

Reducing gastrointestinal tract bleeding in family practice

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Abstract

Upper gastrointestinal bleeding occurs commonly. Fortunately, severe life-threatening bleeding is less common, but can be catastrophic, particularly in the elderly patient with co-morbidity such as cardiac or respiratory disease. In order to reduce the risk of bleeding, it is necessary to examine the causes of bleeding and, where possible, modify the risk factors. This review will focus on the prevention of non-variceal upper gastrointestinal bleeding.

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SA Fam Pract 2008;50(1):13-17

Introduction

Upper gastrointestinal (GI) bleeding represents a substantial clinical and economic burden. It has a prevalence of approximately 170 cases per 100 000 adults per year,¹ at an estimated total cost of \$750 million in US dollars.² Peptic ulcer disease accounts for 50% to 70% of cases of acute non-variceal upper GI bleeding. Despite recent advances in therapy, the mortality rates have remained at about 6% to 8%. This is partly due to the fact that prevention strategies for upper GI bleeding are underutilised.³

The major causes of upper GI bleeding are:

- Duodenal ulcer haemorrhage (25%)
- Gastric ulcer haemorrhage (20%)
- Mucosal tears of the oesophagus or fundus (Mallory-Weiss tear), oesophageal varices and erosive oesophagitis
- Erosive gastritis, Dieulafoy lesion, gastric varices, gastric cancer and ulcerated gastric leiomyoma

Risk factors for upper GI bleeding include:

- Past history of peptic ulcer
- The use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin
- Patients on anticoagulation therapy, e.g. warfarin, clopidogrel
- Age greater than 65 years, which is an independent risk factor
- Helicobacter pylori infection
- High-dose corticosteroid therapy

NSAIDs and upper GI bleeding

Non-selective NSAIDs

The role of NSAIDs and aspirin will be considered separately, as the indication for their use is generally different. NSAIDs are widely prescribed for pain management, and many NSAIDs are available

without prescription. NSAIDs are ulcerogenic, but not all NSAIDs are equal in their ability to cause gastric or duodenal mucosal damage, and hence bleeding. After adjustment for confounding factors, ulcer bleeding was strongly associated with the use of any type of NSAID during the previous three months (odds ratio, 4.5) and increased with NSAID dose. The odds ratios for bleeding varied widely among the most commonly used NSAIDs, and all were significant: ibuprofen, 2.0; diclofenac, 4.2; indomethacin, 11.3; naproxen, 9.1; piroxicam, 13.7; and ketoprofen, 23.7.⁴

With higher doses of NSAIDs, and when more than one NSAID is being used, e.g. diclofenac and aspirin, the risk of bleeding increases. The risk of bleeding is reduced by using a Cox-2 selective anti-inflammatory drug. In a study by Ray et al., current NSAID users with no gastroprotective co-therapy had an adjusted incidence of peptic ulcer hospitalisations of 5.65 per 1 000 person-years, 2.76 times greater than those currently not using NSAIDs or coxibs.⁵

Cox-2 selective NSAIDs

There is a substantial body of evidence that Cox-2 selective NSAIDs cause fewer ulcers and ulcer complications when compared to non-selective NSAIDs. This has been demonstrated in trials with celecoxib vs. ibuprofen or diclofenac,⁶ rofecoxib vs. naproxen,⁷ and lumiricoxib vs. naproxen and ibuprofen.⁸ However, when the Cox-2 agent is combined with aspirin, the benefit is reduced or lost. The cardiovascular risk for myocardial infarction and stroke is increased with both Cox-2 and Cox-1 drugs. Prevention strategies must therefore take into account both GI and cardiovascular safety concerns. Current evidence indicates that selective COX-2 inhibitors have important adverse cardiovascular effects that include increased risk for myocardial infarction, stroke and heart failure, and hypertension. The risk for these adverse effects is likely greatest in patients with a prior history of or at high risk for cardiovascular disease.⁹

Helicobacter pylori infection

Helicobacter pylori is an important cause of peptic ulceration, and is an independent risk factor for upper GI bleeding. Patients with a history of peptic ulcer, dyspepsia or upper GI bleeding should be tested for *H. pylori* infection, and treated if positive.

- Patients who are naïve NSAIDs users should be tested for *H. pylori* and, if positive, receive eradication therapy prior to starting NSAIDs to prevent peptic ulcer and/or bleeding
- In patients on long-term NSAIDs and with peptic ulcer and/or ulcer bleeding, PPI maintenance therapy is superior to *H. pylori* eradication in preventing ulcer recurrence and/or bleeding
- It is important to note that *H. pylori* eradication is insufficient to prevent recurrent ulcer bleeding in high-risk NSAID users. These patients need a gastro-protective drug in addition to *H. pylori* eradication therapy

The recommended first-line therapy remains a PPI, clarithromycin and amoxicillin. Metronidazole may be substituted in the case of penicillin allergy or if clarithromycin resistance is prevalent. In the event of failure to eradicate *H. pylori* infection, second-line therapy would be considered. Bismuth-based quadruple therapies remain the best option. Confirmation of successful *H. pylori* eradication is important in patients with peptic ulcer complications, such as bleeding or perforation.

