Nonsteroidal Antiinflammatory Drugs, Anticoagulation, and Upper Gastrointestinal Bleeding

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KEYWORDS

• Nonsteroidal antiinflammatory drugs (NSAIDs) • Anticoagulation • Elderly
• Upper GI bleeding • Peptic ulcer disease

KEY POINTS

- Advanced age, history of peptic ulcer disease, *Helicobacter pylori*, coadministration of nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, anticoagulation, and antiplatelets are risk factors for gastrointestinal bleeding in the elderly.
- Awareness of these risks and appropriate use of NSAIDs, particularly in those needing antiplatelet or anticoagulant therapy, is critical to optimal management.
- Careful selection of elderly patients requiring antiplatelet, anticoagulation, or chronic NSAID therapy for cotherapy with proton pump inhibitors can significantly reduce morbidity and mortality from gastrointestinal bleeding.

INTRODUCTION

The elderly present constant challenges in medical management, particularly of pain and inflammation. Balancing the risk and benefits of medication requires extra vigilance on the part of care providers because symptoms are often subtle and side effects more frequent, with major adverse events always a concern. This tendency is particularly evident with the use of nonsteroidal antiinflammatory drugs (NSAIDs), anticoagulants, and antiplatelet agents because one of the major complications, gastrointestinal (GI) bleeding, can result in major morbidity in this population. This article discusses issues related to GI bleeding, NSAID complications, and issues related to anticoagulation in the elderly population.

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GASTROINTESTINAL BLEEDING

GI bleeding has been estimated to have a prevalence of around 3% in a large population based study in the elderly aged greater than or equal to 65 years.[1] Age has been suggested as a risk factor for GI bleeding, together with non–acetylsalicylic acid antiplatelet agents, index of comorbidity (Cumulative Illness Rating Scale) greater than 3, and liver cirrhosis. Peptic ulcer disease, hemorrhagic gastropathy, esophageal varices are the most common causes of upper GI bleeding, whereas diverticular bleeding and angiodysplasia are the most common causes of lower GI bleeding.[1–5] Peptic ulcer bleeding continues to be of major consequence in the elderly, with mortality reported to be 5% to 10% worldwide, predominantly related to nonbleeding causes.[6] One meta-analysis showed that increased peptic ulcer bleeding mortality is related to the number of comorbidities, with 3 or more comorbidities having a greater risk of death compared with 1 or 2. Hepatic, renal, and malignant comorbidities are associated with increased risk of death in peptic ulcer bleeding.[7]

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Studies have estimated the prevalence of NSAIDs and aspirin use to be 24.7% in the elderly.[8] Approximately half of the patients who regularly take NSAIDs have gastric erosions, and 15% to 30% have ulcers that are detected endoscopically. Clinical upper GI events (perforations, obstructions, bleeding, and uncomplicated ulcers) may occur in 3% to 4.5% of patients taking NSAIDs annually, and serious complicated events (perforation, obstruction, or major bleeding) develop in approximately 1.5%.[9]

NSAIDs can cause injury anywhere in the GI tract, although the upper GI tract seems most vulnerable. Injuries can be divided into gastroduodenal, small bowel, and colonic.

GASTRODUODENAL INJURY

NSAID-induced upper GI injury is a result of relative deficiency of mucosal prostaglandins leading to secondary acid-related ulceration in a compromised epithelial barrier.[10] Mucosal disruption, decreased bicarbonate secretion, and local vasoconstriction are consequences of cyclooxygenase (COX) inhibition.[10] This condition can lead to ulcer formation, hemorrhage, and perforation.

