NSAID-Associated Gastrointestinal Bleeding: Assessing the Role of Concomitant Medications

See "Risk of upper gastrointestinal bleeding from different drug combinations," by Masclee GMC, Valkhoff VE, Coloma PM, et al, on page 784.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin for cardiovascular prophylaxis, traditional NSAIDs, and cyclo-oxygenase (COX)-2–selective NSAIDs (coxibs), are used by a large proportion of the population. For example, among US adults age ≥65 years, approximately one half take aspirin every 1–2 days[1] and just over one quarter fill ≥1 prescription for traditional NSAIDs or coxibs annually.[2]

Gastrointestinal (GI) side effects, such as upper GI bleeding (UGIB), are the major factor limiting NSAID use. Meta-analyses of randomized trials suggest an annual excess risk of UGIB per 1,000 patients of approximately 1 with low-dose aspirin, of approximately 2 with coxibs, and approximately 4–6 with the traditional NSAIDs ibuprofen or naproxen.[3,4] However, the risk of UGIB varies widely based on other patient characteristics. Knowledge of these risk factors is necessary for physicians and patients to estimate future risk and determine whether to implement strategies to reduce risk. An important category of risk factors for UGIB with NSAIDs is the concomitant use of other medications, the primary focus of the study by Masclee et al in this issue of *Gastroenterology*.[5]

Study Design in Assessment of NSAID-Associated GI Complications

> *"There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say, we know there are some things we do not know. But there are also unknown unknowns–the ones we don't know we don't know."*
>
> — Donald Rumsfeld

When assessing the impact of an intervention (eg, medication) on an outcome (eg, UGIB), the intervention and control group ideally should be comparable in every way other than the intervention being studied. If the groups have differences in characteristics that impact the outcome, bias may be introduced.

Potential confounding factors that may introduce bias include factors that are known to influence the outcome and are collected for the study ("known knowns"), factors that are known to impact outcome but are not available or collected for the study ("known unknowns"), and factors that are not known, measured, or collected but may influence outcome ("unknown unknowns"). Large, randomized trials of an intervention are preferred because the "knowns" can be predefined and collected, and the distribution of the "knowns" and "unknowns" should be similar in the intervention and control groups. Thus, a difference in outcome is attributable to the intervention being studied.

With the exception of some trials of low-dose aspirin plus concomitant antithrombotic agents, few randomized trials are available to assess the risk of NSAIDs plus concomitant medications. Random assignment of a second medication, such as a selective serotonin reuptake inhibitor (SSRI), vs placebo to all patients in a clinical trial of NSAID users generally is not practical or ethical.

Prospective observational studies provide an opportunity to predefine and collect data on known risk factors and the outcome. Multivariable analysis may be done to assess whether the risk factors are independently associated with the outcome. However, prospective studies also are difficult to perform for rare events such as UGIB, given the requirement for large numbers of patients followed over long periods of time.

Retrospective, observational studies such as case-control studies are often necessary to assess associations with rare events such as UGIB. Outcomes in observational studies also are attractive because they may be more representative of "real-world" practice than results from the restricted populations in randomized trials.

Case-control studies, such as that of Masclee et al,[5] commonly use large computerized databases, including administrative databases constructed primarily for financial purposes and medical record databases, which provide more extensive clinical information. These studies have the important benefit of large sample size, but also have potential limitations, including reliability of the data collected and adequacy of the control group.

Ascertainment of Outcomes and Medication Use

Outcomes are typically ascertained by diagnostic coding (eg, International Classification of Disease [ICD]-9), which may not always accurately reflect or be specific for the outcome being sought. For example, hematochezia and melena have the same ICD-9 code (578.1); thus, studies using this code enroll patients with both UGIB and lower GIB. Masclee et al used this code, another code for unspecified GIB, and several codes for perforation to identify their cases of UGIB. Thus, they likely included a number of patients without UGIB. In validating their strategy in several of their databases, Masclee et al report its positive predictive value for UGIB was 21%–78%.[5]

Information about medication use is also an issue because over-the-counter medications typically are not captured in these databases, and over-the-counter traditional NSAIDs and low-dose aspirin are widely available. In addition, compliance with prescribed medications is not known and inpatient medications may not be captured.

Adequacy of Controls

Patients who receive a medication (eg, corticosteroids, proton pump inhibitors) likely have meaningful differences from those who do not in characteristics that may influence the outcome being studied. Investigators use a number of strategies to help overcome these differences, including statistical adjustment for potential confounding characteristics. However, all known confounders (eg, nonprescription medications) are not recorded in databases, the reliability of confounder data and outcomes (eg, UGIB) is less than in prospective studies with predefined criteria, and unknown factors that impact outcomes cannot be included.

