

A Guideline for the Treatment and Prevention of NSAID-Induced Ulcers

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PREAMBLE

Guidelines for clinical practice are intended to indicate preferred approaches to medical problems as established by scientifically valid research. Double-blind, placebo-controlled studies are preferable, but compassionate use reports and expert review articles are used in a thorough review of the literature conducted through Medline with the National Library of Medicine. When only data that will not withstand objective scrutiny are available, a recommendation is identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject without regard to specialty training or interests and are intended to indicate the preferable, but not necessarily the only, acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care, which are inflexible and rarely violated. Given the wide range of specifics in any health care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision.

Guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. Each has been intensely reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision analysis. The recommendations of each guideline are therefore considered valid at the time of their production based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at a time established and indicated at publication to assure continued validity.

INTRODUCTION

The relationship between nonsteroidal anti-inflammatory drugs (NSAIDs) and gastroduodenal injury is now well established (1, 2). Patients with rheumatoid arthritis (RA) and osteoarthritis (OA) taking NSAIDs have an ulcer incidence of approximately 15–20% (3, 4). Complications of ulcer disease, *i.e.*, hemorrhage and perforation, occur far more often in patients taking these agents than in comparable control groups (5–7). The overall risk for serious adverse gastrointestinal (GI) events in patients taking NSAIDs is about three times greater than that of controls. In elderly patients (>60 yr), this risk rises to more than five times that of controls, whereas the risk for younger patients is only slightly more than one-and-one-half times (6). In elderly patients taking NSAIDs the relative risk of GI surgery is ten times, and for GI cause of death, about four-and-one-half times greater than in control groups (6). Approximately 20 million patients in the US take NSAIDs on a regular basis; the risk for hospitalization for serious GI adverse effects is 1–2%, resulting in approximately 200,000 to 400,000 hospitalizations per year at an average cost of \$4,000 per patient, or 0.8–1.6 billion dollars annually (8, 9). The economic impact of this problem is increased by multiple other factors, including lost wages, postop care, *etc.*

Two major issues confront clinicians using these agents: 1) the prevention of NSAID-induced ulcers, especially in high risk groups, and 2) their treatment, often when underlying disease mandates continued NSAID use. A third problem is the recent recognition of small bowel and colon NSAID-related mucosal injury. The purpose of this guideline is to make recommendations based on the pertinent medical literature addressing these problems.

PREVENTION OF NSAID-INDUCED ULCERS

Recommendation

Patients at high risk for hemorrhage and perforation from aspirin and other NSAID-induced ulcers should be considered for prophylaxis with misoprostol. Proton pump inhibitors are an acceptable alternative for prevention of NSAID-related complications. H₂ receptor antagonists have been shown to prevent only duodenal ulcer, and there-

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TABLE 1
Factors Related to Increased Risk of NSAID Induced GI Complications

Risk Factor	Relative Risk	95% CI	Ref #
Overall	2.74	2.54–2.97	6
Age (>60)	5.52	4.63–6.60	6
Prior GI event	4.76	4.05–5.59	6
High dosage (>2 × normal)	10.1	4.6–22.0	43
Concurrent corticosteroids	4.4	2.0–9.7	44
Concurrent anticoagulants	12.7	6.3–25.7	45

fore cannot be recommended for prophylaxis. Factors that have been identified as placing patients at increased risk for NSAID-related GI complications include the following:

1. Prior history of gastrointestinal event (ulcer, hemorrhage)
2. Age >60 yr
3. High dosage
4. Concurrent use of corticosteroids
5. Concurrent use of anticoagulants

Although a direct link has not been established between NSAID-induced ulcers and gastrointestinal hemorrhage and perforation, these complications occur significantly more often in patients taking NSAIDs when compared with control groups. As noted above, these serious adverse events also tend to occur more often in high risk groups which include patients with a prior history of a GI event, advanced age (>60 yr), high NSAID dosage, and concomitant use of corticosteroids or anticoagulants (Table 1). Several randomized controlled trials (RCTs) have been published attempting to show that various therapeutic maneuvers can prevent the development of gastric ulcer (GU) and duodenal ulcer (DU) in patients taking NSAIDs. However, only one study has been published linking any cotherapy with prevention of the complications of ulcer disease, *i.e.*, bleeding and perforation (10). It is not unreasonable, however, to assume that prevention of NSAID-induced ulcer should be associated with a similar prevention of the complications of ulcer disease.