Aspirin

Aspirin is widely used as an analgesic agent, and for cardiovascular disease prophylaxis. It is recommended for secondary prophylaxis of acute myocardial infarction, thrombotic stroke and acute coronary syndrome. It has become something of a 'lifestyle drug', believed by many to prevent cardiovascular disease. As with NSAIDs, aspirin should be avoided in patients with a history of peptic ulcer, particularly when complicated by GI bleeding. If aspirin therapy is deemed necessary in a high-risk patient, co-treatment with a PPI should be considered. As mentioned above, combining a Cox-2 selective NSAID with aspirin results in the loss of gastric safety from the Cox-2 drug. Using aspirin with a non-selective NSAID further increases the risk of GI bleeding. The adjusted odds ratios associating drug use with upper gastrointestinal bleeding was found to be 1.8 (95% confidence interval 1.5 to 2.1) for low-dose aspirin.¹⁰ The use of enteric coated aspirin does not confer greater safety than plain aspirin. The use of aspirin for the primary prevention of cardiovascular (CV) events, as recommended by many cardiologists, may be ill-advised (especially in those patients with no known CV risk), however, because the potential CV benefits are outweighed by the increased risk of GI bleeding

One should not, however, lose perspective of the benefit/risk ratio of low-dose aspirin. Low-dose aspirin increases the risk of major bleeding by approximately 70%, but the absolute increase is modest: 769 patients (95% CI, 500–1250) need to be treated with aspirin to cause one additional major bleeding episode annually.¹¹

Anticoagulants and the risk of GI bleeding

Warfarin

Patients taking warfarin for a variety of reasons are at increased risk of gastrointestinal bleeding. It is not the warfarin per se that causes bleeding, but in the event of a bleed it may prevent clotting, which could otherwise limit the severity of the bleed. Prior to embarking on treatment with warfarin it is important to exclude, on history and, if

needed, on endoscopy, potential causes of bleeding such as peptic ulcer. A greater risk of upper GI bleeding is related to the addition of aspirin or NSAIDs to patients taking warfarin. In a large United Kingdom retrospective study of the risk of upper GI bleeding, the adjusted relative risk (RR) of bleeding in patients taking aspirin and warfarin was 6.48, (95% CI 4.25–9.87), whilst for the combination of warfarin and an NSAID the RR was 4.6.¹⁰

Clopidogrel

Clopidogrel is an inhibitor of ADP-induced platelet aggregation, acting by direct inhibition of adenosine diphosphate (ADP). The use of Clopidogrel is increasing in patients with acute coronary syndrome and following coronary artery stenting.

The drug may be prescribed in combination with low-dose aspirin. In the UK general practice study, the relative risk of upper GI bleeding in patients on Clopidogrel alone was 1.1 (95% CI 0.6–2.1), and for clopidogrel and aspirin it was 7.4 (95% CI 3.5–15).¹⁰

Upper GI bleeding: prevention strategies

Gastroprotective agents

Proton pump inhibitors (PPIs)

The available evidence shows that patients on low-dose aspirin, NSAIDs and anti-platelet drugs who are at high risk of upper GI bleeding can be protected by the co-administration of anti-secretory drugs. In a study by Lai et al., the efficacy of lansoprazole 30 mg and aspirin 100 mg was compared to aspirin 100 mg plus placebo for 12 months in patients who had experienced upper GI bleeding and *H. pylori* infection.¹² All the subjects were given *H. pylori*-eradication therapy. Recurrent bleeding rates were 1.6% in the PPI/aspirin group vs. 14.8% in the placebo/aspirin cohort. Two-thirds of those in the placebo group had failed *H. pylori* eradication or had taken NSAIDs.¹² Patients at high risk of upper GI bleeding who require NSAIDs should be treated with a PPI or misoprostil. Misoprostil is seldom used today, and most patients would therefore receive a PPI. Omeprazole and other PPIs have been shown to prevent recurrent bleeding in such patients. In a six-month study of high-risk patients requiring NSAIDs, the incidence of ulcers was significantly decreased in the groups taking esomeprazole 20 mg or 40 mg with either a non-selective NSAID or a Cox-2 NSAID, compared to the group on NSAIDs and placebo. There was no significant dose response between the esomeprazole 20 mg and 40 mg dosage, suggesting that the esomeprazole 20 mg dose is effective in preventing NSAID-induced ulcers.¹³

An alternative strategy would be to use a Cox-2 selective NSAID in such patients, provided they had no cardiovascular risk factors. In selected high-risk cases one might consider the use of a Cox-2 selective NSAID with a PPI.

