, codisease and cotherapies, and the effects of such compromise on neutrophil function and mucosal blood flow. The role of prostaglandins, molecular energy interactions, and superoxide radicals are all under continuing investigative scrutiny.[16] It is a dynamic defensive role that responds to the additive offensive punitive challenge from NSAIDs. When these morphologic barriers are compromised for a prolonged period, gastropathy can evolve to clinical complications.

The fundamental work of Vane[19] demonstrated that the mechanism of action of NSAIDs involves inhibition of prostaglandin synthesis via inhibition of prostaglandin cyclooxygenase (COX). This inhibition of prostaglandin production results in anti-inflammatory effects, but it also compromises the normal protection of the gastric mucosa. Individual NSAIDs have varying half-lives and renal clearance. They differ in topical mucosal toxicity[20] and potential for biliary recirculation with reexposure to the gastric mucosa, and they have variable gastric COX isoenzyme-sparing characteristics.[21]

A more sophisticated appreciation of the isoenzymes of prostaglandins is now available.[22] Two forms of COX enzyme are now recognized as COX-I and COX-II.[23,24] The isoenzyme COX-I is specific to the stomach, intestine, kidney, and platelets; COX-II is mitogen inducible, mainly in inflammatory cells. Since the adverse GI tract events of NSAIDs most often seem to relate to the inhibition of COX-I, a selective COX-II NSAID is thought to be gastrosparing. At least 1 such NSAID (nabumetone) has been identified by basic investigation (see below).

In 1974, Sun et al[25] first reported a 28% incidence of peptic ulcers with NSAID therapy and rheumatoid arthritis. In that study, we found esophageal dysfunction in one third of the 143 patients. They exhibited low esophageal sphincter pressure and motility derangement, findings similar to those in scleroderma esophagus. This may explain the dyspepsia and pyrosis commonly associated with NSAID use and not well correlated with endoscopic findings of gastropathy. We subsequently reported the high incidence of mucosal lesions associated with aspirin use in patients with rheumatoid arthritis.[26]

RISK FACTORS FOR NSAID GASTROPATHY

The following factors are associated with increased risk for developing NSAID gastropathy: increasing age older than 60 years[7,12,27,28]; female sex[12]; history of previous GI tract disease[28]; concurrent use of other ulcerogenic substances, eg, corticosteroids[29] and anticoagulants[30]; and for older NSAIDS, higher dose.[6,7,28]

There are conflicting data on the influence of smoking and alcohol on NSAID gastropathy, although these elements are known to increase the risk of developing classic peptic ulcer disease.[31]

It is now generally believed that *Helicobacter pylori* infection is associated with active chronic gastritis and with the vast majority of duodenal and gastric ulcers. However, there is substantial evidence to suggest that *H pylori* is not a particular risk factor for NSAID gastropathy.[32-35] In 1 double-blind comparison of etodolac, naproxen, and placebo for 4 weeks in 46 healthy volunteers, there was no evidence of worsening gastric mucosal histological injury with NSAID ingestion. In addition, the presence of *H pylori* had no effect on the degree of gross GI tract damage induced by NSAIDs.[35] Thus, the authors concluded that it may not be necessary to determine *H pylori* status or to attempt to eradicate *H pylori* before initiating NSAID therapy.

The NSAIDs and salicylates are still the most accepted treatments for musculoskeletal and arthritic disorders. However, in very high-risk patients with recent major hemorrhages or recurrent ulcer, alternative agents, such as topical and systemic analgesics, are recommended.[5]

NSAID TOLERABILITY PROFILE

Upper GI Tract Toxic Effects

Extensive clinical and epidemiological evidence supports the association of older NSAIDs with upper GI tract toxic effects.[28] Relative risks for upper GI tract toxic effects between different NSAIDs have been determined by many investigators in randomized clinical studies, cohort studies, or case-control studies. Case-control studies may overestimate the risk because patients who present with GI tract hemorrhage are more likely than controls to be questioned about NSAID use. On the other hand, cohort studies may underestimate the risk by overestimating the duration of NSAID use. Finally, clinical studies usually lack statistically power to show clinically relevant differences.[36] In addition, the endoscopic scoring system used in many studies emphasizes mucosal erosions, but recent reevaluation suggests that this system may not be clinically relevant.[37] Epidemiological data appear to provide the best "real-life" estimate.[5]