Masclee et al used a strategy designed to improve comparability of cases and controls, self-controlled case series analysis.[5] This has the advantage of using the patient as his or her own control, thus overcoming concerns regarding differences in fixed confounding characteristics such as sex and genetics. Of course, changes in characteristics (eg, new health condition leading to new prescription) do occur over time, and this type of analysis also assumes that occurrence of an event (eg, UGIB) does not impact subsequent interventions (eg, medications). Masclee et al's finding of a significant association of UGIB with gastroprotective monotherapy,[5] presumably the result of confounding, illustrates the difficulty in eliminating bias despite the best efforts of investigators.

UGIB Risk with NSAIDs and Other Medications

Masclee et al assessed the interaction between NSAIDs and concomitant medications and determined if combinations were synergistic (more than additive effect) or had a negative interaction (less than additive effect).[5] They report significant synergy of traditional NSAIDs with corticosteroids, SSRIs, aldosterone antagonists, and antithrombotic agents other than low-dose aspirin. Low-dose aspirin was synergistic with antithrombotic agents and corticosteroids, whereas coxibs were synergistic with only low-dose aspirin and SSRIs and had a negative interaction with antiplatelet agents. Prior studies generally have not assessed synergy, but increased GI risk for many of these combinations is supported by previous studies[6–15] and has biological plausibility.

NSAIDs and Antithrombotics/SSRIs

Ulcers develop frequently with traditional NSAID monotherapy but bleed uncommonly, whereas non–low-dose aspirin antithrombotic agents and SSRIs may promote bleeding without causing mucosal injury. The combination of antithrombotic activity and an NSAID-associated ulcer would reasonably be expected to have greater than additive risk for UGIB. And addition of another antithrombotic agent to low-dose aspirin not unexpectedly increases GIB—by roughly 2-fold in randomized trials.[6,7] However, it is not clear why adding non-aspirin antiplatelet agents to coxibs would decrease UGIB risk.[5]

NSAIDs and Corticosteroids

If corticosteroids do not induce ulcers but interfere with healing once lesions are present, greater synergy of corticosteroids with traditional NSAIDs than coxibs would be expected. The risk of UGIB with concomitant corticosteroids may increase with higher corticosteroid doses.[14]

Low-Dose Aspirin and Other NSAIDs

Masclee et al found that combining low-dose aspirin with either traditional NSAIDs or coxibs increased UGIB risk, but was synergistic only for coxibs.[5] Low-dose aspirin plus a coxib has greater than additive effect for development of ulcers,[15] presumably owing to combined COX-1 inhibition (from low-dose aspirin) and COX-2 inhibition (from the coxib). An important question is whether the beneficial GI effect of coxibs vs traditional NSAIDs disappears or decreases when low-dose aspirin is added. A meta-analysis assessing aspirin users in randomized trials comparing coxibs versus traditional NSAIDs revealed no difference in UGI complications (relative risk [RR], 0.93; 95% CI, 0.68–1.27), but a modest benefit for coxibs in overall UGI clinical events (RR, 0.77; 95% CI, 0.62–0.95),[16] suggesting that the primary potential benefit for coxibs over traditional NSAIDs in aspirin users may be a decrease in uncomplicated symptomatic ulcers.

Although determining whether drug combinations are synergistic or merely additive is important biologically, it may be less relevant in clinical practice. The primary issue in practice is determining when a factor or combination of factors predicts an absolute incidence of UGIB high enough to trigger a change in management. Absolute and relative risks from randomized, cohort, and case-control studies have been used to develop recommendations to identify patients at increased risk who should have a change in management.

Recommendations to Decrease GI Risk in Patients Taking NSAIDs

Recommendations adapted from American professional organizations regarding identification of risk factors for UGIB in NSAID users and management strategies in those with increased risk are shown in Figure 1.[17–20] In patients at increased risk, it is important to first reassess the need for NSAID therapy (or for the concomitant medication). If feasible, discontinuation of NSAIDs is the preferred strategy in high-risk patients. When NSAIDs are necessary, they should be used at the lowest effective dose for the shortest possible duration. Future guideline panels will need to consider whether the marked synergy of traditional NSAIDs and aldosterone antagonists in the 76 cases identified by

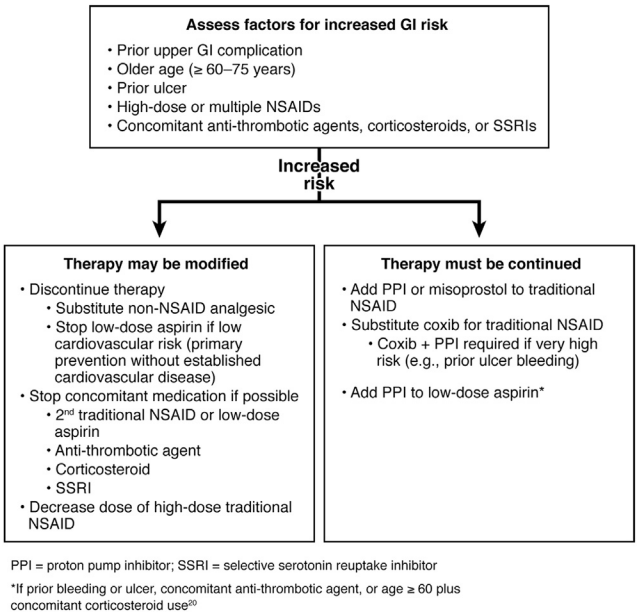

Figure 1. Risk assessment and management strategies for nonsteroidal anti-inflammatory drug users at increased risk of upper gastrointestinal bleeding (adapted with permission from recommendations of American professional organizations[17–20]).