Numerous RCTs have been carried out, both in normal volunteers and in patients with arthritic disorders, to evaluate the efficacy of coadministration of various agents for the prevention of both NSAID-related, nonulcer gastropathy and GU and DU (11–28). Generally, these have shown that concomitant administration of the prostaglandin E1 analog misoprostol along with various NSAIDs can prevent both GU and DU (11–23); that the proton pump inhibitor (PPI) (24–26) omeprazole reduces GU and prevents DU; and that H2 receptor antagonists are effective in preventing DU but not GU (27, 28).

Prophylaxis with prostaglandins or PPIs for all patients taking NSAIDs is unnecessary and cost-prohibitive. Studies

with misoprostol have shown that in high risk groups, prophylaxis may be cost-effective (7). The numerous factors involved in these analyses, *i.e.*, the time lost from work, expense of hospitalization with or without surgery, varying costs of prophylactic and therapeutic drugs, and quality of life issues make it very difficult to determine the cost effectiveness of prophylactic therapy for NSAID-related ulcer disease and its complications.

Risk Factors

All patients taking NSAIDs do not require prophylaxis. These drugs are used extensively as treatment for limited illnesses. Anti-inflammatory doses of numerous NSAIDs have been administered for short periods of time (up to 7 days) to large numbers of young, healthy volunteers without any reports of significant GI bleeding or other serious event (29). Many patients of all ages, however, take anti-inflammatory NSAID doses for longer periods, and many case-control studies have shown that, in these patients, significant GI bleeding and other severe adverse events occur more commonly than in matched control patients (30–37). An increased risk of GI bleeding has even been noted in patients taking low dose aspirin therapy for cardiovascular prophylaxis (38–41). Obviously, as all patients taking NSAIDs do not develop serious complications, risk factors must exist in some patients that increase the incidence of GI bleeding, perforation, surgery, and even death.

A series of nested case-controlled studies based on hospitalization for GI hemorrhage of Medicaid recipients aged >65 yr in the state of Tennessee showed an increased bleeding risk for patients >65 yr (odds ratio 4.7), increased dose (odds ratio 8.0), concomitant corticosteroid (odds ratio 4.4), or anticoagulant therapy (odds ratio 12.7), and short term onset of use (<1 month) (7.2) (42–45). A large autopsy series on patients with a history of NSAID use showed that gastric and duodenal lesions were more common in patients who took NSAIDs for <3 months, whereas patients with a longer duration of therapy tended to have more lesions in the small bowel and colon (46).

A large retrospective cohort study, also based on data from Medicaid patients, confirmed the overall increased risk for GI bleeding in patients taking NSAIDs, especially over the aged >60 yr (47). Similar data have been obtained from other large cohort studies (40, 48, 49). In a large prospective, multicenter study in patients with RA (N = 2747) and OA (N = 1091), the principal risk factors for hospitalization for serious GI events were age, prior NSAID GI side effect, prior GI hospitalization, corticosteroid use, and debility expressed as a level of disability. The overall risk in this study for hospitalization during NSAID therapy in patients with RA was 1.58% (5).

A large meta-analysis of these and other studies showed an overall odds ratio for GI bleeding of 2.74 in all patients taking NSAIDs. Patients with a prior gastrointestinal event had an odds ratio of 4.76. Age (>60 yr), concurrent corticosteroids, and shorter duration (>3 months) of NSAID

TABLE 2
NSAID Protection Studies With Misoprostol for Gastric Ulcer

Ref.	Misoprostol			Placebo			<i>p</i>
	Dose	N	Ulcers	N	Ulcers	%	
16	100 µg <i>q.i.d.</i>	143	8	138	30	21.7	0.001
	200 µg <i>q.i.d.</i>	139	2				0.001
17	200 µg <i>q.i.d.</i>	320	6	323	25	7.7	0.001
19	200 µg <i>b.i.d.</i>	465	27	465	47	10.3	0.05
	200 µg <i>t.i.d.</i>	474	15				0.01
21	200 µg <i>q.i.d.</i>	229	7	38	11	28.9	0.01
	200 µg <i>t.i.d.</i> or <i>q.i.d.</i>	32	4				0.05
18	200 µg <i>q.i.d.</i>	122	2	131	Sucralfate 1 gm <i>q.i.d.</i>		0.001
					21	16.0	
22	200 µg <i>q.i.d.</i>	180	1	194	Ranitidine 150 mg <i>t.i.d.</i>		0.01
					11	5.7	

consumption were all associated with an increased relative risk ratio for serious adverse GI events (Table 1). Gender, smoking, and alcohol were not found to be independent risk factors (6).

