

Mitigating GI Risks Associated with the Use of NSAIDs

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Abstract

Objective. Nonsteroidal anti-inflammatory drugs (NSAIDs) have multiple established adverse effects on various organ systems. Among those associated with high mortality are gastrointestinal complications. We address the scope of the problem and the scientific basis for risk mitigation.

Design. This review covers the most successful of such strategies published to date.

Results. Mitigation strategies to enable ongoing anti-inflammatory benefit are well studied, albeit imperfect.

Conclusions. Such strategies may involve the choice of NSAID or the combined use of gastroprotective measures in association with NSAIDs.

Key Words. Anti-Inflammatory; Gastrointestinal; NSAIDs

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain and suppress inflammation.

Approximately 30 million people worldwide take NSAIDs on a daily basis, of which 40% are older than 60 years [1–3]. As many as 1–2% of NSAIDs users experience serious complications, which in turn are associated with a high mortality rate [4].

Physicians prescribing NSAIDs are, therefore, confronted with two problems: 1) identification of high-risk patients, and 2) the selection of appropriate strategies to prevent peptic ulcer and its complications. Proton pump inhibitors (PPIs) and H₂ receptor antagonists have been evaluated as prophylactic therapies for patients taking NSAIDs. In addition, the advent of selective COX-2 inhibitors introduced a novel strategy for limiting NSAID-related gastroduodenal toxicity. However, the advantage of these COX-2 inhibitors over nonselective NSAIDs is still controversial [5].

Risk Factors for NSAID-Related Complications

Risk factors for gastrointestinal (GI) complications associated with NSAIDs have been identified through a series of case-control and cohort studies. These risk factors include age > 65 years, history of prior complicated peptic ulcer disease, and concurrent use of either, low-dose aspirin, anti-coagulants, or corticosteroids [6].

Analysis of data on the role of *H. pylori* infection as a risk factor for GI bleeding in NSAID users was complicated by a failure, in many studies, to account for the variable influence of multiple other coexistent risk factors. Not surprisingly, therefore, several studies yielded conflicting results [7,8].

Leontiadis et al. found that the most cost-effective strategy for primary prevention of NSAID-associated ulcer was *H. pylori* eradication in patients above the age of 50 years [9]. It should be noted, however, that eradication of *H. pylori* infection alone is not sufficient for the secondary prevention of peptic ulcer bleeding in chronic NSAID users [10–14]. A randomized, controlled trial (RCT) showed that after *H. pylori* eradication, co-therapy with a PPI (lansoprazole 30 mg daily) significantly reduced the risk of re-bleeding in high-risk patients taking low-dose aspirin when compared with those taking aspirin and placebo [10].

Misoprostol

The risk for NSAID-induced gastric or duodenal ulcer can be decreased with concomitant use of the prostaglandin E analog misoprostol. A large, randomized, controlled outcome trial comparing misoprostol 200 mcg q.i.d. with placebo in 8,843 elderly patients with rheumatoid arthritis taking various NSAIDs showed a 40% reduction in serious upper GI complications among those taking the prostaglandin analog [15].

However, more patients receiving misoprostol as opposed to placebo withdrew from the study during the first month (20% vs 15%), primarily because of diarrhea and abdominal discomfort. One way to avoid or reduce misoprostol-induced diarrhea in clinical practice is to begin misoprostol at 100 mcg three times daily or four times daily, and then to increase the dose as tolerated up to the maximum dose of 200 mcg four times daily. Doses of misoprostol lower than 200 µg four times daily have been used with fewer side effects. In one endoscopic trial, 1,200 patients taking long-term NSAIDs were randomly assigned to one of four regimens: 200 mcg of misoprostol four times daily, three times daily, twice daily, or once daily. Each group had a matched placebo group [16]. In the placebo group, the incidence of gastric ulcers detected by endoscopy was 15.7%. The incidence of gastric ulcers was significantly lower in the groups receiving 200 mcg misoprostol twice daily (8.1%), three times daily (3.9%), or four times daily (4%). The 7.5% incidence of duodenal ulcers detected by endoscopy with placebo was reduced to 2.6%, 3.3%, and 1.4%, respectively, with the three different drug dosing regimens. Moreover, there were fewer withdrawals due to adverse events in the groups receiving misoprostol twice and three times daily (12% for both) than in the group receiving it four times daily (20%). Despite the possible clinical efficacy and improved patient tolerance, lower doses of misoprostol have not yet received an approval from the Food and Drug Administration.