Salicylates. Aspirin is no longer a prototype for anti-inflammatory therapy because of its recognized high incidence of gastric symptoms as well as known gastric toxic effects.[1] Mucosal adaptation has been shown to develop after short-term administration,[38] but this adaptation appears to fail after long-term administration.[26] Failed mucosal adaptation during long-term aspirin therapy in the elderly is supported by data from the Aspirin Myocardial Infarction Study.[39]

Nonacetylated salicylates appear to be prostaglandin-sparing but are actually anti-inflammatory as well as analgesic.[1] However, they may be less frequently prescribed for arthritis and pain management because of concerns of allegedly lower efficacy and inferior analgesic benefits, tinnitus, and dosing issues related to salicylism.

Older NSAIDs. The link between the use of older NSAIDs and gastropathy is undisputed. The risks are generally similar for gastric and duodenal abnormalities.[31] From the late 1970s to the early 1980s, the increase in NSAID prescriptions paralleled the increase in hospital admissions for ulcer complications.[27] The Arthritis Rheumatism and Aging Medical Information System database has documented a 1.5% annual increase in the incidence of hospitalization associated with NSAID use in patients with rheumatoid arthritis.[28] The US Food and Drug Administration and the UK Committee on Safety of Medicines have confirmed that the number of ulcer bleeding episodes reported in connection with NSAID use is in excess of all complications reported for all other drugs.[40,41]

The overall relative risk for development of upper GI tract bleeding with older NSAID use is approximately 3 (2.5-10). Overall, there appears to be a 6.5-fold increased risk of hospitalization from GI tract illness in NSAID recipients.[11]

Several studies and meta-analyses have attempted to evaluate the relative risks of NSAID gastropathy for individual NSAIDs (**Table 2**).[7,30,42-44] Although the differences in patient populations confound direct comparisons between studies, most data consistently suggest that ibuprofen has the lowest relative risk and piroxicam the highest for gastropathy.[7,30,43,44] This may in part result from the use of low-dose ibuprofen for short-term indications. These data are consistent with the Food and Drug Administration and Committee on Safety of Medicines rankings among available NSAIDs.[40,41]

Newer NSAIDs. Newer NSAIDs may demonstrate a more favorable GI tract tolerability profile than older NSAIDs. However, there are limited available data to rank individual NSAID GI tract tolerability accurately, especially in comparing older vs newer NSAIDs. Nabumetone has been studied in large enough patient cohorts to report a low incidence of NSAID gastropathy with 95% confidence intervals (CIs).[42] There are no data with oxaprozin from case or cohort studies and no data in large enough samples to report 95% CIs. Similarly, the risks for adverse GI tract effects with etodolac have not been reported with 95% CIs.

Nabumetone is a nonacid prodrug that is rapidly converted to its active metabolite, 6-methoxy-2-naphthylacetic acid, in the liver. It has no in vitro effect on prostaglandin synthesis in human gastric tissue[45] and is a weak inhibitor of gastric prostaglandin synthesis in animals.[46] Nabumetone undergoes minimal enterohepatic circulation, and, because of the lack of accumulation in gastric mucosal cells, it has been postulated to pose less risk for gastric damage than other NSAIDs.[46] This reduced risk is supported by animal data[47-51] and also appears to be supported by recent clinical experience.