A large, double blind, randomized, controlled treatment prevention trial in >8000 patients with RA also identified a history of cardiovascular disease as a risk factor for UGI complications of NSAID use (odds ratio 1.84). In this same trial, age >75 yr (odds ratio 2.48), prior peptic ulcer (odds ratio 2.29), and prior GI bleeding (odds ratio 2.56) were again associated with increased risk (10).

There appears to be some difference between the various NSAIDs with reference to the incidence of significant GI bleeding and other adverse events. Four large cohort studies have been published comparing the risk of these complications associated with the various NSAIDs. Overall, these studies show an increased toxicity for ketorolac and piroxicam, and intermediate toxicity for naproxen, indomethacin, ketoprofen, and diclofenac. Ibuprofen in all studies was less toxic than the other agents, but this is probably related to the generally lower doses employed with this agent, which is available over the counter (50–54).

No good prospective controlled data for GI bleeding and other ulcer complications is available for the recently introduced, newer NSAIDs purported to be less toxic to the upper GI mucosa (nabumetone, etodolac, oxaprofen). Several large postmarketing, open label studies involving thousands of patients in Europe suggest that bleeding rates with these agents are in the range of 0.5% (55–59). These studies have recently been reviewed in the American literature (60). Of these agents, nabumetone has been the most extensively studied. A 12-wk endoscopic study compared nabumetone (1000 mg *q.d.*), ibuprofen (600 mg *q.i.d.*), and the same dose of ibuprofen plus misoprostol in 171 patients with OA. There was no difference in the number of ulcers found in the nabumetone and nabumetone/misoprostol groups (one and zero, respectively), which were significantly less ($p < 0.01$) than the eight ulcers found in the ibuprofen group (61). Another endoscopic study compared nabumetone 1000 mg

q.d. with naproxen 500 mg *b.i.d.* in RA patients for 4 wk. One ulcer was found in the 22 patients taking nabumetone and eight in the 30 patients treated with naproxen ($p = 0.01$) (62). In a third study, 27 patients with either RA or OA were followed for 5 yr taking either naproxen 250 mg *b.i.d.* or nabumetone 1000 mg *q.d.* Ulcers were found in eight of 12 patients taking naproxen and in one of 15 taking nabumetone ($p = 0.02$). No bleeding was found in either group (63).

The combination of advanced age with any of the other noted risk factors has also been noted to further increase the probability of ulcer complications in NSAID users, especially in the first month of therapy. The relative risk of requiring GI surgery or GI cause of death increases dramatically in patients >60 yr (6). Although a 15–25% incidence of gastric and/or duodenal ulcer has been demonstrated in all patients taking NSAIDs (3, 4), the bleeding rate is estimated by most experts at only 2–4%. In a meta-analysis of 100 trials of NSAID therapy, bleeding occurred in 24 of 1157 patients taking active drug (2%), compared with only eight of 1103 taking placebo (0.6%) (64). It can be derived from these data that about only one in 10 NSAID-induced ulcer bleeds. A recent large, multicenter, double-blind RCT in >800 arthritic patients taking NSAIDs showed that the incidence of perforation, outlet obstruction, and hemorrhage was reduced by 40% in those subjects taking misoprostol compared with placebo. In this study, these complications were seen in 22 of 4404 patients on misoprostol compared with 42 of 4439 taking placebo ($p = 0.049$) (10).

Prostaglandins

Currently, the only available prostaglandin is misoprostol, a synthetic prostaglandin E1 analog. A series of RCTs in normal volunteers have shown that this agent can prevent acute NSAID-related erosion and ulceration (11–15). Subsequent RCTs in patients with OA and RA have demonstrated that misoprostol was significantly better than placebo, sucralfate, and ranitidine for the prevention of NSAID-related GU (Table 2). Misoprostol was also signif-

TABLE 3
NSAID Protection Studies With Misoprostol for Duodenal Ulcer

Ref.	Misoprostol			Placebo			<i>p</i>	
	Dose	N	Ulcers	N	Ulcers	%		
17	200 μ g <i>q.i.d.</i>	320	2	0.6	323	15	4.6	0.002
19	200 μ g <i>b.i.d.</i>	465	10	2.2	465	26	5.7	0.05
	200 μ g <i>t.i.d.</i>	474	12	2.5				
	200 μ g <i>q.i.d.</i>	229	2	0.9				
Ranitidine 150 mg <i>b.i.d.</i>								
22	200 μ g <i>q.i.d.</i>	181	2	1.1	185	2	1.1	NS

