Management of Patients with High Gastrointestinal Risk on Antiplatelet Therapy

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KEYWORDS

• Antiplatelet therapy • Clopidogrel prasugrel • Thienopyridines • Aspirin • Gastrointestinal bleeding • Risk • *Helicobacter pylori*

In treating cardiovascular disease, clinicians are commonly caught between competing considerations of cardiovascular benefit and gastrointestinal (GI) risks. Because platelets have an important role in the pathophysiology of coronary artery and coronary stent thrombosis, drugs that prevent platelet thrombosis have acquired a critical role in the prevention of atherothrombotic complications of vascular disease. In recent years, the use of antiplatelet therapies has been markedly increasing, primarily for the prevention of coronary artery and coronary stent occlusion.[1–4] Additionally, in the prevention of cerebrovascular occlusion, antiplatelet therapies are among the principal treatments.[5] As evidence accumulates regarding the benefits of antiplatelet therapies in the treatment of cardiovascular and cerebrovascular diseases, the use of these agents in clinical practice continues to increase even more.

Currently, two categories of oral antiplatelet therapies, aspirin and the thienopyridines (clopidogrel and prasugrel), are available or are under clinical development for the prevention of atherothrombotic complications in patients with the acute coronary syndrome or who are undergoing percutaneous coronary intervention (PCI).[6] Although the evidence is clear from several well-designed trials that antiplatelet therapies have clinical benefit, the increasing use of these agents in clinical practice is associated with increasing GI complications, such as ulceration and GI bleeding. Because of the increasing rates of ulcer and GI complications being encountered with these drugs, this article focuses on management strategies that may reduce the GI risks of patients who take antiplatelet therapy, especially those patients at highest risk for development of a GI event while using these antiplatelet agents.

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MECHANISMS OF GASTROINTESTINAL INJURY WITH ANTIPLATELET THERAPIES

Aspirin reduces platelet activity by inhibiting the cyclooxygenase (COX) enzymes. Although aspirin can inhibit COX-1 and COX-2 isoenzymes, the platelet primarily comprises COX-1. Aspirin permanently inhibits platelet COX-1 at relatively low dosages, resulting in inhibition of platelet activity.[7] COX-2–mediated effects of aspirin, primarily the analgesic and anti-inflammatory consequences, are inhibited at higher aspirin dosages. Aspirin irreversibly inhibits the metabolism of arachidonic acid to thromboxane A_2 (TXA_2), which is highly sensitive to aspirin's effects, causing complete suppression of platelet TXA_2 production with a few doses of aspirin.[7] This inhibition of TXA_2 decreases platelet aggregation, causes vasodilation, reduces the proliferation of vascular smooth muscle cells, and decreases atherogenicity.

In the GI mucosa, the principal metabolic products of COX enzymes are the prostaglandins, substances that protect against GI mucosal injury. In the presence of a COX inhibitor, such as aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), GI COX is inhibited, which results in increased degrees of GI mucosal injury. At daily aspirin dosages that are much lower than that desired for optimal cardiovascular efficacy, such as with 10 mg aspirin per day, gastric COX is markedly inhibited, mucosal prostaglandins are reduced to 60% of baseline, and GI ulceration occurs.[8] Therefore, there is likely no dose of daily administered aspirin that is therapeutically efficacious without conferring gastric mucosal injury.

Clopidogrel is an effective antithrombotic, because it blocks platelet activation of adenosine diphosphate (ADP) by irreversibly binding to platelets' ADP receptor, thereby preventing the ADP-dependent activation of the GpIIb-IIIa complex, the primary platelet receptor for fibrinogen. In the CAPRIE trial, a randomized trial comparing clopidogrel and aspirin for the prevention of ischemic events, a randomized, prospective study of the efficacy of clopidogrel 75 mg and aspirin 325 mg daily for secondary prevention of thrombotic vascular events, clopidogrel was marginally more effective than aspirin and resulted in modestly lower GI bleeding than aspirin (0.5% vs 0.7%).[9] In short-term endoscopic evaluations of healthy volunteers, clopidogrel causes less gastroduodenal damage than aspirin 325 mg daily,[10] and, in observational trials of populations undergoing antiplatelet therapies, clopidogrel has a nonsignificant, slightly lower rate of GI bleeding than that with aspirin.[11] Despite this reduction, the GI risks of thienopyridines are not zero. In fact, the use of prasugrel in patients with acute coronary syndromes with scheduled PCI is associated with significantly reduced rates of cardiovascular ischemic events when compared with those with clopidogrel.[12] However, prasugrel's increased cardiovascular efficacy is somewhat offset by an increased risk of major GI bleeding, including fatal bleeding.[12] Furthermore, the use of thienopyridines in high GI risk patients can result in high rates of GI bleeding. In patients with a prior history of GI bleeding, recurrent GI bleeding after only 1 year of clopidogrel can be observed in as high as 9% of patients taking this agent.[13] These observations indicate that, although it may have previously been assumed that the thienopyridines were the GI-safe alternatives to aspirin, these agents in fact are associated with considerable GI risks as well.

The mechanism that underlies the GI injury of thienopyridines is currently unclear. However, it has been hypothesized that agents such as clopidogrel and prasugrel may cause their GI injury through an impairment of ulcer healing.[14] Platelet aggregation plays a critical role in ulcer healing through the release of various platelet-derived growth factors that promote angiogenesis, which is essential for ulcer healing. For example, thrombocytopenic animals have reduced ulcer angiogenesis and impaired gastric ulcer healing.[15] ADP receptor antagonists impair gastric ulcer healing by