EDITORIAL COMMENT

Gastroprotective Strategy in Aspirin Users

Jiing-Chyuan Luo*

Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, and Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Aspirin, acetylsalicylic acid, was synthesized by Hoffman of Bayer Laboratories in 1897. Aspirin irreversibly inhibits platelet cyclooxygenase (COX-1) activity, thus preventing the synthesis of thromboxaneA_2, and thereby inhibiting platelet aggregation and thrombi formation. A low dose of aspirin, commonly defined as 75–325 mg daily, is effective in preventing cardiovascular (CV) and cerebrovascular disease with decreasing vascular mortality.[1] Meta-analysis data including 142 randomized trials involving approximately 100,000 patients at risk of vascular events showed that aspirin (75–150 mg/day) reduces by 25% the incidence of ischemic stroke, myocardial infarction, and vascular death when compared with placebo.[2] The efficacy of low-dose aspirin for secondary prevention of CV disease is well documented. However, studies investigating the use of aspirin in primary prevention have produced inconsistent results.

The major factor limiting the use of aspirin is concern about the development of gastrointestinal (GI) events, especially GI ulcer and bleeding due to its inhibition of prostaglandin formation in GI mucosa. A study showed that low-dose aspirin (75–325 mg/day) for 3 months was associated with a 7% incidence of endoscopic gastroduodenal ulcer.[3] The use of low-dose aspirin is associated with a 2- to 4-fold increased risk of upper GI (UGI) events. The pooled incidence of major GI bleeding in a meta-analysis of several placebo-controlled trials, using aspirin 75–325 mg daily, was 0.12% per year (95% confidence interval, 0.07–0.19), with an odds ratio (OR) of 2.07.[4] This means that 833 patients would need to be treated with low-dose aspirin rather than no aspirin to cause an additional episode of major GI bleeding over 1 year. But in high-risk patients who had a past history of aspirin-related ulcer bleeding, a very high rate of recurrent ulcer bleeding (15%) within 1 year was noted when they continued to take aspirin for cardioprevention after their ulcers had healed and *Helicobacter pylori* (*Hp*) had been eradicated.[5] Elderly patients, history of peptic ulcer or ulcer bleeding, *Hp* infection, concomitant use of steroid, anticoagulant, and nonsteroidal anti-inflammatory drugs (NSAIDs) are all risk factors for ulcer bleeding in aspirin users. The ulcerogenic effects of aspirin are systemic rather than topical, which is supported by several studies showing no difference in UGI bleeding occurrence between enteric coated or uncoated aspirin. Observational studies showed an association between higher aspirin dose and risk of UGI complications. The 2008 ACG and AHA expert consensus document recommends lowering the dose from 325 mg to 81 mg among those with a high risk of UGI events. However, it is unknown what the optimal dose of aspirin really is.[6]

Three key strategies have been proposed for minimizing the UGI side effect of low-dose aspirin. These are the use of an alternative platelet inhibitor, such as clopidogrel, the use of co-therapy with a gastroprotective agent, such as proton pump inhibitor (PPI), and strong consideration of *Hp* eradication.[7]

Clopidogrel is an alternative antiplatelet agent that inhibits adenosine diphosphate-induced platelet aggregation through irreversible inhibition of P2 nucleotide receptors on the platelet surface. Clopidogrel does not inhibit COX function and prostaglandin formation and does not cause endoscopically evident mucosal injury in healthy volunteers. It is commonly used for secondary CV prevention in place of low-dose aspirin in patients who have experienced GI intolerance to aspirin-related adverse events or with aspirin allergy. Inconsistent results from population-based observational studies and case-control studies have been found

*Correspondence to: Dr Jiing-Chyuan Luo, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: jcluo@vghtpe.gov.tw • Received: March 31, 2009 • Accepted: May 1, 2009

with regard to whether clopidogrel is safer than aspirin for GI bleeding. The CAPRIE trial showed that clopidogrel 75 mg/day significantly lowered all GI bleeding and severe GI bleeding and significantly reduced the risk of ischemic stroke, myocardial infarction and ischemic death when compared with aspirin 325 mg/day in high-CV-risk patients.[8] However, clopidogrel is not safe enough for patients with high GI risk. Eight to 13% of patients developed recurrent ulcer bleeding within 1 year when they took clopidogrel instead of aspirin after their ulcers had healed and *Hp* had been eradicated, while only 1% of patients developed recurrent ulcer bleeding when they used aspirin combined with PPI after their ulcers had healed and *Hp* had been eradicated.[9,10] The 2008 ACG and AHA expert consensus document recommends that substitution of clopidogrel for aspirin is not recommended strategy to reduce the risk of recurrent ulcer bleeding in high-risk patients and is inferior to the combination of aspirin and PPI.[6] It appears that impairment of ulcer healing by inhibition of platelet aggregation and angiogenesis may be the mechanism by which antiplatelet agents may cause existing asymptomatic ulcers to bleed. Thus, while such agents may not be the primary cause of ulcers, they may impair healing of background ulcers.[11]