TABLE 4
NSAID Protection Studies With Omeprazole

Ref.	Regimen	Ulcers (%)		
		GU	DU	<i>p</i> *
24	O 20 <i>q.d.</i>	2/85 (2.4)	2/85 (2.4)	>0.005 vs placebo
	Placebo	6/90 (6.6)	15/90 (16.7)	
25	O 20 <i>q.d.</i>	35/274 (12.0)	7/274 (3)	O .001 vs M and placebo
	M 200 <i>b.i.d.</i>	31/296 (9.5)	30/296 (10)	
	Placebo	50/155 (30.3)	19/155 (12)	
26	O 20 <i>q.d.</i>	11/210 (5.2)	1/210 (0.5)	0.004 vs R
	R 150 <i>b.i.d.</i>	35/215 (16.3)	7/215 (4.2)	

* All ulcers combined (GU and DU).

O = omeprazole (in mg); M = misoprostol (in μ g); R = ranitidine (in mg).

icantly better than placebo for the prevention of duodenal ulcer. Ranitidine and misoprostol were equally effective in preventing DU (Table 3). Lower doses of misoprostol were also effective in preventing GU and DU with a side effect profile indistinguishable from that of placebo (16–19, 21, 22). In another double blind RCT, two groups of arthritic patients requiring chronic NSAID therapy with either endoscopically normal (N = 223) or nonulcer-injured gastroduodenal mucosa (N = 778) were treated with NSAIDs for 2 wk with concurrently administered misoprostol (400–800 μ g/day) or placebo. The incidence of severe mucosal damage, including ulcer, was significantly reduced by misoprostol in the previously endoscopically normal subjects and also in the group with preexisting nonulcer damage ($p < 0.001$) (20). A recent large meta-analysis of RCTs of prevention of NSAID-induced gastric mucosal injury by misoprostol or H₂ receptor antagonists, published between 1970 and 1994, showed that misoprostol (but not H₂ receptor antagonists) was beneficial in the prevention of NSAID-induced GUs. It was also found that the number of patients to be treated to prevent one GU with short and long term NSAID therapy is 11 and 15, respectively (23).

Proton pump inhibitors

Omeprazole, the most extensively studied PPI, has a protective effect against NSAID-related mucosal injury. Not unexpectedly, because of its potent acid-inhibiting property, it prevents DU in patients taking NSAIDs. There is evidence that omeprazole also protects against GU. In a crossover,

double-blind RCT, 20 normal volunteers were given aspirin 650 mg *q.i.d.* with either placebo or omeprazole 40 mg/day for 14 days, with endoscopy before and after each treatment period. Omeprazole significantly decreased aspirin-induced gastric mucosal injury ($p < 0.01$) by protecting 85% of the subjects from extensive erosions or ulcer, whereas 70% of the subjects developed severe injury (rate 3 or 4 on 0–4 scale) on aspirin and placebo. No duodenal injury was seen in any grade or any subject on omeprazole, whereas 50% on placebo developed erosions and 15% had DU ($p < 0.001$) (65).

Three large RCTs have been carried out in patients with OA and RA comparing omeprazole with placebo, misoprostol, and ranitidine for the prevention of GU and DU (Table 4) (24–26). Overall, omeprazole significantly reduced the total number of NSAID-related ulcers when compared with placebo and ranitidine (26). It was more effective than misoprostol in preventing DU, and equally so in reducing GU (25). It should be noted that the lowest effective dose of misoprostol was used in this study, and that most of the overall prevention in NSAID-related ulcer in the placebo-controlled studies was due to a reduction in the numbers of duodenal ulcers.