NSAIDs are divided into nonselective and selective COX inhibitors. Nonselective NSAIDs inhibit both COX-1 and COX-2, whereas selective COX inhibitors inhibit only COX-2. COX isoenzymes catalyze the rate-limiting step in the formation of prostaglandins, thromboxane, and levuloglandins. COX-1–derived prostaglandins play an important role in cytoprotection of the gastroduodenal mucosa, whereas COX-2 mediates tumor angiogenesis, inflammatory response, and thrombosis. Therefore, damage of gastroduodenal mucosa and resulting GI bleeding is associated with inhibition of COX-1, whereas COX-2 has been studied as a potential target for chemoprevention.[11]

It is of some surprise that the risk of GI bleeding has been reported to be higher in acute NSAID use compared with chronic use.[12] Up to 37% of patients develop severe gastric mucosal damage with short-term NSAID use, and 13% develop duodenal damage. Short-term use of NSAIDs may not be benign in the elderly.[13]

SMALL BOWEL INJURY

Small bowel injury, similar to gastroduodenal injury, involves both systemic and local mechanisms of injury. In addition to the decrease in prostaglandin cytoprotection,

breach in local epithelial barrier, and changes in microcirculation, bile acids, pancreatic secretions, and bacteria can further exacerbate injury.[10]

Advances in small bowel imaging, capsule endoscopy, and enteroscopy have allowed the acute documentation of the spectrum of small bowel mucosal damage from NSAIDs. The so-called NSAID-induced enteropathy has various presentations, ranging from erythema, erosions, and ulcers to diaphragmlike strictures and small bowel bleeding.[14]

In healthy volunteers given a short course of nonselective NSAIDs (14 days), capsule endoscopy identified visible mucosal changes in 68% of volunteers. These changes included mucosal breaks (40%), erythema (35%), petechiae (33%), denuded mucosa (20%), and blood in lumen (8%).[15] In chronic NSAID use (>6 months), up to 8.4% of users developed small bowel ulcerations.[16] One study examined 120 asymptomatic patients on nonselective COX inhibitors and 40 patients on COX-2 inhibitors who underwent capsule endoscopy. Twenty-nine patients had mucosal breaks in the conventional NSAID group, whereas 22% had mucosal breaks in the COX-2 selective inhibitor group.[17] Strictures, obstruction, and perforation are far less common.

COLONIC INJURY

Although uncommon compared with gastroduodenal and small bowel injury, NSAID-induced colopathy has been reported in case reports. NSAID-induced colopathy can mimic symptoms of colorectal cancers, presenting with iron deficiency anemia, rectal bleeding, occult bleeding, and abdominal pain. When colonoscopy is performed, it can reveal fibrous strictures and ulcerations.

Risk Factors

Risk of NSAID-related injury and complications are influenced by demographic factors, duration of NSAID use, coadministration of medications, and comorbidities.

Age

Age has been shown to be a significant risk factor for adverse GI events related to NSAID use. Several age-related gastric changes, including reduced mucosal protective mechanisms and decreased gastric blood flow, compromise the mucosal barrier and further predispose the gastroduodenal mucosa to the adverse effects of NSAIDs.[18] A meta-analysis showed that elderly patients (defined as aged greater than or equal to 60 years) have an odds ratio (OR) of 5.52 versus 1.65 in younger patients for developing adverse events while on NSAIDs.[19]

Length of nonsteroidal antiinflammatory drug use

Short-term NSAID use is also associated with higher risk of NSAID-related adverse events. Surprisingly the odds of NSAID mucosa injury may decrease over time. The summary OR for less than 1 month of NSAID exposure was 8.00 (95% confidence interval [CI], 6.37–10.06); for more than 1 month but less than 3 months of exposure, the summary OR was 3.31 (95% CI, 2.27–4.82); and for more than 3 months of exposure, the summary OR was 1.92 (95% CI, 1.19–3.13).[19]

Prior history of gastrointestinal event

Prior upper GI bleeding is identified to be the strongest and most consistent risk factor for GI bleeding on antiplatelet therapy.[20] This finding forms the basis of several guidelines suggesting the use of gastroprotective prophylaxis in patients on chronic or dual antiplatelet therapy to prevent GI bleeding in those at risk, especially in those who require coadministration of long-term NSAID therapy.

