LONG TERM LOW-DOSE ASPIRIN THERAPY: IS GASTRIC PROTECTION NECESSARY?

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ABSTRACT

Aspirin is commonly used in primary and secondary prevention of cardiovascular events. However, its long-term use leads to gastrointestinal compromise, such as gastric mucosal erosions, peptic ulcer, and GI bleeding. These complications are common in our daily clinical practice, as illustrated in the case of a 67-year-old male who has ischaemic heart disease and was on long-term aspirin without any gastric protection for 9 years. He was subsequently admitted for bleeding from gastric ulcers and diagnosed to be positive for *H. pylori* infection.

The risk factors for GI damage and bleeding, and the evidence for gastric protection in long-term aspirin users are reviewed here. High-risk patients, such as those with a history of ulcer disease or gastrointestinal bleeding, should undergo screening and treatment of *H. pylori* infection. Concomitant use of proton-pump inhibitors is recommended as they are superior to histamine-2 receptor antagonists in prevention of GI bleeding. PPI use should also be encouraged if patients have two or more of the following risk factors: over 60 years old, corticosteroid use, dyspepsia, or gastroesophageal reflux disease symptoms. Further research is needed to determine if *H. pylori* screening is required prior to commencement of long-term aspirin in the general population.

Keywords:
Keywords: Gastroduodenal Ulcer; Upper Gastrointestinal Bleeding; Low-dose Aspirin; Proton-pump Inhibitor; Helicobacter pylori;

SFP2017; 43(2): 35-38

INTRODUCTION

Mr. G was a 67-year-old male I encountered in 2014. I was privileged to follow up and follow through his journey from outpatient polyclinic appointments, to two hospitalisations for gastrointestinal bleeding and anaemia, and subsequently back to the community for continued care. His case raised the awareness of the need for gastro-protective interventions for patients on long-term aspirin. The evidence of these interventions is reviewed.

PATIENT'S REVELATION: WHAT HAPPENED?

Mr. G was a 67-year-old Chinese male with Type 2 diabetes mellitus for 29 years on follow-up with the polyclinic. His illness was complicated by retinopathy and nephropathy with proteinuria. His other comorbidities included hypertension, hyperlipidaemia, anaemia of chronic disease, and peripheral vascular disease. He also had ischaemic heart disease with ejection fraction of 25 percent. Coronary angioplasty was done in 2005 which showed severe triple vessel disease, but in view of high risk for surgery, Mr. G was treated with medical therapy including beta-blockers and aspirin 100mg daily.

Initially Mr. G had omeprazole 20mg OM along with his aspirin, however he thought this additional capsule made him drowsy, and the extra cost of medication further decreased his compliance. Mr. G had no other gastro-protective medications for the past nine years despite recommendations by various doctors in the polyclinic.

Mr. G presented to the emergency department with giddiness and hypotension in 2014. Examination revealed melena but no overt bleeding. Investigations were unremarkable except for marked decrease in haemoglobin from baseline of 10 to 6.8g/dL. Oesophageogastroduodenoscopy showed erosive gastritis at corpus and antrum, with Forrest 2c ulcer in corpus, and multiple Forrest 3 ulcers at antrum. Biopsies of the corpus and antrum were positive for *H. pylori*. He was treated with IV esomeprazole infusion for 72 hours, triple therapy for eradication of *H. pylori*, and aspirin was restarted before he was discharged with gastroenterology follow-up. Mr. G was readmitted 2 weeks later with type 2 myocardial infarction secondary to anaemia. He was transfused 2 pints of packed cells, before the medical team switched him from aspirin to clopidogrel. Mr. G was finally agreeable to taking omeprazole 40mg BD regularly.

GAINING INSIGHT: WHAT ARE THE ISSUES?

Could the episode of gastrointestinal (GI) bleeding be prevented if Mr. G had taken his aspirin with gastric protection, such as histamine-2 antagonists or proton-pump inhibitors? Is it necessary for everyone on aspirin to have gastric ulcer prophylaxis? Should we screen for *H. pylori* in all aspirin users? What is the most effective approach and therapy? If one would like to avoid additional pill burden, is the enteric-coated aspirin good enough?

STUDY THE MANAGEMENT: HOW DO WE APPLY THE INSIGHTS IN OUR CLINICAL PRACTICE?

