Upper Gastrointestinal Bleeding During Anti-platelet Therapy

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Introduction

Anti-platelet therapy is effective in reducing the incidence of cerebrovascular accident, myocardial infarction and death from vascular causes in individuals with symptomatic atherothrombotic diseases. Low-dose aspirin is most commonly used for the secondary prevention of vascular events. However, its use is frequently associated with adverse gastrointestinal events, which ranged from mild dyspepsia (31%) to life-threatening bleeding or perforation from peptic ulcer (3.1%) over a study period of 4 years in the UK Transient Ischaemic Attack study. The elderly are regarded as a high-risk group. Clinically evident gastrointestinal bleeding occurred in 3% of elderly patients (70 years of age or older) receiving 100 mg of daily aspirin for 12 months.

Clopidogrel (Plavix, Bristol-Myers Squibb Co.), another form of antiplatelet agent, has been approved by the Food and Drug Administration for use in secondary prevention of heart attacks and stroke. Clopidogrel, a thienopyridine derivative similar to ticlopidine, inhibits platelet aggregation through a different mechanism from aspirin. Aspirin inhibits platelet aggregation by irreversibly blocking the enzyme cyclooxygenase. This is essential for the synthesis of thromboxane A2, a substance which causes vasoconstriction and amplifies the platelet activation process leading to platelet aggregation. By contrast, the thienopyridines inhibit platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate, a substance released from platelets during activation that amplifies the aggregation process. Thienopyridines do not impair the prostaglandin-dependent mucosal protective and ulcer healing mechanism, which is a side effect of aspirin.

This review aims to investigate the role of clopidogrel in patients with a history of peptic ulcers or erosions and to examine upper gastrointestinal bleeding in patients receiving aspirin and clopidogrel co-therapy. Since long-term proton pump inhibitors are widely prescribed in the prevention of antiplatelet-induced peptic ulcer complications, its long-term safety is briefly reviewed.

Clopidogrel alone in patients with history of bleeding peptic ulcer is unsafe

The clinical efficacy of clopidogrel in secondary prevention of coronary heart disease, peripheral vascular disease and ischaemic stroke is demonstrated to be marginally more effective than aspirin in a randomised controlled clinical trial [Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)]. The incidence of severe adverse upper gastrointestinal (GI) events was significantly lower for clopidogrel than aspirin (dyspepsia 0.97% versus 1.22%; p<0.05; severe GI haemorrhage 0.52% versus 0.72%; p<0.05). Therefore, clopidogrel is safer than aspirin in average-risk patients, although the number needed to be treated by clopidogrel to prevent one excess aspirin-induced severe GI bleeding was 500. Indeed, in healthy volunteers without endoscopic gastroduodenal disease at baseline, an 8-day course with clopidogrel (75 mg/day), in contrast to aspirin (325 mg/day), did not induce any erosions on repeat endoscopic examination.

Since clopidogrel causes less GI bleeding than aspirin in average-risk patients, can clopidogrel replace aspirin in higher risk patients with peptic ulcer disease? In patients with active bleeding peptic ulcer, clopidogrel is definitely contraindicated. In patients with previous peptic ulcer, there have been one retrospective study and two prospective randomised controlled studies on the safety of replacement of aspirin by clopidogrel therapy. In a retrospective study (n=70), 9 (12%) patients developed gastrointestinal bleeding after clopidogrel therapy for a median follow-up of one year. Clopidogrel-associated GI bleeding was significantly more common in patients with a history of GI bleeding associated with the use of aspirin or H. pylori infection than in those without (22% versus 0%, p=0.007). Previous history of GI bleeding was the only independent predictor of clopidogrel-associated rebleeding. All except one lesion found during rebleeding were identical to the previous lesions, suggesting that impaired haemostasis from clopidogrel therapy might precipitate bleeding from an unhealed or relapsed ulcer. However, rebleeding occurred in none of the patients receiving a proton pump inhibitor. Hence, clopidogrel treatment alone may not be safe in high-risk patients and concomitant long-term proton pump inhibitor prophylaxis should be considered in this setting. Subsequently, this was followed by two randomised controlled studies. The first study recruited patients who took aspirin to prevent vascular events and presented with ulcer bleeding (n=320). After ulcer healing and eradication of H. pylori (if infected), patients were randomised to receive either clopidogrel (75 mg daily) plus placebo or aspirin (80 mg daily) plus esomeprazole (20 mg twice daily) for 12 months. The cumulative incidence of recurrent bleeding was significantly higher in the clopidogrel group (8.6%), as compared to the aspirin plus esomeprazole group (0.7%).
Continuation of aspirin with proton pump inhibitor or conversion to clopidogrel with proton pump inhibitor is safe in moderately severe peptic ulcer disease

In patients with low-dose aspirin induced symptomatic peptic ulceration, what is the best initial treatment? By analogy with trials using full-dose conventional non-steroidal anti-inflammatory drugs, our current practice is to prescribe a proton pump inhibitor while continuing aspirin in patients without severe gastrointestinal bleeding. Although discontinuation of aspirin during the period of ulcer healing may offer a theoretical advantage, there is always a potential of precipitating an ischaemic vascular event, particularly in high-risk patients with unstable angina.