Controlled clinical studies have documented the low ulcerogenic potential of nabumetone in comparison with older NSAIDs.[52-54] In addition, the ulcerogenic potential of nabumetone is comparable with that of fixed-combination ibuprofen-misoprostol.[55] The cumulative inci-

Table 2. Estimated Risks for Gastropathy With Individual NSAIDs*

	Relative Risk Ratios (95% CI)			Cumulative Frequency, % (95% CI)
	Peptic Ulcer Disease	GI Hemorrhage	GI Complications	
Older NSAIDs				
Piroxicam	6.4 (4.8-8.4)‡	18.0 (8.2-39.6)§ 13.7 (7.1-26.3)¶	4.8 (2.6-8.7)‖	
Naproxen	4.3 (3.4-5.4)‡	3.1 (1.7-5.9)§ 9.1 (5.5-15.1)¶	2.8 (1.8-4.3)‖	
Sulindac	4.2 (2.8-6.3)‡	2.9 (1.5-5.6)§	2.1 (1.1-4.1)‖	
Indomethacin	3.8 (2.4-6.0)‡	6.3 (3.3-1.2)§ 11.3 (6.3-20.3)¶	2.5 (1.5-4.1)‖	1.4 (0.5-2.4)†
Diclofenac	...	3.9 (2.3-6.5)§ 4.2 (2.6-6.8)¶	1.7 (1.1-2.5)‖	
Ibuprofen	2.3 (1.8-3.0)‡	2.9 (1.7-5.0)§ 2.0 (1.4-2.8)¶	0.7 (0.4-2.4)‖	
Newer NSAIDs				
Nabumetone	...	...	...	0.2 (0.01-0.3)†
Oxaprozin	...	...	...	NA
Etodolic acid	...	...	...	NA

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; CI, confidence interval; GI, gastrointestinal tract; and NA, data with 95% CIs not available.
†Lipani and Poland.[42]
‡Griffin et al.[7]
§García-Rodríguez and Jick.[30]
‖Henry et al.[43]
¶Langman et al.[44]

dence of gastric perforations, ulcers, and hemorrhages in more than 6000 patients treated with nabumetone, 1 to 2 g daily, for 3 to 6 months in clinical trials is 0.1% at 3 months and 0.2% at 6 months.[42]

Pharmacoeconomic analyses appear to support the cost-effective use of nabumetone in arthritis. In 1 analysis, the lower incidence of perforations, ulcers, and GI tract hemorrhages associated with nabumetone resulted in lower direct medical costs than comparable NSAID treatment.[56] In another study in patients with osteoarthritis, the lower incidence of endoscopic lesions with nabumetone compared with fixed-combination ibuprofen-misoprostol resulted in lower overall costs.[57]

Etodolac is a member of the pyranocarboxylic acid class of NSAIDs. It appears to be well tolerated in both regular and sustained-release formulations.[58,59] In a recent review, the reported rate of GI tract complications was 0.8%.[60] However, there are no data with 95% CIs. Further epidemiological data are needed to confirm the long-term GI tract safety of etodolac.

The propionic acid derivative oxaprozin has recently been approved in the United States for the treatment of rheumatoid arthritis and osteoarthritis. However, there are limited published data available on the tolerability of oxaprozin.

It is difficult to compare newer NSAIDs directly with older NSAIDs because doses, characteristics of patients, and study design have changed since the association between older NSAID use and GI tract hemorrhage, ulcers, and NSAIDs was recognized. Nabumetone appears to be the only NSAID with available data from large patient populations to give an estimated risk for gastropathy with 95% CIs. Further postmarketing surveillance data are required in similar patient populations to compare directly the relative risks of GI tract adverse effects associated with individual NSAIDs and to confirm the superior tolerability of any NSAID.

Lower GI Tract Toxic Effects

The effects of NSAIDs on the lower GI tract have been less well investigated and documented than those on the upper GI tract. However, there does appear to be an association between aspirin and lower GI tract hemorrhage.[61] In another study, Allison and colleagues[62] showed that NSAID recipients have an increased risk of nonspecific ulceration of the smaller intestine (8.4% vs 0.6% in non–NSAID-treated patients). Although the risk of lower GI tract gastropathy is somewhat lower than that of gastric or duodenal effects, these effects should not be overlooked, since life-threatening complications can result.

