Risk and Benefit of Proton Pump Inhibitor for Patients Undergoing Anti-Platelet Therapy Including Clopidogrel

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Anti-platelet therapy is now widely performed in patients with stroke, myocardial infarction or peripheral arterial disease. Aspirin and clopidogrel are the most important cornerstone agents in this therapy. Aspirin and clopidogrel are prescribed as a monotherapy or a combination therapy. To prevent stent thrombosis after implantation of drug-eluting stents, dual anti-platelet therapy with aspirin and clopidogrel is now a standard therapy (1). Aspirin sometimes induces gastric mucosal injuries. Because the prevalence of aspirin use for primary and secondary prophylaxis against cardiovascular and cerebrovascular diseases is increasing, the incidence of aspirin-related peptic ulcer appears to now be increasing (2). To prevent gastric injury, aspirin is commonly used with an anti-secretory agent, such as a proton pump inhibitor (PPI). Lai et al (3) demonstrated that a PPI significantly reduced the recurrence rate of ulcer complications in patients with the long-term use of low-dose aspirin. Fortunately, incidences of clinically severe adverse events of PPIs are rare. Moreover, a PPI is effective not only for gastric protection but also for the rapid relief of several symptoms, such as heartburn, dyspepsia and epigastralgia in many cases (4). Accordingly, a PPI is now often prescribed with aspirin. In 2008, the consensus and guidelines of the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG) and American Heart Association (AHA) on antiplatelet therapy were published (5-7), and stated that patients with a risk of peptic ulcer and/or treated with two or more antiplatelet agents are recommended to be treated with a PPI.

In contrast, recently the drug-drug interaction between clopidogrel and a PPI has received attention. Clopidogrel is activated on the metabolization by CYP2C19. Therefore, the plasma level of the active metabolite of clopidogrel depends on the activity of CYP2C19. As a matter of fact, the inhibitory effect of clopidogrel on platelet aggregation depends on CYP2C19 genotype status (8). Interestingly, CYP2C19 is the main metabolizing enzyme of PPIs. Therefore, concomitant use of clopidogrel and a PPI induces a drug-drug interaction, resulting in decreased activation of clopidogrel, which leads to an increased risk of reinfarction and/or thrombosis. Juurlink et al (9) reported that concomitant therapy with a PPI other than pantoprazole was associated with an increased risk of reinfarction. Ho et al (10) reported that concomitant use of clopidogrel and a PPI was associated with an increased risk of adverse outcomes compared to the use of clopidogrel without a PPI and they suggested that the use of a PPI may be associated with attenuation of benefits of clopidogrel. Together, there are merits (i.e., gastric protection) and demerits (i.e., attenuation of clopidogrel efficacy) in the concomitant use of a PPI in patients undergoing antiplatelet therapy including clopidogrel. This is the therapeutic dilemma of prophylaxis use of PPI in anti-platelet therapy. However, there was no previous study which compared the risk and benefit of the concomitant use of a PPI in a cohort of patients undergoing antiplatelet therapy including clopidogrel.

In this issue of Internal Medicine, Yasuda et al (11) for the first time retrospectively compared the risk and benefit of anti-secretory agents in the cohort of patients undergoing dual antiplatelet therapy with clopidogrel and aspirin. They found that no UGI bleeding was observed in patients taking an anti-secretory agent such as a PPI or an H2 receptor antagonist (H2RA), but that the 1- and 2-year cumulative incidences of UGI bleeding were 4.5% and 9.2%, respectively, in patients without such anti-secretory agents. Here, usefulness of anti-secretory therapy as the prophylaxis therapy for UGI bleeding in patients treated with anti-platelet agents has been reconfirmed. However, they found that the incidence of coronary restenosis or new coronary lesion was increased in patients treated with a PPI in comparison with those with an H2RA or without anti-secretory therapy. They reported that the PPIs used in patients who experienced re-stenosis or
new coronary lesion were low doses PPIs (i.e., lansoprazole 15 mg and omeprazole 10 mg). Therefore, a low dose of a PPI was proved to have a risk of attenuation of clopidogrel efficacy. Together with the report by Ho et al (10), all PPIs used in Japan have the risk of attenuation of clopidogrel efficacy. Because the incidence of intermediate or poor metabolizers of CYP2C19, whose capacity of active metabolism of clopidogrel is decreased and whose plasma PPI levels are increased compared with rapid metabolizers, is higher in Asians than in Caucasians, low dose PPI could easily attenuate the efficacy of clopidogrel in Asians as observed in the study of Yasuda et al (11).

Recently, an H2RA is reported to be effective for the prevention of aspirin-induced gastric injury (12). Yasuda et al (11) demonstrated that an H2RA as well as a PPI completely prevented GI bleeding and that an H2RA did not increase the risk of restenosis or a new lesion of coronary arteries in patients taking dual antiplatelet therapy after coronary stenting, suggesting that an H2RA could replace a PPI as the prophylaxis agent in patients taking dual antiplatelet therapy. However, this study is retrospective and no prospective study has been performed. Therefore, which anti-secretory agent, a PPI or an H2RA, is better as the prophylaxis agent in the dual anti-platelet therapy must be verified from the point of view of risk and benefit in future prospective studies.

References


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