Another RCT compared a standard dose of misoprostol (200 mcg q.i.d.) with the lansoprazole (in doses of 15 and 30 mg daily). After 12 weeks, the incidence of endoscopically detected gastroduodenal ulcer was 49% with placebo, whereas it was significantly reduced with misoprostol (7%) and to a lesser extent with either dose of lansoprazole (20% and 18%, respectively) [17].

An extensive meta-analysis of RCTs evaluating prevention strategies of NSAID-induced gastric ulceration confirmed that misoprostol is significantly more effective than H2 receptor antagonists [18].

PPIs

PPIs have been utilized extensively as co-therapy to prevent NSAID-induced peptic ulcers. Two multicenter RCTs have compared esomeprazole 20 mg or 40 mg with placebo in the prevention of ulcers in patients taking NSAIDs or COX-2 inhibitors over a 6-month period. Patients in both studies were *H. pylori*-negative and were

considered at increased risk on the basis of age (above 60 years), or a history of documented gastric or duodenal ulceration within 5 years of entry into the study. Four hundred out of the combined total of 1,429 were on COX-2 inhibitors, and pooled data from the two studies for this subgroup revealed ulcer rates of 16.5% for placebo, 0.9% for esomeprazole (20 mg), and 4.1% for esomeprazole (40 mg) [19].

A recent case-control study matched 2,777 patients with endoscopically confirmed upper GI bleeding with 5,532 controls. In patients taking NSAIDs, PPI therapy was associated with a significant risk reduction for upper GI bleeding [20].

Another recent endoscopic ulcer prevention study compared pantoprazole 20 and 40 mg daily with omeprazole 20 mg daily in 595 rheumatoid arthritis patients (>55 years of age) taking traditional NSAIDs daily. After 6 months, the probability of remaining in ulcer remission were 91% and 95% for pantoprazole 20 mg and 40 mg, respectively, and 93% for omeprazole 20 mg [21].

For these reasons, PPIs have assumed dominance in NSAID-related upper GI injury prophylaxis and therapy. However, it should be pointed out that, to date, there have not been any randomized, prospective, controlled outcome trials to evaluate the efficacy of PPIs in preventing the occurrence of complications resulting from NSAID-related ulcers. One notable exception was a randomized trial of NSAID users with *H. pylori* infection who had prior ulcer bleeding. Here, co-therapy with omeprazole was documented to be effective in preventing recurrent ulcer bleeding [13].

Further data from observational studies along with a secondary analysis of a large-scale, randomized trial also indicate that PPIs reduce the risk of NSAID-associated ulcer bleeding [22,23].

H2 Receptor Antagonists

Standard doses of H2 receptor antagonists were not effective for the prevention of NSAID-induced gastric ulcers in most reports, although they may prevent duodenal ulcers [18]. One study evaluated the efficacy of two doses of famotidine (20 mg and 40 mg, each given orally twice daily), as compared with placebo, in preventing peptic ulcers in 285 patients without peptic ulcers who were receiving long-term NSAID therapy for rheumatoid arthritis (82%) or osteoarthritis (18%). Treatment with high-dose famotidine significantly reduced the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving NSAID therapy. However, studies that detect such a benefit on gastric ulcer prevention are generally short term (12–24 weeks) and focused on endoscopic rather than clinical endpoints [24,25]. Most notably, in two randomized trials (REDUCE-1 and REDUCE-2), patients who required daily NSAIDs for at least 6 months were assigned to receive either ibuprofen 800 mg plus famotidine 26.6 mg or ibuprofen 800 mg three times per

Momeni and Katz

day [26]. The outcome of interest was ulcer development over 24 weeks of treatment. The data analysis of these two studies showed significantly reduced upper GI ulcer development (14% vs 24%), gastric ulcer development (13% vs 21%), and duodenal ulcer development (2% vs 7%) owing to combination therapy.