Coadministration of medications

Prior studies have reported an increased risk of adverse GI events related to NSAID use in the setting of coadministration of corticosteroids, antiplatelets, and anticoagulants. Corticosteroids have not been shown to increase risk for peptic ulcer disease when used alone. When combined with NSAID, the estimated relative risk (RR) for development of peptic ulcer disease increases to 4.4 compared with using steroids alone.[21]

The risk of development of peptic ulcer disease is significantly lower with low-dose aspirin (81 mg) compared with full-dose aspirin (325 mg). The RR of low-dose aspirin has been shown to be 2.07 compared with full dose for major GI bleeding.[22] When low-dose aspirin is used with an NSAID, there is an additive increase risk of bleeding in patients in developing gastroduodenal ulcer.[23]

The risk of bleeding with anticoagulants is presumably caused by bleeding from clinically silent lesions caused by *Helicobacter pylori* or NSAID-induced ulcers. The risk of the combined effect of NSAIDs and anticoagulants has not been extensively studied. However, use of anticoagulants has been reported to confer double the risk of GI bleeding compared with low-dose aspirin.[24]

Helicobacter pylori

The risks of peptic ulcer disease with NSAID use and *H pylori* infection have been estimated to be 3-fold to 4-fold. Although these are independent risk factors, they seem to have synergistic and additive effects for development of peptic ulcer disease.[25]

Management of nonsteroidal antiinflammatory drug–related complications

Management of NSAID-induced injury depends on patient symptoms, acuity, and hemodynamic stability. Symptoms may range from dyspepsia and obstructive symptoms to life-threatening GI bleeding and perforation.

Dyspepsia

As previously mentioned, up to half of chronic NSAID users can be found to have endoscopic evidence of mucosal damage. Patients presenting with dyspepsia who do not require chronic NSAID therapy generally improve with cessation of NSAIDs. Patients who require chronic NSAID use should be considered for prophylaxis with gastroprotectants and *H pylori* testing (discussed later).

Bleeding

Initial assessment The most essential initial assessment is the evaluation of the patient's mental status and hemodynamics. Hypotension and/or tachycardia should prompt timely fluid resuscitation. Altered mental status and/or inability to protect the airway should lead to prompt assessment for airway protection or intubation. Several commonly used risk assessment tools (ie, Glasgow-Blatchford score and Rockall score) can assist in risk stratification regarding safety to discharge the patient. The Glasgow-Blatchford score ranges from 0 to 23, with higher score indicating higher risk. Various clinical variables, including blood urea nitrogen, hemoglobin, systolic blood pressure, heart rate, melena, syncope, hepatic disease, and cardiac failure, are included in the score. A low Glasgow-Blatchford score (defined as 0–1, 0–2 for patients younger than 70 years of age) has been shown to be associated with minimal risk of intervention and death.[26,27] Although care must be taken with the elderly, those with a low score can be considered for early discharge with close outpatient follow-up.

Initiation of proton pump inhibitors is a common practice across hospitals when patients present with symptoms of upper GI bleeding. The role of preendoscopic proton

pump inhibitors (PPIs) has been studied and defined. A meta-analysis showed that preendoscopic PPI did not improve mortality, need for surgery, or further bleeding. However, it was found to decrease the frequency of high-risk endoscopic findings and the need for endoscopic therapy.[28]