In a randomised controlled study, patients (n=129) with aspirin induced peptic ulcer disease treated with omeprazole (20mg/day) were randomised to receive clopidogrel or to continue with low-dose aspirin. Before randomisation, around 40% of patients in each group had minor gastrointestinal bleeding. These patients had small ulcers without adherent clot or visible vessels or patients with moderately severe gastro-duodenitis. Clopidogrel and aspirin were re-started after 0.86 and 0.44 days after upper endoscopy respectively. The result of this study demonstrated the incidence of unhealed ulcers or erosions at the 8th week was similar in both groups (converted to clopidogrel plus omeprazole 6% versus. continue aspirin 5%). Furthermore, no patient in either group had a re-bleed or perforated peptic ulcer during the study period. Therefore, in patients with moderately severe active peptic ulcer disease while receiving treatment with proton pump inhibitors, either approach of early conversion to clopidogrel or continuation of aspirin is safe. Future study is required to address anti-platelets strategies in bleeding peptic ulcers with endoscopic stigmata of re-bleeding.

Adverse impact of gastrointestinal bleeding in acute coronary syndrome

The efficacy of a combination of aspirin, clopidogrel and anti-coagulation has been established in patients with acute coronary syndrome. The American College of Cardiology / American Heart Association guidelines recommend the use of unfractionated or low molecular weight heparin in addition to aspirin and clopidogrel for the management of unstable angina or non-ST elevation myocardial infarction (class I indication). Enoxaparin is preferable to unfractionated heparin in the absence of renal failure and if coronary artery bypass graft surgery is not planned within 24 hours.

The major adverse event of the combination of heparin, aspirin and clopidogrel is bleeding, particularly from the gastrointestinal tract. However, information on gastrointestinal bleeding is scarce. The incidence rate of bleeding can only be inferred from The Clopidogrel in Unstable Angina To Prevent Recurrent Events Trial. This randomised controlled study primarily examined the efficacy and safety of the addition of clopidogrel to aspirin in patients with acute coronary syndrome over a mean follow-up of 9 months. Anti-coagulation was used in ~ 70% of patients in both groups. Furthermore, thrombolysis was used in 1%-2% of patients and glycoprotein IIb/IIIa receptor antagonist was used in 6%-7% of patients in each group. Overall, the rate of early major bleeding within 30 days after randomisation was significantly higher in the combination group than the aspirin alone group (2.0 % versus 1.5 %). The most frequent site of excess major bleeding episodes was the gastrointestinal tract followed by bleeding at arterial puncture sites.

Recently, the adverse impact of bleeding in acute coronary syndrome has been recognised. In the first study, the association between bleeding and death or ischaemic events in 34 146 patients with acute coronary syndrome enrolled in three registries was examined. Patients with major bleeding were older, more often had diabetes or a history of stroke, had a lower blood pressure and higher serum creatinine and more often had ST-segment changes on the presenting ECG. Patients with major bleeding had a 5-fold-increase in mortality rate at 30-day (12.8% versus 2.5%; p=0.0001) and a 1.5-fold-increase in mortality rate between 30 days and 6 months (4.6% versus 2.9%; p=0.002). The severity of bleeding was associated with mortality (minor less than major less than life-threatening; P for trend =0.0009). In the second study, gastrointestinal bleeding after percutaneous coronary intervention for acute myocardial infarction in the Primary Angioplasty in Myocardial Infarction trials involving 3,130 patients was evaluated. 2.3% developed gastrointestinal bleeding, which was more likely to occur in elderly patients. Gastrointestinal bleeding was independently associated with a prolonged hospital stay (6.4 versus 12.6 days p=0.0001) and greater in-hospital mortality (2.8% versus 10%, p=0.0046) and 6-month mortality (4.6% versus. 14%, p=0.0016). This difference may be partly accounted by the premature termination of anti-platelet therapy during bleeding. In fact, premature discontinuation of antiplatelet therapy 30 days after drug-eluting stent placement for acute myocardial infarction resulted in more deaths during the next 11 months (7.5% versus 0.7%, p=0.0001; adjusted hazard ratio 9.0; 95% confidence interval 1.3 to 60.6). Therefore, evaluation of strategies to reduce bleeding and thereby improve clinical outcomes is urgently needed.
Prevention of upper gastrointestinal bleeding in acute coronary syndrome

What is the strategy to prevent gastrointestinal bleeding during aspirin and clopidogrel co-therapy? Unfortunately, the information is sparse. Currently, there has been no randomised controlled study published in the English literature. There are only two cohort studies.