H₂ receptor antagonists

Although commonly coadministered with NSAIDs, H₂ receptor antagonists (H₂RAs) have not been shown to prevent gastric ulcer, the most common NSAID-related lesion, but do prevent DU. Ranitidine has been the most extensively

studied H2RA. In two large, multicenter RCTs, ranitidine (150 mg, *b.i.d.*) or matching placebo was given to patients with OA and RA in conjunction with various NSAIDs. In both studies there was no difference in the occurrence of gastric ulcer between the two groups; however, the incidence of duodenal ulcer was significantly reduced in both studies in the ranitidine group (27, 28). Nizatidine (150 mg *b.i.d.*), in an RCT of 496 patients with OA, did not lower the overall incidence of NSAID-related ulcers. However, a separate analysis of high risk groups (patients with ulcer history and patients >65 yr of age) showed statistically less GU and DU in patients receiving nizatidine ($p = 0.035$ and $p = 0.042$, respectively) (66). In a nonplacebo-controlled RCT of 221 arthritic patients with recently healed NSAID-related ulcers, cumulative relapse rates for nizatidine 150 mg HS and 150 mg *b.i.d.* were 5.5% and 1.8%, respectively (67). A double-blind RCT of famotidine for the prevention of gastric and duodenal ulcers caused by NSAIDs was performed in arthritic patients receiving placebo, famotidine 20 mg *b.i.d.*, and famotidine 40 mg *b.i.d.*, concurrently with the usual NSAID. The cumulative incidence of GU was 20% in the placebo group ($n = 93$), 13% in the patients receiving famotidine 20 mg *b.i.d.*, (NS), and 8% in the group receiving famotidine 40 mg *b.i.d.*, ($p = 0.03$ vs placebo) (68). This study, however, has been criticized because of the small minimum ulcer size of 0.3 cm. In a similar study from the same group of investigators, patients with RA or OA with GU or DU were treated with famotidine 40 mg *b.i.d.* The subjects with healed ulcers were then randomized to 6 months of therapy with famotidine 40 mg *b.i.d.* or placebo. Ulcer recurrence was seen in 26% of the subjects on famotidine, compared with 54% with placebo ($p = 0.01$). Despite the superiority over placebo, the recurrence rate of ulcer in patients on famotidine was unacceptably high (69). High dose ranitidine (300 mg *b.i.d.*) was found to be ineffective for the prevention of gastric ulcers, but was protective against duodenal ulcer. Patients with rheumatoid arthritis and a past history of peptic ulcer disease were followed for 1 yr on NSAIDs with either high dose (300 mg *b.i.d.*) ranitidine ($n = 10$) or placebo ($n = 10$). Four patients in the placebo group had recurrent DU and none in the ranitidine group ($p = 0.04$). Six recurrent GUs were found in the placebo group and three in the ranitidine group ($p = 0.18$) (70). Recurrence of DU in patients taking NSAIDs is more likely when there is a past history of that disease.

Other agents

Sucralfate has not been shown to be effective in preventing NSAID-related ulcers (13, 18, 71). In a recent study from two sites in Europe, 107 arthritic patients were randomly allocated to receive diclofenac 200 mg/day or naproxen 1 g/day, plus sucralfate gel 1 g *b.i.d.* ($n = 53$) or identical placebo ($n = 54$) for 14 days in an RCT. Although there was an unexplained difference in the incidence of ulcer between the two centers, there was an overall decrease in the occurrence of ulcer between patients receiving sucralfate

(8%) compared with placebo (28%) ($p < 0.05$). Both GU and DU were analyzed together in this study, and the proven efficacy of sucralfate for DU may account for these results (72). Studies have shown that antacids and buffered tablets do not protect against NSAID injury (73–75). Enteric coating may be helpful in reducing aspirin-related gastric and duodenal ulcer (74, 75), but does not reduce the risk of NSAID-related ulcer complications (76).

Several new compounds have shown promise in both animal studies and patients. In a double-blind RCT, sulglycotide 200 mg *t.i.d.* or placebo was coadministered with an NSAID to patients with rheumatoid arthritis. Gastric or duodenal ulcer was seen in six of 42 (18%) in the sulglycotide group and in 15 of 44 (34%) in the placebo group ($p = 0.02$) (77). Another new agent under study is zinc acexonite (ZAC). Either ZAC 300 mg/day or placebo was randomly assigned in a double blind manner to 276 arthritic patients receiving NSAIDs. Of 141 patients receiving ZAC, no GU and only one DU (0.9%) was found, whereas 12 of 135 subjects (6.0%) on placebo developed an ulcer. Unfortunately, this study suffers from a high withdrawal and loss to follow up rate (67/276) (78). Because of lack of confirmatory studies, no recommendations can be made at this time concerning either of these agents.

