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EDITORIAL

Increased susceptibility of aging gastric mucosa to injury and delayed healing: Clinical implications

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Abstract

In this editorial we comment on the article by Fukushi K *et al* published in the recent issue of the *World Journal of Gastroenterology* 2018; 24(34): 3908-3918. We focus specifically on the mechanisms of the anti-thrombotic action of aspirin, gastric mucosal injury and aging-related increased susceptibility of gastric mucosa to injury. Aspirin is widely used not only for the management of acute and chronic pain and arthritis, but also importantly for the primary and secondary prevention of cardiovascular events such as myocardial infarcts and strokes. Clinical trials have consistently shown that antiplatelet therapy with long term, low dose aspirin (LDA) - 75 to 325 mg daily, dramatically reduces the risk of non-fatal myocardial infarcts, stroke and mortality in patients with established arterial diseases. However, such treatment considerably increases the risk of gastrointestinal (GI) ulcerations and serious bleeding by > 2-4 fold, especially in aging individuals. This risk is further increased in patients using LDA together with other antiplatelet agents, other nonsteroidal anti-inflammatory agents (NSAIDs) and/or alcohol, or in patients with *Helicobacter pylori* (*H. pylori*) infection. Previous studies by our group and others have demonstrated prominent structural and functional abnormalities in gastric mucosa of aging individuals (which we refer to as aging gastric mucosa or "aging gastropathy") compared to the gastric mucosa of younger individuals. Aging gastric mucosa has impaired mucosal defense, increased susceptibility to injury by a variety of noxious agents such as aspirin, other NSAIDs and ethanol, and delayed and impaired healing of injury. The mechanism underlying these abnormalities of aging gastric mucosa include reduced mucosal blood flow

causing hypoxia, upregulation of PTEN, activation of pro-apoptotic caspase-3 and caspase-9, and reduced survivin (anti-apoptosis protein), importin-α (nuclear transport protein), vascular endothelial growth factor, and nerve growth factor. The decision regarding initiation of a long-term LDA therapy should be made after a careful consideration of both cardiovascular and GI risk factors. The latter include a previous history of GI bleeding and/or ulcers, age ≥ 70, male gender, concurrent use of other NSAIDs, alcohol consumption and *H. pylori* infection. Furthermore, the incidence of GI ulcers and bleeding can be reduced in patients on long term LDA treatment by several measures. Clinicians treating such patients should test for and eradicate *H. pylori*, instruct patients to avoid alcohol and non-aspirin NSAIDs, including cyclooxygenase-2-selective NSAIDs, and prescribe proton pump inhibitors in patients on LDA therapy. In the future, clinicians may be able to prescribe one of several potential new drugs, which include aspirin associated with phosphatidylcholine (PL2200), which retains all property of aspirin but reduces by approximately 50% LDA-induced GI ulcerations.

Key words: Aging gastric mucosa; Injury; Low dose aspirin; Platelets; Cyclooxygenase-1; Cyclooxygenase-2; Thromboxane A-2

Core tip: Low dose aspirin is widely used to prevent cardiovascular events such as myocardial infarcts and strokes; however, this therapy significantly increases the risk of gastrointestinal injury and induces ulceration and serious bleeding especially in aging individuals. This risk is further increased in patients using low dose aspirin concurrently with other antiplatelet agents, other nonsteroidal anti-inflammatory agents and/or alcohol, or in patients with *Helicobacter pylori* infection.