In the first case-control study, upper gastrointestinal bleeding in the 30 days following PCI for stable angina and acute coronary syndromes was evaluated. The incidence of upper gastrointestinal bleeding following PCI was 1.2% (70 of 5,673 patients). The risk factors were primary PCI (odds ratio 27.80, P < 0.001), cardiac arrest (odds ratio 6.17, P = 0.003), inotropic requirement (odds ratio 5.85, P = 0.001), thienopyridine use before PCI (odds ratio 2.40, P = 0.02), and advanced age (odds ratio 1.08, P < 0.001). Endoscopy provided therapeutic intervention in 33% of patients with no serious complications during endoscopy. Prescription of proton pump inhibitors (odds ratio 0.08, P = 0.002) was accompanied with a reduced risk. The 30-day mortality for patients with upper gastrointestinal bleeding was significantly higher (11.9% versus 0.5%, P = 0.001).

In the second study, a cohort of 666 patients receiving a combination of aspirin, clopidogrel and enoxaparin was evaluated for upper gastrointestinal bleeding at the 7th day after stopping combination therapy. Gastrointestinal bleeding occurred in 2.7% patients. The age adjusted odds ratio (95% confidence interval) for gastrointestinal bleeding was 5.07 (1.31-16.58) for previous peptic ulcer and 21.41 (2.56-146.68) for cardiogenic shock. Co-prescription of proton pump inhibitors could reduce the risk [odds ratio 0.07 (0.01-0.27)]. A prospective randomised controlled study to evaluate the efficacy of proton pump inhibitors is warranted.

Safety of long-term proton pump inhibitors

The safety of long-term administration of proton pump inhibitors in humans is not totally clear yet. In general, long term PPI therapy appears to be safe in humans. However, gastric cancer did occur in rats receiving high dose PPI therapy. Enterochromaffin-like cell carcinoids developed in 20% of rats after life long high dose omeprazole therapy. Gastric carcinoma developed in 90% of rats with duodenogastric reflux after one year of omeprazole therapy. Fortunately, these have not been observed in humans. Lamberts et al reported that only argyrophil cell hyperplasia secondary to PPI- induced hypergastrinaemia developed in 19% patients receiving high dose omeprazole (40 mg - 60 mg daily) for 10 years. There was no gastric atrophy, intestinal metaplasia, argyrophil cell dysplasia or neoplasia. Despite this assurance, there have been reports of development of gastric fundic gland polyps and hyperplastic polyps in both adults and children receiving long-term omeprazole therapy, although their natural history and long-term clinical significance is currently unknown.

Conclusion

In summary, in patients with no history of peptic ulcer disease or gastrointestinal bleeding, clopidogrel appears to be safer than aspirin. However, the cost-effectiveness should be analysed since 500 patients need to be treated with clopidogrel to prevent only one aspirin-induced severe gastrointestinal bleeding. In patients with dyspeptic or moderately severe bleeding peptic ulcers, both approaches of early conversion to clopidogrel or continuation of aspirin are safe if the patients are maintained by proton pump inhibitors. Future studies are required to address anti-platelet strategies in very high risk bleeding peptic ulcers, particularly requiring endoscopic haemostasis. On the other hand, long-term administration of clopidogrel alone, without proton pump inhibitor prophylaxis is unsafe in patients with history of bleeding peptic ulcer. In patients with acute coronary syndrome, the addition of clopidogrel to standard aspirin therapy reduces the rate of major adverse cardiovascular events but is associated with gastrointestinal bleeding. Bleeding is associated with adverse cardiovascular outcome. The co-prescription of proton pump inhibitors appears to reduce the risk. Long-term administration of proton pump inhibitors appears to be safe in humans. Further prospective studies for the prevention and management of gastric ulcer disease during aspirin and clopidogrel ± antiocoagulation therapy and the role of H2-receptor antagonist in the prevention of antiplatelet drug-induced peptic ulcer disease are warranted.

References

Clinical Quiz

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Clinical Information:
Two-month old baby boy presented with poor oral feeding and bilious vomiting.

Questions:
What were the radiological findings and diagnosis?

(See P.37 for answers)