COX-2 Inhibitors

Data are conflicting about whether COX-2 inhibitors provide additional protection when compared with conventional NSAIDs combined with either a PPI or misoprostol. In a randomized trial (Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis [CONDOR] trial) of 4,484 patients with osteoarthritis or rheumatoid arthritis, 2,238 patients were assigned to receive celecoxib, and 2,246 patients were assigned to receive diclofenac plus omeprazole [27]. Patients in the celecoxib arm were significantly less likely to develop GI toxicity compared with patients in the diclofenac/omeprazole arm [28]. However, this result is different from a meta-analysis by Wang et al. showing no benefit of COX-2 inhibitors over NSAID plus PPI regarding upper GI adverse events and other minor GI complications [29]. Another meta-analysis compared 7,616 participants from nine randomized, double blind, and placebo-controlled trials. COX-2 inhibitors were found to significantly reduce the risk of major upper GI complications and small bowel complications, when compared with NSAID plus PPI. However, the benefit was significantly higher for patients who were at high risk for NSAIDs-related GI complications. Subgroup analysis confirmed protective effects of COX-2 inhibitors over NSAID plus PPI for major GI complication at midgut, while comparable protection of major upper GI complications between COX-2 inhibitors and NSAIDs plus PPI were similar to the result found by Wang et al. Specifically, the risk of diarrhea was significantly lower in subjects on COX-2 inhibitors, while the risk of dyspepsia was higher [22]. Finally, a randomized, endoscopic trial in low-dose aspirin users compared celecoxib (200 mg per day) with the combination of a nonselective NSAID (naproxen 500 mg twice daily) and lansoprazole [30]. There was no difference between these two approaches in terms of gastroduodenal ulcer formation, with ulcers seen in 10% and 9% of patients, respectively.

Summary and Recommendations

Several risk factors, including patient age, comorbidities, concurrent medications, prior medical history, and *H. pylori* infection, have been demonstrated in a variety of studies, with a considerable degree of consistency, to increase the risk of NSAID-related GI injury. An approach to risk mitigation was developed by the American College of Gastroenterology (ACG) in 2009 [31] (Table 1).

- Patients with a history of a recent complicated peptic ulcer are at very high risk and should be treated with NSAIDs with extreme caution and in the presence of maximal protective measures. Among such patients, it

Table 1 Patients at increased risk for NSAIDs GI toxicity

High risk

1. History of a previously complicated ulcer, especially recent
2. Multiple risk factors (>2)

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

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drugs.

is best to avoid NSAID treatment; however, if anti-inflammatory treatment must be used, a COX-2 inhibitor plus misoprostol or PPI therapy is reasonable.

- Patients with a past history of peptic ulcer disease, with or without complications, and requiring concurrent use of aspirin (including low dose), antiplatelet drugs (e.g., clopidrogel), anticoagulants (e.g., warfarin), or corticosteroids, or two or more risk factors should be placed in the high-risk category; these patients should also be treated with a COX-2 inhibitor and either misoprostol or PPI therapy.
- Patients considered to be at moderate risk (Table 1) can be treated with a COX-2 inhibitor alone or an NSAID plus misoprostol or a PPI.
- Patients without risk factors are at low risk for NSAID-related peptic ulcer complications, and no protective measures are required.
- Current evidence indicates that *H. pylori* infection increases the risk of peptic ulcer in patients taking NSAIDs [32–36], and that eradication of *H. pylori* reduces their ulcer risk [9,10,12–14,37]. Furthermore, economic modeling strongly suggests that eradication of *H. pylori* is cost-effective in primary prevention of peptic ulcers in average-risk NSAID users. Thus, there is a potential advantage of testing for *H. pylori* infection and eradicating the infection (if positive) in all patients requiring NSAID therapy. Whether co-therapy with a gastroprotective agent is needed after eradication of *H. pylori* depends on individual patients' underlying GI risk.
- Misoprostol, when given in full doses (800 mcg/day), is effective in preventing ulcers and ulcer complications in patients taking NSAIDs. Unfortunately, its usefulness is limited by adverse GI effects. When given in lower doses, its side-effect profile is the same as that of PPIs, while retaining equal effectiveness.
- PPIs significantly reduce gastric and duodenal ulcers, and their complications in patients taking NSAIDs or COX-2 inhibitors.
- COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when

compared with traditional NSAIDs. However, this beneficial effect is negated when the patient is taking concomitant low-dose aspirin.

- Although superior to placebo, high-dose H2 receptor antagonists 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.

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Momeni and Katz

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