Endoscopy assessment

Timing of endoscopy for nonvariceal bleeding For patients presenting with acute GI bleeding, most guidelines recommend endoscopy within 24 hours after adequate resuscitation has been achieved.[29] Data for urgent endoscopy (<6–12 hours) have been mixed. Some studies suggest that early endoscopy (<6–12 hours) confers worse outcomes,[30] whereas other studies suggest improvement of outcomes in high-risk patients.[31,32] This difference is likely related to degree of resuscitation and definition of high-risk patients. The general consensus is to perform endoscopy within 24 hours after adequate resuscitation and considers early endoscopy within 12 hours in patients with suspected variceal bleeding. A gastroenterology consult to evaluate the need for endoscopy is mandatory in patients presenting with GI bleeding. Endoscopic assessment for high-risk lesions and need for endoscopic intervention is based on Forrest classification and the risks of rebleeding associated with these lesions without therapy. Forrest classification categorizes ulcers into active bleeding (IA), oozing (IB), visible vessel (IIA), adherent clot (IIB), pigmented spot (IIC), and clean base (III). Ulcers with endoscopic features of active bleeding (IA), oozing (IB), and visible vessel (IIA) benefit from endoscopic therapy because of the high risk of recurrent bleeding without therapy (60%–100% for active bleeding ulcer and up to 35%–50% for nonbleeding visible vessel). Treatment of these high-risk lesions should involve dual endoscopic therapy with both injection (eg, epinephrine) and thermal therapy (eg, bipolar cautery or heater probe) rather than epinephrine alone whenever possible.

Postendoscopy proton pump inhibitors When NSAID ulcers with high-risk stigmata are identified during endoscopy, continuous intravenous infusion of PPIs for 72 hours has been shown to significantly reduce risks of further bleeding, the need for surgery, and mortality.[33,34] Subsequent studies have shown that intermittent oral and intermittent intravenous PPI therapy are noninferior to continuous intravenous PPI therapy, suggesting such therapy may be used as alternatives.[35]

On discharge, patients found to have ulcers with high-risk stigmata should receive twice-daily PPI therapy for 2 weeks, followed by a PPI once daily. In patients found to have low-risk ulcers and erosions, once-daily PPI for 6 to 8 weeks is sufficient for healing.[27] If NSAIDs are needed long term, PPI cotherapy to reduce bleeding risk is recommended, even if COX-selective NSAIDs are used.

Obscure bleeding In elderly patients on chronic NSAIDs with persistent bleeding symptoms where upper endoscopy and colonoscopy are unrevealing, small bowel bleeding should be suspected. NSAID-induced small bowel ulceration can usually be identified on capsule endoscopy. Small bowel enteroscopy and/or single-balloon enteroscopy may be needed for diagnosis or therapy. Multiple studies have shown that misoprostol is an effective treatment of small bowel ulcers and erosions in patients using low-dose aspirin and NSAIDs.[36,37]

Stricturing disease and obstruction Rarely, chronic NSAID use can cause a diaphragmlike stricture and/or small bowel obstruction. Double-balloon enteroscopy is an effective diagnostic and therapeutic tool in tissue sampling and balloon dilation in patients with persistent stricture.[38] Rarely, surgical intervention is required in

cases of complete obstruction and recurrent obstruction refractory to endoscopic therapy.

Perforation Although perforated peptic ulcer (PPU) is uncommon compared with bleeding as a complication from NSAID-induced ulcer disease, short-term mortality can reach up to 30%.[39] Although there has been a decrease in prevalence of *H pylori* in many Western countries, there has been a proportional increase of PPU caused by NSAID use, especially in the elderly population.[40,41] Older age, presence of comorbidity (heart disease, liver disease, renal disease, diabetes mellitus), and surgical delay (>24 hours) have been associated with increased mortality in patients presenting with PPU.[40]

PREVENTION OF NONSTEROIDAL ANTIINFLAMMATORY DRUG–RELATED INJURY AND RISK MODIFICATIONS

Role of Helicobacter pylori

Eradication of *H pylori* has been shown to reduce risk of recurrent bleeding caused by peptic ulcer disease with and without NSAID use.

Early eradication of *H pylori* seems to be more effective in reducing the risk of rebleeding. One study compared early eradication (within 120 days of peptic ulcer diagnosis) and late eradication, and showed that the late eradication group had a higher rate of complicated recurrent peptic ulcers.[42]

Because of the synergistic effect on peptic ulcer formation in patients infected with *H pylori* on chronic NSAID therapy, current recommendation is eradication of *H pylori* without long-term antisecretory maintenance if there are no other indications for prophylaxis.