Aspirin and its GI complications

Low-dose aspirin (LDA), defined as 75–325mg/day, has been widely used for the primary and secondary prevention of cardiovascular and cerebrovascular disease. It has been shown to reduce all-cause mortality by 18 percent, number of strokes

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by 20 percent, myocardial infarctions by 30 percent, and other vascular events by 30 percent when used as secondary prevention.[1] However, long-term use of LDA increases the risk of gastrointestinal injury such as gastric mucosal erosions, peptic ulcer, and bleeding.[2] Aspirin blocks production of prostaglandins via the cyclooxygenase-1 pathway, which in turn reduces mucosal flow, mucus and bicarbonate secretion, and impaired aggregation. Systemically, through inhibiting the cyclooxygenase-2 pathway, aspirin reduces angiogenesis leading to impaired healing of the gastric mucosa.[3] The inhibition of both pathways by aspirin results in a gastric environment that is more susceptible to mucosal injury.

Various studies have shown that patients who took aspirin are 2 to 2.5 times more likely than those in the placebo group to have gastrointestinal tract bleeding.[2,4] Some studies quoted 1 in 100 patients taking aspirin over a 28-month period will experience a gastrointestinal haemorrhage.[4] The risk of upper GI bleeding in patients taking low-dose aspirin is similar to the risk in the patients taking non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs).[5]

Risk Factors for Aspirin-induced GI Damage and Bleeding

GI complications associated with LDA are more frequently present in patients who are older than 65 years, have a history of peptic ulcer, have an infection with *H. pylori*, or have concomitant drug therapies with NSAIDs, other antiplatelet agents or anticoagulants, and glucocorticosteroids.[6]

Aspirin dose and duration Similar to the dose-dependent ulcer and GI bleeding risks of NSAIDs and high-dose aspirin,[7] LDA up to a daily dose of 300mg has a significantly higher risk of GI haemorrhage compared to placebo.[4,8] The risk of GI bleeding also remains elevated with longer duration of aspirin treatment. Indeed, the GI complications can be seen as early as 3 months,[9] and the risk of GI bleeding after 1 year of aspirin is more than double relative to non-users.[10]

Concurrent use with other medications The risk of GI complications is increased when LDA is used concurrently with some medications. For instance, a cohort study shows that the standardised incidence ratio for GI bleeding is 2.6 (range 2.2-2.9) for LDA alone, and it is 5.7 (4.4-7.0) for combined use of LDA and other NSAIDs, indicating high risk of combined aspirin and NSAIDs use.[11] The risk of GI haemorrhage is also increased when LDA is used in combination with clopidogrel (RR, 2.08; 95% CI, 1.34 to 3.21), and high-dose oral corticosteroids (RR, 4.43; 95% CI, 2.10 to 9.34)[6]. There is some evidence to suggest GI bleeding risk increases with the concomitant use of selective serotonin reuptake inhibitors and aspirin but the relationship is not conclusive.[12,13]

Age and comorbidities Baseline rates of major extracranial bleeding events and GI complications increase with age. A systematic review quotes that there is an almost threefold to fourfold increase observed from age 50–54 to 70–74 years.[14] The presence of comorbidities such as diabetes have also been shown to increase the risks for GI ulcers and bleeding, compared to non-elderly patients on long-term aspirin therapy.[15,16]

***H. pylori* infection** The effects of *H. pylori* infection on long-term risk of GI damage and bleeding in LDA users remains controversial. In Western countries, the prevalence of gastroduodenal ulcers is consistently higher in *H. pylori* positive LDA users than in *H. pylori* negative users, which suggests *H. pylori* infection exacerbates aspirin-induced GI mucosal injuries.[17] A recent multicentre, retrospective, case-controlled study in Japan also showed that *H. pylori* infection exacerbates severe gastric mucosal injury among chronic LDA users.[18]

On the other hand, previous studies in Japan have reported a similar prevalence of aspirin-induced gastroduodenal mucosal injury regardless of the presence of *H. pylori* infection.[17] One possible explanation is that the different phenotypes of *H. pylori* gastritis may contribute to contradictory data concerning its effect on gastric damage in LDA users.[19] Current evidence is insufficient to allow meta-analysis and provide firm conclusion on whether *H. pylori* acts as an independent or synergistic risk factor for gastrointestinal damage in chronic aspirin users.[20]

Approaches to the Prevention of GI Injuries from Low-Dose Aspirin

Enteric-coated and buffered aspirin Buffered aspirin is a combination of aspirin and antacid, such as calcium carbonate or alumni hydroxide. Enteric-coated aspirin is a special aspirin formulation that resists disintegration in the stomach, and allows the tablet to dissolve in the more neutral to alkaline environment of the duodenum. Although studies show that enteric-coated aspirin diminishes endoscopic signs of gastroduodenal injury, specially formulated aspirins do not appear to protect against the clinically relevant end-point of gastrointestinal bleeding, probably because they do not protect against the systemic effect of the COX mechanism.[4,21]