More promising is the development of new, purportedly nontoxic, NSAIDs. These fall into two groups: COX-2-selective inhibitors, and nitric oxide (NO)-releasing NSAIDs. Studies of these agents are very limited. Meloxicam (15 mg/day), a weak COX-2 inhibitor (COX 1: COX-2 ratio 0.33), has been studied in an uncontrolled manner in 357 patients with rheumatoid arthritis. Severe side effects (bleeding, perforation, and ulcer) were seen in only three patients (0.8%) (79). The GI effects of more potent COX-2 inhibitors have thus far only been studied in normal volunteers. These studies have shown a lesser degree of overall erosive injury and ulcer when compared with other NSAIDs (80, 81). At this time, there are no published RCTs of NO-NSAIDs in patients or human volunteers.

TREATMENT OF NSAID-INDUCED ULCERS

Recommendation

NSAID-induced ulcer disease may be treated with any approved therapy for ulcer disease. It is preferable to stop NSAID therapy when ulcer disease occurs. A proton pump inhibitor is the agent of choice when NSAIDs must be continued in the presence of ulcer disease and for large ulcers. Treatment for H. pylori is recommended for patients taking NSAIDs who have ulcers and are infected with this organism.

NSAID-related ulcers may be treated effectively with any approved therapy for peptic ulcer disease. Healing generally is more rapid when the NSAID is discontinued and compares favorably with healing rates for peptic ulcer disease not associated with NSAID intake. Several recent RCTs provide what are probably the best data on the healing rates

TABLE 5
Treatment of NSAID-Related Ulcers

Ref.	Based on Treated	Regimen	% Healed		<i>p</i>	
			4 wk	8 wk		
25	All ulcers NSAIDs con't	O 20 <i>q.d.</i>	65	80	<0.001 vs R 150 <i>b.i.d.</i>	
		O 40 <i>q.d.</i>	63	79	<0.001 vs R 150 <i>b.i.d.</i>	
		R 150 <i>b.i.d.</i>	52	63		
26	All Ulcers NSAIDs con't	O 20 <i>q.d.</i>	56	75	NS vs O 40 and M 200	
		O 40 <i>q.d.</i>	60	75	NS vs O 20 and M 200	
		M 200 <i>b.i.d.</i>	56	71	NS vs O 20 and O 40	
84	GU only NSAIDs con't	O20 <i>q.d.</i>	61	82	<0.001 vs R 150 <i>b.i.d.</i>	
		O 40 <i>q.d.</i>	81	75	<0.03 vs R 150 <i>b.i.d.</i>	
		R 150 <i>b.i.d.</i>	332	63		
82	GU	R 150 <i>b.i.d.</i>	8 wk	12 wk	8 wk	12 wk
		NSAIDs DC'd	95	100	0.001	=0.004
	DU	NSAIDs Con't	63	79	DC'd vs con't NSAIDs	
		NSAIDs DC'd	100	100	0.006	
		NSAIDs con't	84	92	DC'd vs con't NSAIDs	
83	GU	R 150 <i>b.i.d.</i>	4 wk			
		NSAIDs Con't	67	NS vs placebo		
		NSAIDs DC'd	68	NS vs placebo		
	DU	Placebo				
		NSAIDs DC'd	47			
		R 150 <i>b.i.d.</i>				
		NSAIDs Con't	61	NS vs placebo		
		NSAIDs DC'd	81	0.02 vs Placebo		
		Placebo				
NSAIDs DC'd	42					

O = omeprazole (in mg); M = misoprostol (in μ g); R = ranitidine (in mg).

of NSAID-related ulcers treated with H2 RAs or PPI's (Table 5). These studies showed that good healing rates could be obtained at both 4 and 8 wk with all of the agents employed. Generally, healing rates were better for all treatments when NSAIDs were discontinued, but satisfactory healing still occurred with prolonged therapy when it was necessary to continue NSAID treatment. Healing rates in patients taking omeprazole were significantly better than those in patients taking ranitidine when NSAIDs were continued (25, 26, 82–84). In an uncontrolled study, famotidine 40 mg/day was given to 71 patients with endoscopically-proven GU for 8 wk. The healing rate for patients with NSAID-related ulcers was compared with that for idiopathic ulcer. It was found that healing occurred in 46 of 48 (96%) of patients with NSAID-related ulcer, which was significantly greater than the 17 of 23 (74%) seen for idiopathic ulcer ($p = 0.01$) (85). In a nonplacebo-controlled study, three doses of nizatidine (150 mg HS, 150 mg *b.i.d.*, 300 mg *b.i.d.*) were given to patients with active GU or DU while they continued their original NSAID. After 8 wk of therapy, >90% of the ulcers of all three groups were healed. There was a tendency to higher healing rates for GU after four weeks in the high dose (300 mg *b.i.d.*) nizatidine group (67).