Role of Proton Pump Inhibitors, H2-Receptor Antagonists, Prostaglandin Analogue Prophylaxis

Numerous studies have examined the efficacy of various gastroprotective agents in prevention of NSAID complications. One large meta-analysis compared PPIs, prostaglandin analogues, and H2-receptor antagonists (H2RAs) with controls in prevention of NSAID-induced peptic ulcer disease. PPIs showed greater degree of reduction in upper GI bleeding (OR, 0.21; 99% CI, 0.12–0.36) compared with H2RA (OR, 0.49; 99% CI, 0.30–0.80) and prostaglandin analogues (OR, 0.63; 99% CI, 0.35–1.12).[43]

The American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) 2010 Consensus recommended cotherapy with PPIs in patients on antiplatelet therapy if there is a history of GI bleeding, and that it is appropriate to consider in patients with multiple risk factors (advanced age not specifically defined, concomitant use of warfarin, steroids, NSAIDs, and *H pylori* infection).[20] The American College of Cardiology (ACC)/AHA recommends PPI prophylaxis in patients with history of GI bleeding on dual antiplatelet therapy (**Tables 1** and **2**). PPI is reasonable and can be considered in patients at increased risk of GI bleeding, including advanced age, concomitant anticoagulation, and concomitant steroids or NSAIDs.[44]

Role of Selective Cyclooxygenase-2 Inhibitor

Selective COX-2 inhibitors, such as celecoxib, are associated with a lower risk of upper GI bleeding than are nonselective COX inhibitors; therefore, they are recommended for patients who require long-term NSAID therapy.[45–47]

Table 1
Consideration of cotherapy in reduction of gastrointestinal bleeding risk in patients on antiplatelet therapy

Risk Factors[a]	Consider
Prior history of peptic ulcer disease Prior history of GI bleeding Concomitant anticoagulation or antiplatelet Two or more of the following risk factors: • Age $\geq$ 60 y, steroid use, dyspepsia, or gastroesophageal reflux disease symptoms	Proton pump inhibitor daily

[a] ACCF/ACG/AHA consensus document.

ANTICOAGULATION

Risk of Gastrointestinal Bleeding

Vitamin K antagonists versus no anticoagulation

Anticoagulants do not seem to cause direct mucosal injury. The mechanism of GI bleeding is likely related to interference of the normal hemostatic process and conversion of otherwise subclinical bleeding into clinical bleeding.

The risk of major bleeding in patients taking vitamin K antagonists has been reported to have an OR of 3.2 (95% CI, 1.3–7.8) compared with no therapy.[48] The annualized rate of major bleeding with warfarin was estimated to be 3.43%.[49]

Warfarin versus novel oral anticoagulants

There have been newer anticoagulants introduced over the past 12 years, expanding the options for anticoagulation in the elderly. These anticoagulants include direct factor Xa inhibitors (apixaban, rivaroxaban, darexaban, edoxaban) and direct thrombin inhibitors (dabigatran). Many randomized trials compared the efficacy and safety of warfarin compared with direct oral anticoagulants (DOACs). The risk of fatal and major bleeding seems to be lower with DOACs than warfarin.[49,50] However, some novel oral anticoagulants NOACs have been suggested to confer a small increased risk of intracranial hemorrhage.[49] The risks of bleeding among various NOACs also seem to vary, with rivaroxaban showing the highest risk of bleeding complications, similar to or potentially higher than warfarin, whereas apixaban has been associated with lowest risk of any bleeding (RR, 0.73) and major bleeding (RR, 0.60).[51–55] Therefore, apixaban is recommended in patients at increased risk of bleeding.