PROPHYLAXIS AND TREATMENT OF NSAID GASTROPATHY

The effectiveness of several agents as treatment or prophylaxis against NSAID gastropathy has been investigated. In general, while mucosal protective agents, such as antacids and sucralfate, are efficacious in peptic ulcer disease, they have not been proved to be effective in NSAID-related GI tract complications.[63] The effectiveness of antacids against NSAID gastropathy has recently been documented in a double-blind controlled clinical study.[64] However, while antacid use was associated with reduced dyspeptic symptoms, the risk of ulcer complications is not addressed by usual casual use of these agents. There are no data to support the use of sucralfate in NSAID-induced gastropathy.[63]

The effectiveness of the histamine$_2$-antagonist cimetidine against NSAID gastropathy has been studied extensively. These studies have failed to document successful prevention of gastropathy when NSAID use is continued.[5,37,65,66] Ranitidine was

effective against NSAID-associated duodenal, but not gastric, ulceration in 1 study,[67] and a recent report also suggests that famotidine may effectively prevent NSAID gastropathy.[68] Several studies suggest that the proton pump inhibitor omeprazole may treat and prevent gastropathy when administered concomitantly with an NSAID,[69,70] although as with cimetidine, omeprazole appears to be more effective against duodenal than gastric ulceration.[71,72]

In the United States, misoprostol is the only agent currently approved as cotherapy with NSAIDs. Misoprostol has been documented as both effective treatment[26,73] and effective long-term protection[38,74,75] against NSAID-associated GI tract effects. On the basis of these data, various pharmacoeconomic analyses of misoprostol data[76] suggested that cotherapy with NSAIDs is cost-effective.[77-80] These conclusions have been questioned because of the lack of evidence to link prospectively various GI tract end points to clinical outcomes.[81] However, the recently published Misoprostol Ulcer Complications Outcome Study provides evidence to support the conclusions of these pharmacoeconomic analyses. In this study, concurrent administration of misoprostol with NSAIDs significantly reduced GI tract end points in patients with rheumatoid arthritis.[75] The results suggest that misoprostol would have an impact on the costs associated with NSAID gastropathy in patients with rheumatoid arthritis. Although this study documented prospective outcome data, it did not directly address economic issues. Economic analyses of the data from the Misoprostol Ulcer Complications Outcome Study may conclusively demonstrate the cost-effectiveness of misoprostol as cotherapy with NSAIDs.

Fixed-ratio combinations of misoprostol with an NSAID are currently undergoing investigation. Diclofenac-misoprostol is now available in the United Kingdom. It is anticipated that such fixed-combination treatment will be targeted to patients at high risk for developing NSAID gastropathies.

Other agents currently undergoing investigations as gastroprotective cotherapies with NSAIDs include rebamipide. Rebamipide is a quinolone derivative with topical gastric mucosal protective effects that is undergoing investigation for NSAID gastropathy.[82]

Several agents may potentially afford gastroprotection when administered as cotherapy with NSAIDs, but there is a concern that these agents will lead to an increased financial burden of such diseases as rheumatoid arthritis. Careful identification of patients who are at increased risk of developing NSAID gastropathy should influence the choice of gastrosparing NSAIDs or cost-effective cotherapies.

CONCLUSIONS

The NSAIDs remain the single most frequently used group of drugs in medicine, especially to relieve pain and suppress inflammation. Cost-benefit and cost-utility issues determine and limit therapeutic choices of NSAIDs including gastroprotective GI cotherapy or non-NSAID alternatives in high-risk gastropathy patients. This includes oral and topical analgesics, or even nondrug management. The serious outcomes of ulcers and hemorrhages drive the cost of NSAID gastropathy. Gastropathy symptoms require costly intervention, including consultation, procedural interventions, and possible short- and long-term cotherapy to permit continued NSAID management. However, newer NSAIDs have been proved to be effective in both rheumatoid arthritis and osteoarthritis. Of the newer NSAIDs, nabumetone appears to have an improved safety profile over older NSAIDs, with a clinically documented reduction in the incidence of serious adverse GI tract effects. Ultimately, the choice of an NSAID will be based on host response with proper clinical monitoring, and selection should be decided by safety data, which are now known. Cost-effective and risk-benefit considerations are demanded not only by our managed care systems but by an informed medical conscience.

Just as we entered NSAID gastropathy into the medical literature through this journal a decade ago with the admonition "we started it," so now through these new understandings, pharmacotherapies, and strategies, we can now more assuredly prevent and stop it.

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