In another RCT, substitution of enteric-coated aspirin in patients with ASA-related ulcers did not increase healing rates in patients treated with cimetidine (400 mg/day) and

antacids and, in fact, seven patients given enteric-coated aspirin failed to heal their ulcers, whereas 15 of 16 healed after aspirin was discontinued in all forms (86).

Helicobacter pylori infection has been strongly associated with peptic ulcer disease, especially duodenal ulcer. However, this association has not been demonstrated in patients with NSAID-related ulcer (87–90). In one study, however, gastropathy was more severe in *H. pylori*-positive patients (88). Some recent studies have shown that the incidence of DU is increased in *H. pylori*-positive patients taking NSAIDs (91, 92). However, in another study *H. pylori* eradication did not increase the healing of GU and DU associated with long-term NSAID use (93). It has been recently reported that eradication of *H. pylori* before NSAID therapy strikingly reduces the incidence of ulcer disease in patients being treated with naproxen (750 mg/day). Standard triple therapy (bismuth subcitrate 120 mg *q.i.d.*, tetracycline 500 mg *q.i.d.*, and metronidazole 400 mg *q.i.d.*) was given to 45 *H. pylori*-positive patients before 8 wk of naproxen therapy. Naproxen alone was given to 47 patients over the same period. In the triple therapy group, only three patients (7%) developed ulcer, two of whom were found to have failed *H. pylori* eradication. In the naproxen group, 12 patients (26%) had ulcers, one of which bled (94). Another recent case-control study of ulcer bleeding in 487 elderly patients revealed that NSAID usage (odds ratio 4.93) and *H.*

pylori status (odds ratio 2.80) increased risk substantially, but there was no evidence of interaction (95). In view of the conflicting data, screening for *H. pylori* infection cannot be recommended for all patients receiving NSAIDs. There is some recent evidence that *H. pylori*-negative patients heal more slowly than those who are positive for this organism (26). However, experts still agree that *H. pylori*-positive patients with a past or current history of ulcer requiring NSAID therapy should be treated for the infection, as it cannot be determined whether the prior ulcer was due to NSAID therapy or to *H. pylori* infection.

NSAID INJURY TO THE SMALL BOWEL AND COLON

Recommendations

NSAID-related injury to both the small and large bowel has includes occult and frank bleeding, perforation, obstruction, an acute colitis, and exacerbation of existing colon disease. Physicians prescribing NSAIDs should be aware of these potential complications.

NSAID-related injury to the small bowel and colon has only recently been described and has been documented primarily by anecdotal case reports. However, these are numerous and constitute a significant body of literature. The overall incidence of NSAID-related injury to the gastrointestinal tract distal to the duodenum is much less than that seen in the stomach and proximal duodenum. Nevertheless, it occurs frequently enough to warrant serious consideration by physicians treating patients with NSAIDs.

Small bowel injury

Injury to the small intestine can be manifested by perforation, ulceration and stricture, or by an NSAID-induced enteropathy (31, 46, 96–98). Perforation of the small bowel, although a rare complication of NSAID use, was found in one retrospective review to be significantly more common among patients taking NSAIDs when compared with controls (31). More commonly seen are small intestinal ulcers and strictures (95). Diaphragm-like strictures, often with a very small lumen, are highly characteristic of NSAID injury to the small bowel. Broader-based strictures, often associated with intestinal ulceration, have also been reported. These lesions are commonly associated with obstructive-like symptoms. In a retrospective review of all small bowel resections over an 11 yr period, seven of 456 resections were thought to be related to NSAID injury (97). A more recently reported prospective autopsy series looked at the small bowel of 713 consecutive patients. Seventy-four of these patients had taken NSAIDs on a regular basis, and 249 had ingested them to some degree during the preceding 6 months. Small intestinal ulceration, unrelated to any known pathologic condition, *i.e.*, Crohn's disease, *etc.*, were found in 21 subjects who had taken NSAIDs, which was significantly greater than those patients who were non-NSAID users (46). These small intestinal lesions are extremely

difficult to diagnose. Careful small bowel x-rays or small bowel enemas may be necessary, especially in the case of the diaphragm-like lesions that often resemble the normally occurring plicae circularis. Small bowel enteroscopy is now being used more regularly and may well be necessary to diagnose some of these lesions (99, 100).