Table 2
Consideration of cotherapy in reduction of gastrointestinal bleeding risk in patients on dual antiplatelet therapy

Risk Factors[a]	Consider
Prior history of GI bleeding Advanced age (age not specified) Concomitant anticoagulation Concomitant steroids or NSAIDs	Proton pump inhibitor daily

[a] ACC/AHA 2016 guidelines.

PREENDOSCOPIC MANAGEMENT OF ANTICOAGULATION (URGENT VS ELECTIVE ENDOSCOPY)

When planning an endoscopic procedure in patients on antithrombotics, the urgency or elective nature of the procedure should be balanced with (1) bleeding risk of the procedure, (2) the patient's thromboembolic risk, and (3) indication and duration of antithrombotic. In patients with urgent need for endoscopy (ie, clinically significant bleeding), several guidelines have provided recommendations on reversal agents to optimize bleeding risks. Note that NOACs depend on renal excretion and, therefore, timing for perioperative medication adjustment depends on creatinine clearance.

Several guidelines have slight variations in the perioperative management of antithrombotics. In cases of urgent or emergent endoscopic procedures in patients on chronic warfarin therapy, American Society for Gastrointestinal Endoscopy (ASGE) and AHA/ACC recommend 4-factor prothrombin complex concentrate (4F-PCC), which contains the human coagulation factors II, VII, IX, and X together with the endogenous inhibitor proteins S and C, and vitamin K or fresh frozen plasma for life-threatening GI bleeding, whereas American College of Chest Physicians (ACCP) only advocates 4F-PCC and vitamin K. International Normalized Ratio (INR) less than 2.5 is considered an acceptable threshold for endoscopic therapy and endoscopy should not be delayed. Unfractionated heparin can be used in patients with subtherapeutic INR at high risk of thromboembolic events.[56]

In elective procedures, patients who had recent acute coronary syndrome or recent placement of intracoronary stent should have their procedures deferred until minimum duration of antithrombotic therapy has been reached. Low-dose aspirin can be safely continued throughout the periendoscopic period. In patients at low risk of thromboembolic events, thienopyridines can be continued through low-risk endoscopic procedures, but discontinued for 5 to 7 days or switched to aspirin monotherapy before high-risk endoscopic procedures.[56]

Resumption of antithrombotics should depend on ability to achieve hemostasis during endoscopic therapy. Note that risk of cardiovascular event may increase after 1 to 2 weeks on discontinuation of aspirin indicated for secondary prevention, and therefore should be resumed within 7 days when hemostasis is achieved.[27,57] When hemostasis is achieved without significant risk of delayed bleeding or need for repeat intervention, warfarin can generally be safely resumed the same day given that the therapeutic level is not achieved for several days. Clopidogrel and NOACs can generally be safely restarted within 48 hours.[58]

In addition, risks of bleeding from antithrombotic and antiplatelet treatment should be continuously assessed and balanced with risks of thromboembolic events, especially in the geriatric population.

SUMMARY

Adverse events related to NSAIDs and anticoagulant-associated GI bleeding is of concern in elderly patients on these medications. Awareness of these risks and appropriate use of NSAIDs, particularly in patients needing antiplatelet or anticoagulant therapy, is critical to optimal management. Judicious use of proton pump inhibitor prophylaxis should be considered in chronic users, particularly those a higher risk for ulcer or GI bleeding. Management of antiplatelet/anticoagulants in patients needing diagnostic or therapeutic endoscopic procedures is in the purview of the geriatrician in conjunction with appropriate specialists. Complications of these excellent medications can be avoided (or treated) in the elderly.

CLINICS CARE POINTS

- Cotherapy with a proton pump inhibitor should be recommended in patients at risk for NSAID complications.
- Apixiban has the lowest risk for GI bleeding amongst the novel oral anticoagulants.
- Consider selective Cox2 inhibitors in patients at high risk for bleeding if the patient is not already on aspirin.
- NSAIDs can cause clinically important ulceration anyway in the GI tract though gastric ulceration is most common.

DISCLOSURE

Dr Katz is a Consultant for Phathom Pharma.

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