Histamine-2 receptor antagonist and proton pump inhibitor Another strategy to decrease upper gastrointestinal injury associated with LDA is through the co-administration of histamine-2 receptor antagonists (H2RA) such as famotidine, or proton pump inhibitors (PPI) such as esomeprazole and omeprazole. Although studies have demonstrated that both H2RA and PPI can lead to similar healing of gastroduodenal ulcers,[22] H2RAs do not demonstrate reduction of GI bleeding risk. In fact, PPIs are superior to H2RAs in the prevention of GI ulcers and bleeding.[23-28] The concomitant use of PPI, LDA and clopidogrel do not increase the risk of major adverse cardiovascular events, as shown in a recent meta-analysis of 10 randomised controlled trials by Chen et al.[28]

Eradication of *H. pylori* Although current evidence is insufficient to conclude whether *H. pylori* acts as an independent or synergistic risk factor for GI bleeding in aspirin users, the general consensus is to screen for and eradicate *H. pylori*.[29] The long-term incidence of recurrent ulcer bleeding with aspirin use is low after *H. pylori* infection is eradicated.30 A recent systemic review shows that eradication of *H. pylori*

infection before aspirin use could reduce the incidence of upper GI complications by 25–30 percent.[14]

However, aspirin users without current or past *H. pylori* infections who develop ulcer bleeding have a higher risk of recurrent bleeding.[30] Screening and eradication of *H. pylori* prior to commencement of long-term low-dose aspirin can be useful as *H. pylori*-positive and negative aspirin users may require different gastro-protective strategies. The long-term cost-effectiveness of such screening, whether via stool antigen test (SAT), urea breath test (UBT), or serology (IgG detection via ELISA), has yet to be determined.[19]

Consensus statements and guidelines According to a joint consensus statement by the American College of Cardiology Foundation, the American College of Gastroenterology, and the American Heart Association in 2008[31] and 2010[32] on prevention strategies in patients taking antiplatelet agents, testing for and eradicating *H. pylori* in patients with a history of ulcer disease is recommended before starting chronic antiplatelet therapy. Both American[31,32] and European[33] guidelines recommend the use of PPI for high-risk patients, namely patients with a history of ulcer complications, ulcer disease (non-bleeding), gastrointestinal bleeding, and those receiving dual antiplatelet therapy or concomitant anticoagulant therapy. Patients without the above risk factors, but with two or more other risk factors for gastrointestinal complications (including age 60 years or more, corticosteroid use, dyspepsia or gastroesophageal reflux disease symptoms) should also be treated with a PPI. The routine use of either a PPI or an H2RA for patients at lower risk of upper GI bleeding is not recommended, as these patients have much less potential to benefit from prophylactic therapy.

Current practices in Primary Care Adherence to the clinical recommendations vary among countries. Although there is evidence of reasonable utilisation of gastro-protection in aspirin-users in Spain, primary care physicians in Netherlands[34] and Japan[35] may not adhere to the recommendations as stringently. Primary care physicians tend to prescribe less gastro-protective drugs in high-risk aspirin initiators than in high-risk NSAID initiators.[36] Even when they are prescribed, the choice and dosage of H2RA or PPI is questionable.[37]

Moreover, data on actual number of *H. pylori* screening prior to commencement of long-term aspirin therapy in primary care is limited. A survey done in 2001 in Singapore showed that less than 50 percent of polyclinic or private general practitioners had prescribed *H. pylori* eradication therapy. Only 70 percent of these prescribers confirmed *H. pylori* infection before eradication therapy as there is a lack of facilities for testing.[38]

The U.S. Preventive Services Task Force has recently released a new recommendation statement on long-term LDA use in the primary prevention of cardiovascular disease and colorectal cancer in adults.[39] It is not difficult to predict there will be more elderly aspirin users in the near future, and the incidence and prevalence of GI complications associated with aspirin use may increase if preventive measures are not implemented consistently in our clinical practices.

CONCLUSION

GI mucosal injury associated with the use of LDA is a serious clinical concern, especially as there is an increasing proportion of the general population who are taking it for primary or secondary prevention of cancer or cardiovascular diseases.

Current guidelines recommend screening and treating *H. pylori* infection for patients with a history of ulcer disease, and concomitant use of PPI in high-risk patients. Patients like Mr. G who has age as the sole risk factor for GI bleeding, are not required to be treated with PPIs. However, they may have undiagnosed *H. pylori* infection or comorbidities such as diabetes which may further increase the GI bleeding risk. Further studies are required to ascertain the relationship of comorbidities and GI bleeding risks in LDA users, and the need for *H. pylori* screening prior to commencement of LDA in the general population.

Acknowledgement

I would like to thank Dr. Ong Chooi Peng for her wisdom and guidance in preparing this manuscript.

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