Masclee et al supports inclusion of aldosterone antagonists as a high-risk concomitant medication.

Cardiovascular risk, an important issue related to non–low-dose aspirin NSAID use, is not considered in the recommendations in Figure 1. Meta-analyses and guidelines indicate that naproxen is the preferred NSAID in patients with increased cardiovascular risk because it has less vascular risk than coxibs or other traditional NSAIDs.[3,18,19]

Conclusion

Although the excess risk of UGIB with NSAID use is low, a large number of NSAID users present with bleeding owing to the large proportion of the population taking NSAIDs, including low-dose aspirin. Importantly, risk varies dramatically from patient to patient based on underlying characteristics, necessitating careful review to assess risk in each individual receiving NSAIDs. Studies such as that of Masclee et al help to further define risk factors and their relative importance, with the ultimate goal of improving care and decreasing NSAID-associated complications.

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Conflicts of interest
The author discloses the following: Data safety monitoring boards: Eisai, BMS, Bayer; Consultant: AstraZeneca.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.08.021

Preventing Diverticulitis Recurrence by Selecting the Right Therapy for a Complex Disease

See "Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials," by Raskin JB, Kamm MA, Jamal MM, et al, on page 793.

Diverticulosis of the colon is an anatomic alteration commonly found in those residing in developed countries, slightly more frequent in the United States than in Europe.[1] Diverticulitis is the most common complication of diverticulosis: The majority of patients suffer from an "uncomplicated" form of the disease, generally undergoing outpatient medical management, whereas the "complicated" form is generally managed with inpatient medical-surgical treatment.[1] It has been thought that diverticulitis affects ≤15% of patients with symptomatic diverticular disease.[1] However, a colonoscopy-based study hypothesized that the actual rate of diverticulitis occurrence is lower, occurring in only 5% of patients harboring simple diverticulosis.[2]

There is little evidence regarding appropriate management of diverticulitis after an acute episode, even though the long-term recurrence rate of diverticulitis is ≤20%.[3] In this issue of *Gastroenterology*, Raskin et al present the results of 2 phase III, randomized, double-blind, placebo-controlled studies (PREVENT 1 and PREVENT 2) conducted to examine role of mesalamine in preventing recurrence of diverticulitis. More than 1,000 adult patients (590 in PREVENT1and 592 in PREVENT2) with ≥1 episode of acute diverticulitis in the previous 24 months that resolved without surgery were randomised to receive 1 of 3 dose regimens of MMX mesalamine (1.2, 2.4, or 4.8 g/d) or placebo.[4] The primary endpoint was the proportion of patients free of recurrent diverticulitis, defined as surgical intervention at any time for diverticular disease or presence of computed tomography (CT) results demonstrating bowel wall thickening (>5 mm) and/or fat stranding consistent with diverticulitis. The authors found that any dose of MMX mesalamine was not better than placebo for reducing diverticulitis recurrence at week 104 by using a CT-only definition of recurrent diverticulitis (recurrence-free rates for PREVENT1: Mesalamine, 53%–63% vs placebo, 65%; recurrence-free rates for PREVENT2: Mesalamine 59%–69% vs placebo 68%).[4] Thus, mesalamine does not seem to be effective in preventing diverticulitis recurrence.

Given that these controlled trials suggest that mesalamine does not work, how can we prevent diverticulitis recurrence in clinical practice?

Once the acute episode has resolved, patients are generally advised to maintain a high-fiber diet to optimize their bowel movements.[1] However, the collective literature investigating the role of dietary modification in preventing diverticular disease or a recurrence of diverticulitis is inconsistent, with conflicting results, and does not provide consistent support for recommending a high-fiber diet.[5] Another interesting point is related to the typical advice to avoid consuming seeds, popcorn, and nuts, which is based on the assumption that such substances could theoretically enter, block, or irritate a diverticulum and result in diverticulitis, and possibly increase the risk of perforation. However, there is no evidence to date to support this practice.[6]

Several treatments have been proposed and are used in clinical practice (Figure 1). Given the potential involvement of microbial imbalance in the pathogenesis of diverticular disease,[1] 1 option to prevent recurrence after an acute episode may be to use a single, broad-spectrum antibiotic that has activity against both Gram-negative and anaerobic bacteria. Recently, an open-label, pilot study found cyclic administration of rifaximin (800 mg/d for 10 days every month) to be effective for improving symptoms, but not for prevention of acute diverticulitis.[7] However, the lack of a placebo-controlled arm is a limitation; therefore, the role of rifaximin in preventing diverticulitis recurrence needs definitive confirmation.