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INTRODUCTION

Aspirin (acetyl salicylic acid) synthesized in 1897 by Felix Hoffman in Bayer Laboratories in Germany, has become one of the most successful drugs used initially for the treatment of acute and chronic pain and arthritis. More recently a regular treatment with low dose aspirin (LDA) it is used for a primary and secondary prevention of cardiovascular events (CVE) such as myocardial infarcts (MI) and strokes in which it reduces mortality[1-3]. As demonstrated by Vane *et al*[4], aspirin is a non-selective inhibitor of cyclooxygenase (COX), an enzyme synthesizing prostaglandins and thromboxanes. The COX-1 isoform is expressed constitutively in most tissues. In the gastrointestinal (GI) mucosa and kidneys, COX-1 plays a critical role in maintaining these tissues' integrity by generating prostaglandin E2 (PGE_2) and prostacyclin (PGI_2) from arachidonic acid[5,6]. In blood platelets, COX-1 generates thromboxane A_2 (TXA_2), which promotes their aggregation and thrombi formation. The COX-2 isoform is constitutively expressed in brain, kidneys, intestine, and endothelial cells, and is induced in variety of tissues in response to proinflammatory cytokines and growth factors[5,6]. COX-2 generated prostaglandins play critical roles in gastric mucosal defense, cytoprotection, angiogenesis and ulcer healing[5-7]. While aspirin inhibits both COX-1 and COX-2 isoforms, in low doses it predominantly inhibits COX-1; while in higher doses it also inhibits COX-2. LDA treatment acetylates COX-1 at serine-529 residue and irreversibly inhibits COX-1 activity in platelets for about 10 d (life time of platelets) resulting in almost complete inhibition of production of TXA_2 from arachidonic acid, and inhibition of platelet aggregation and thrombi formation[8,9]. These actions of aspirin are summarized in Table 1.

Due to the anti-thrombotic and cardioprotective effects, LDA defined as 75 to 325 mg daily, alone or in combination with other antiplatelet agents (*e.g.*, clopidogrel) became a standard treatment for the secondary prevention of CVE (MI and stroke). Clinical trials consistently showed that antiplatelet therapy with LDA daily dramatically reduces the risk of nonfatal MI, stroke and mortality in patients with established arterial diseases[1-3]. The Second International Study of Infarct Survival (ISIS-2) showed that a daily 160 mg LDA administered for 30 d confers significant cardioprotection that resulted in a significant reduction of reinfarction and strokes[1] LDA treatment significantly reduces the risk of MI, stroke, and mortality in a wide range of high-risk patients[2,9]. The Antithrombotic Trialist's Collaboration meta-analysis of 287 trials that included over 200000 patients with high cardiovascular risk, showed that daily antiplatelet therapy with 75-150 mg LDA significantly reduced the risk of CVE by approximately 32%[2]. These and other studies show that aspirin confers significant cardioprotection to the majority of patients with coronary heart disease, ischemic stroke, peripheral arterial disease and systemic embolism[1,2]. Importantly this treatment has a simple dosage, low cost, and a good safety record and therefore is widely used world-wide. The cardioprotective action of aspirin appears to be unique; the other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, do not significantly impact cardiovascular diseases. Unlike aspirin, the latter NSAIDs bind only reversibly to COX-1 and inhibit platelet function for only brief time. Selective COX-2 inhibitors do not inhibit formation TXA_2 by platelets and do not have substantial cardioprotective

Table 1 Action of Aspirin on platelets and gastrointestinal mucosa and its unique features compared with other nonsteroidal anti-inflammatory drugs

Aspirin is a non-selective inhibitor of cyclooxygenase (COX), an enzyme involved in the synthesis of prostaglandins and thromboxanes (TXA) from arachidonic acid
Aspirin inhibits both COX-1 and COX-2 isoforms with a greater inhibition of COX-1 than COX-2 (approximately 100-fold) in low doses COX-1 isoform is expressed constitutively in most tissues: Gastrointestinal mucosa and kidneys and by generating prostaglandin E2 (PGE_2) and prostacyclin (PGI_2) and plays a critical role in maintaining tissue integrity at basal level COX-1-induced thromboxane A_2 (TXA_2) generation causes platelet aggregation and thrombi formation and is the basis for cardiovascular events
COX-2 isoform is constitutively expressed in some tissues (the brain, kidneys, intestine, and endothelial cells). In other tissues COX2 is induced in response to local irritants, proinflammatory cytokines and growth factors.
COX2 generated prostaglandins PGE_2 and PGI_2 play a critical role in gastric mucosal defense in response to injury and promote angiogenesis, ulcer healing, and (cancer growth)
Aspirin–has potent antithrombotic and cardioprotective properties: Irreversibly inactivates platelet COX-1 (*vs* only temporary inhibition by other nonselective NSAIDs)
↓ TXA_2 synthesis, platelet aggregation, and thrombi formation which are all basis for cardiovascular events
↓ Cardiocerebrovascular events
In addition, aspirin may prevent and/or reduce cancer. A recent meta-analysis of 8 trials[38,39] showed that LDA reduces cancer incidence and mortality
Aspirin advantage - single daily dose, low cost, good safety profile

action; in fact, some COX-2 selective inhibitors may increase the risk of cardiovascular events[10].