In a prospective study of stroke patients with upper GI bleeding, the safety of clopidogrel was compared to low-dose aspirin plus esomeprazole. *H. pylori*-positive subjects received eradication therapy. The cumulative rate of re-bleeding at the 12-month follow-up was 8.6% in the clopidogrel group compared to 0.7% in the PPI and low-dose aspirin group ($p = .001$).¹⁴

Emergency treatment

Although not strictly a strategy to reduce the risk of bleeding, practitioners must be aware of the benefit of the early recognition and

treatment of upper GI bleeding. Early diagnosis and prompt treatment and referral often make the difference between survival and death. Clinical predictors of increased risk for re-bleeding included age older than 65 years, shock, poor overall health status, comorbid illnesses, low initial haemoglobin level, melaena, transfusion requirement, and fresh red blood on rectal examination, in the emesis, or in the nasogastric aspirate.

Patients presenting with symptoms of GI bleeding must be seen urgently. Pain is frequently absent or mild, even with severe bleeding. Signs that indicate a significant bleed include tachycardia, hypotension and orthostatic hypotension.

The stabilisation of clot formation can be achieved by raising the gastric pH and maintaining it at 6 or higher. This forms the basis for the administration of intravenous PPIs in the setting of acute ulcer bleeding.

In a study by Barkun et al., the benefit of early PPI administration was shown, and it resulted in lower re-bleeding rates. A reduction in mortality rates was shown when PPI administration and endoscopic therapy were evaluated.¹⁵

In a recent study, the benefit of administering an intravenous PPI at the time of presentation with upper GI bleed was examined using Omeprazole vs. a placebo. This is in contrast to the policy in many hospitals, where the intravenous PPI is only administered after endoscopic evidence has been obtained of a bleeding ulcer. Omeprazole was administered as an 80 mg bolus, followed by an infusion of 8 mg/hour. All patients were endoscoped the following morning. The Omeprazole group had less need for endoscopic therapy compared to the placebo group ($p = 0.007$). They also had a shorter hospital stay. There were no significant differences in the volume of blood required, re-bleeding rates, emergency surgery or death.¹⁶

Most general practices will not have the logistics to initiate intravenous PPI therapy. What then of oral PPI therapy? Can a pH of 6 or higher be achieved? This question was addressed by researchers looking at gastric pH in a group of healthy volunteers. Lansoprazole 120 mg was administered orally at 8 am in the morning, followed by 30 mg doses every three hours until 8 pm. Intra-gastric pH was ≥ 6 for 41% (95% CI: 30–53%) of the 15-hour period, from 8 am to 11 pm, and 46% (95% CI: 35–56%) of the 24-hour period (8am–8 pm). Only 25% of the subjects sustained a pH of ≥ 6 for at least 60% of the 15-hour period, and 35% had a sustained pH of ≥ 6 for at least 60% of the 24-hour period. The authors conclude that oral dosing of lansoprazole at the stated doses could not reliably maintain the gastric pH at 6 or above.¹⁷ Although the level of acid control is not as good as that achieved with the 80 mg bolus followed by 8 mg/hour, it may be useful if there is going to be a delay in the patient reaching hospital. 🏥

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Points for the practice

- Stratify the patient's risk category for upper GI bleeding before prescribing aspirin or NSAIDs. A detailed history must be taken. Patients with a history of peptic ulcer, especially with bleeding, should be offered alternative treatment where possible. Be aware that elderly patients and those with co-morbid disease are at greater risk of bleeding. High-risk patients should, where possible, be treated with non-aspirin, non-NSAID drugs such as paracetamol.
- Patients must be warned about the possible life-threatening complications of aspirin and NSAIDs.
- All NSAIDs should be prescribed at the lowest effective dose and for the shortest period of time.
- Beware of drug-drug interactions. A good reason must exist to prescribe drugs in combination, e.g. warfarin and aspirin, and the patient should be informed accordingly. The risk of harm due to drug interactions can be lessened by awareness of the principles of drug-drug interactions, thoughtful prescribing habits and judicious monitoring when new drugs are added to regimens containing warfarin.
- A *Helicobacter pylori* infection 'test and treat' strategy is appropriate in patients with a history of ulcer or ulcer complications.
- H. pylori* eradication only is not adequate treatment for the prevention of bleeding.
- High-risk patients who require NSAIDs should be offered a Cox-2 selective NSAID, provided no cardiovascular contraindication exists.
- High-risk patients on NSAIDs should be co-treated with a PPI.
- Patient selection for low-dose aspirin is important. Consider the risk/benefit ratio before prescribing aspirin. Clinicians should dissuade otherwise healthy patients from using aspirin as a 'lifestyle drug'.
- High-risk patients on the anticoagulants warfarin and aspirin, or clopidogrel, should receive a PPI.
- Replacing aspirin with other antiplatelet agents must be undertaken with due care, given the risks associated with clopidogrel.
- Strategies for the prevention of bleeding are underutilised.

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