PPI, which reduces gastric acid secretion, plays a protective role in aspirin or other NSAID-associated mucosal damage. One observational study reported a low incidence of UGI complications (1 event/100 patients/year) among high-GI-risk patients receiving low-dose aspirin plus PPI.[12] PPI is effective in preventing aspirin-associated recurrent ulcer bleeding after *Hp* eradication and ulcers have healed.[5] In aspirin users who have a history of UGI bleeding and *Hp* infection, PPI is equivalent to *Hp* eradication in preventing recurrent ulcer bleeding.[13] A recent study revealed that PPI co-therapy in patients taking long-term low-dose aspirin for secondary CV prevention was cost-effective.[14]

Misoprostol, an analog of prostaglandin E_1, is also effective in reducing endoscopic gastric erosions in healthy volunteers taking aspirin 300 mg/day. However, the major limitation in using misoprostol is diarrhea, which causes poor compliance. Observational case-control studies in low-dose aspirin users reported a decreased risk of UGI bleeding (OR, 0.4–0.5) when they took histamine receptor 2 antagonists concomitantly.[15]

Hp infection is an important factor for ulcer and ulcer bleeding in the general population. Case-controlled studies have consistently shown that *Hp* is an important risk factor for ulcer and ulcer bleeding in low-dose aspirin users. However, whether *Hp* eradication alone would adequately reduce the risk of ulcer bleeding in aspirin users with high GI risk is uncertain.[15] A more recent study, and the largest one to date, suggested that confirmed *Hp* eradication in aspirin users with prior ulcer bleeding significantly reduces the risk of recurrent bleeding.[16] Therefore, before starting long-term therapy with antiplatelet agents, testing for and eradicating *Hp* in patients with a history of ulcer disease is recommended by the 2008 ACG and AHA expert consensus document.[6]

In conclusion, low-dose aspirin therapy for CV prophylaxis is associated with an increased risk of developing UGI events. The use of non-aspirin antiplatelet agents as an alternative in patients with GI risk may also cause undesirable UGI effects. *Hp* infection has been identified as a clear risk factor in patients taking low-dose aspirin. Current data suggest that PPI seems to be the best choice in reducing UGI events associated with low-dose aspirin therapy in high-GI-risk patients, but concomitant *Hp* eradication may be of additional benefit in all patients, especially in those with previous ulcer history.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106.
2. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
3. Yeomans ND, Lanas AI, Talley NJ, Thomson AB, Daneshjoo R, Eriksson B, Appelman-Eszczuk S, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther* 2005;22:795–801.
4. McQuaid KR, Laine L. Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;119:624–38.
5. Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, Lau GK, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033–8.
6. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol* 2008;52:1502–17.
7. Luk HH. Use of gastroprotective drugs in patients receiving low-dose aspirin. *J Chin Med Assoc* 2009;72:356–61.
8. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events. *Lancet* 1996;348:1329–39.
9. Lai KC, Chu KM, Hui WM, Wong BC, Hung WK, Loo CK, Hu WH, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol* 2006;4:860–5.
10. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, Hui AJ, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238–44.

11. Ma L, Elliott SN, Cirino G, Buret A, Ignarro LJ, Wallace JL. Platelets modulate gastric ulcer healing: role of endostatin and vascular endothelial growth factor release. *Proc Natl Acad Sci USA* 2001;98:6470–5.
12. Lanas A, Rodrigo L, Márquez JL, Bajador E, Pérez-Roldan F, Cabrol J, Quintero E, et al. Low frequency of upper gastrointestinal complications in a cohort of high-risk patients taking low-dose aspirin or NSAIDS and omeprazole. *Scand J Gastroenterol* 2003;38:693–700.
13. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001;344: 967–73.
14. Saini SD, Schoenfeld P, Fendrick AM, Scheiman J. Cost-effectiveness of proton pump inhibitor cotherapy in patients taking long-term, low-dose aspirin for secondary cardiovascular prevention. *Arch Intern Med* 2008;168:1684–90.
15. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention, and treatment. *Curr Med Res Opin* 2007;23:163–73.
16. Chan FK. Long-term incidence of ulcer bleeding with low-dose aspirin after eradication of *Helicobacter pylori*. *Gastroenterology* 2005;128:A133. [Abstract]