ACG Clinical Guideline: Prevention of NSAID-Related Ulcer Complications

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Abstract

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. Only when data that will not withstand objective scrutiny are available is a recommendation 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. These guidelines were developed under the auspices of the American College of Gastroenterology by a committee of experts in the field, reviewed by its Practice Parameters Committee, and approved by the Board of Trustees. The recommendations of these guidelines are therefore considered valid at the time of production based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at an established time and indicated at publication to assure continued validity. Owing to the volume of new data on the subject of non-steroidal anti-inflammatory drug (NSAID)-related injury to the upper gastrointestinal tract, i.e., the advent of cyclooxygenase (COX)-2 inhibitors, new data on interactions between these agents, as well as traditional NSAIDs, with aspirin and *H. pylori*, it was elected by the Committee to confine these guidelines to upper gastrointestinal (GI) injury and to leave post-duodenal injury as the subject of a separate guideline.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are valuable agents in the treatment of arthritis and other musculoskeletal disorders, and as analgesics in a wide variety of clinical scenarios. Unfortunately, their use has been limited by their association with mucosal injury to the upper gastrointestinal tract, including the development of peptic ulcer disease and its complications, most notably upper gastrointestinal hemorrhage, and perforation (1–2). As many as 25% of chronic NSAID users will develop ulcer disease (3–4) and 2–4% will bleed or perforate (5–6). These gastrointestinal events result in more than 100,000 hospital admissions annually in the United States and between 7,000 and 10,000 deaths, especially among those who have been designated as being in a high-risk category (7–9). In a large meta-analysis, the overall relative risk for these complications in patients taking NSAIDs was approximately 2.4 (10). However, this relative risk was markedly increased among patients who fall into various high-risk categories (10–12). Physicians prescribing NSAIDs are, therefore, presented with two problems: (i) identification of high-risk patients and (ii) the selection of appropriate strategies to prevent peptic ulcer and its complications. Concerns raised regarding potential cardiovascular (CV)

hazards of cyclooxygenase (COX)-2 inhibitors and other NSAIDs have complicated clinical decision making further; in selecting an agent for the management of his or her patient, the physician must now balance not only analgesic and anti-inflammatory potency against gastrointestinal toxicity, but must also assess cardiovascular risk for the individual patient in relation to the widely contrasting cardiovascular effects of NSAID classes and individual agents. An additional factor added to this issue is the recognition that aspirin and NSAIDs, including Coxibs, may reduce the risk of colonic adenoma and colorectal cancer occurrence or recurrence; as a consequence, the risk/benefit for gastrointestinal (GI) and CV events for those on low-dose aspirin and NSAIDs in a theoretically healthy population now confronts us (13–14).

Recommendations

1. Patients requiring NSAID therapy who are at high risk (e.g., prior ulcer bleeding or multiple GI risk factors) should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, a COX-2 inhibitor, and co-therapy with misoprostol or high-dose PPI.
   Level of evidence __1__. Strength of recommendation __B__.
2. Patients at moderate risk can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a PPI.
   Level of evidence __1__. Strength of recommendation __B__.
3. Patients at low risk, i.e., no risk factors, can be treated with a non-selective NSAID.
   Level of evidence __1__. Strength of recommendation __A__.
4. Patients for whom anti-inflammatory analgesics are recommended who also require low-dose aspirin therapy for cardiovascular disease can be treated with naproxen plus misoprostol or a PPI.
   Level of evidence __2__. Strength of recommendation __C__.
5. Patients at moderate GI risk who also are at high CV risk should be treated with naproxen plus misoprostol or a PPI. Patients at high GI and high CV risk should avoid using NSAIDs or coxibs. Alternative therapy should be prescribed.
   Level of evidence __2__. Strength of recommendation __C__.
6. All patients regardless of risk status who are about to start long-term traditional NSAID therapy should be considered for testing for *H. pylori* and treated, if positive.
   Level of evidence __2__ Strength of recommendation __A__.

Level of evidence

1. Level of evidence strongly in favor of recommendation.
2. Level of evidence favors recommendation.
3. Level of evidence in favor of recommendation is equivocal.
4. Level of evidence does not favor recommendation.

Strength of recommendations

A. Strong evidence for multiple published, well-controlled randomized trials or a well-designed systemic meta-analysis.
B. Strong evidence from at least one quality-published randomized controlled trial or evidence from published, well-designed, cohort or matched case-control studies.
C. Consensus of authoritative expert opinions based on clinical evidence or from well designed, but uncontrolled or non-randomized clinical trials.

RISK FACTORS FOR NSAID-RELATED COMPLICATIONS

Conclusions

1. Risk factors for NSAID-related GI complications include a previous GI event, especially if complicated, age, concomitant use of anticoagulants, corticosteroids, other NSAIDs including low-dose aspirin, high-dose NSAID therapy, and chronic debilitating disorders, especially cardiovascular disease.
2. Low-dose aspirin is associated with a definite risk for GI complications.
3. *H. pylori* infection increases the risk of NSAID-related GI complications.
4. There is a potential advantage of testing for *H. pylori* infection and eradicating the infection if positive in patients requiring long-term NSAID therapy. Whether co-therapy with a gastroprotective agent is needed after eradication of *H. pylori* depends on individual patients' underlying gastrointestinal risk.

MUCOSAL PROTECTION

Conclusions

1. Misoprostol, when given in full doses (800 mcg/day) is very effective in preventing ulcers, and ulcer complications in patients taking NSAIDs. Unfortunately, its usefulness is limited by its GI side effects. When given in lower doses its side-effect profile is the same as that of PPIs, and it is equally effective.
2. PPIs significantly reduce gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors.
3. COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when compared to traditional NSAIDs. However, this beneficial effect is negated when the patient is taking concomitant low-dose aspirin. The usefulness of these agents has also been reduced by their association with myocardial infarction and other thrombotic CV events. The lowest possible dose of celecoxib should, therefore, be used in order to minimize the risk of CV events.
4. Although superior to placebo, high-dose H_2RAs can reduce the risk of NSAID-induced endoscopic peptic ulcers. They are significantly less effective than PPIs, however, there is no clinical outcome data to prove that this strategy prevents ulcer complications.

STRATEGIES FOR THE PREVENTION OF NSAID-RELATED ULCER COMPLICATIONS

Table 1. Patients at increased risk for NSAID GI toxicity
High risk
1. "History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors
Moderate risk (1–2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors
H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications			
		Gastrointestinal risk[a]	
	Low	**Moderate**	**High**
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk[b] (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy
[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.			