Small intestinal micro bleeding, protein loss and malabsorption have been attributed to an NSAID-related enteropathy (101). Studies using 51Cr-EDTA have shown both in normal volunteers and patients that intestinal permeability was markedly increased in patients shortly after treatment with NSAIDs (102, 103). Studies in rats suggests that the enterohepatic recirculation of NSAIDs is critical to this effect (104). Increased small intestinal inflammation has also been demonstrated using 111 indium-labeled neutrophils (105, 106). Using scintigraphic techniques, it has been shown that $\geq 50\%$ of patients who are on NSAIDs more than 6 months develop abnormalities (105). Unlike inflammatory bowel disease, in which scintigraphic abnormalities are seen on early scans, findings in patients on NSAIDs are noted later (at about 20 h) (106). The relationship in patients taking NSAIDs between increased intestinal permeability, which occurs quite early, and inflammation, which occurs later, is as yet unknown, but is felt to be a part of the evolving complex of small bowel injury due to NSAID ingestion (101). There is no evidence that prostaglandins or any other therapeutic agent prevents or reduces NSAID injury to the small bowel.

Injury to the colon

Injury to the lower gastrointestinal tract can be divided into two types: that which affects a previously normal colon, and that which aggravates preexisting disease. An acute colitis occurring in a previously normal colon of patients taking NSAIDs has been reported. A disproportionately high number of these cases are associated with the fenemate group of NSAIDs (meclofenamate and mefenamic acid). The majority of these data are based on various case reports, and these are summarized in a recent extensive review (107). This "colitis" mimics inflammatory bowel disease and presents most commonly as a bloody diarrhea. The disease remits upon discontinuance of the offending NSAID. Diagnosis is made by endoscopic biopsy, which usually rules out classic inflammatory bowel disease and is reported as showing "nonspecific inflammatory changes". Another entity that is often reported in these patients is that of collagenous colitis. In one review of 30 patients with that disease, 19 were found to have been on NSAID therapy (108). Nevertheless, this type of colitis is a rare complication of NSAID therapy, with < 50 cases being reported in the medical literature (101). In one series of > 250 patients on NSAID therapy for RA and OA, no cases of colonic inflammation were found (109). Solitary ulceration has been reported in the cecum and transverse and sigmoid colons in patients taking NSAIDs (110, 112). In one large, retrospective, case-controlled study reviewing large and small intes-

tinal perforation and hemorrhage, one in four patients presenting in this manner had a history of NSAID ingestion that was twice that seen with normal controls (31). Proctitis and rectal bleeding (113, 114), as well as ulceration of the rectum (115), is more commonly associated with the use of suppositories, usually indomethacin or aspirin (114). Stricture of the rectum has also been reported (106). Biopsies differentiate this lesion from Crohn's disease. The incidence of these lesions has not been determined, especially in the United States where the use of NSAID suppositories is rare.

NSAID-related complications have been reported in patients with pre-existing diverticulosis (116, 117) and inflammatory bowel disease (119, 120). In a controlled prospective study evaluating both complications of diverticulosis and perforation, it was found that 31 of 92 patients with complicated diverticular disease were taking NSAIDs, and this was significantly greater than the age-matched control group. Nineteen of 31 patients taking NSAIDs had presented with perforation, whereas only 8 of 61 patients were non-NSAID users ($p < 0.001$) (116). Another case-controlled study of patients with severe complications of diverticulosis showed that 48% of these patients were taking NSAIDs when compared with matched controls ($p < 0.01$) (117). More recently, in a retrospective review of 13 patients with unequivocal stigmata of recent diverticular hemorrhage, 12 (92%) were found to have been recently exposed to NSAIDs and/or aspirin (118).

There are some data to indicate that NSAIDs may have a detrimental effect on patients with inflammatory bowel disease and in patients previously in remission, inducing a relapse only a few days after starting NSAIDs (119, 120). A recent case-control study of 200 hospital admissions for acute inflammatory bowel disease showed that the overall odds ratios for current and recent exposure to NSAIDs were 1.77 and 1.93, respectively, when compared with 1198 community controls (121).

There are no data to support any type of prophylactic therapy directed at the prevention of NSAID-related injury to the colon.

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