A long-term, LDA treatment is not without risk since it can induce gastroduodenal injury, ulcers and severe bleeding especially in elderly patients[11-18]. The main underlying mechanism is that aspirin inhibits generation of PGE_2 and PGI_2 which are critical for mucosa defense, protection and maintenance of gastrointestinal mucosal integrity[7] (Figure 1). In addition, inhibition of TXA2-dependent platelet function by aspirin prevents thrombi formation in injured vessels and causes uncontrolled bleeding. Cryer and Feldman showed that long-term LDA treatment in healthy subjects significantly reduces gastric mucosal prostaglandin levels by approximately 60% and causes gastric and duodenal injury in some patients[19]. The risk of development of peptic ulcers in aspirin (or non-aspirin NSAIDs) users was examined in approximately 460000 patients (between 1995 and 1999) and shown to be increased to 2.9 for aspirin and 4.0 for non-aspirin NSAIDs, compared with control patients[20]. LDA-induced gastric injury was increased in patients using LDA plus other NSAIDs and/or alcohol, or in patients with *Helicobacter pylori* (*H. pylori*) infection[21-23]. In the latter group eradication of *H. pylori* in patients on LDA therapy significantly reduced the re-bleeding rate[23]. These risks associated with long-term LDA therapy are significantly higher in elderly patients[8,18,24-30].

MECHANISMS OF INCREASED SUSCEPTIBILITY OF AGING GASTRIC MUCOSA TO INJURY

The mechanisms of increased susceptibility of aging gastric mucosa to injury were described in detail in our previous publications[24-29] and are summarized in Table 2. In brief, we demonstrated that aging gastric mucosa has partial atrophy of gastric glands, impaired mucosal defense, increased susceptibility to injury (by ethanol, aspirin and other NSAIDs), impaired angiogenesis and a delayed and abnormal injury healing[24,25]. Aging gastric mucosa has reduced mucosal blood flow causing hypoxia, which leads to activation of the early growth response-1 transcription factor that in turn upregulates the dual specificity phosphatase (PTEN) resulting in activation of pro-apoptotic caspase-3 and caspase-9 and reduced expression of the anti-apoptosis protein, survivin[24]. The imbalance between pro-apoptosis and anti-apoptosis factors results in increased apoptosis and injury. This paradigm demonstrated experimentally has also a direct human relevance since increased expression of PTEN and reduced expression of survivin were shown in gastric mucosa of aging ≥ 70 years of age *vs* younger (< 40 years) individuals[24]. Other potential mechanisms operating in aging gastric mucosa include reduced telomerase activity, increase in replicative cellular senescence, and reduced expression of vascular endothelial growth factor and importin α - a transport protein essential for transport of transcription factors to the nucleus. In aging individuals, endothelial cells of blood vessels are very abnormal with significantly reduced angiogenic capacity and decreased levels of angiogenic factors such as VEGF and nuclear hypoxia inducible factor-1α[25,27]. Our recent study demonstrated that reduced levels of the nuclear transporter, importin α in aging endothelial cells is the key mechanism for impaired angiogenesis and reduced VEGF[25,27,28]. We also demonstrated that nerve growth factor (NGF) is critical for angiogenesis and injury healing and that reduced expression of NGF in aging gastric endothelial cells is one of the main cause of impaired angiogenesis and delayed healing in aging gastric mucosa[26,31,32]. Specifically, we found that aging gastric endothelial cells in rats and humans have dramatically approximately 5-fold reduced expression of NGF, and that NGF gene therapy restores *in vitro* angiogenesis in these aging endothelial cells[26]. Moreover, in that study we also demonstrated that treatment of gastric ulcers in aging rats with a local

Table 2 Structural, functional and biochemical abnormalities of aging gastric mucosa

Partial atrophy of gastric glands and their replacement with connective tissue
Degenerative changes in parietal and chief cells
↓ Sensory innervation and abolished hyperemic response to mild and moderate irritants
↓ Bicarbonate and prostaglandin generation and secretion
↓ Mucosal blood flow (by > 60%) and profound hypoxia of all mucosal cells
↑ Expression and transcriptional activity of early growth response-1→ ↑ PTEN and ↓ survivin (anti-apoptosis protein) → ↑ apoptosis
Other abnormalities include:
↓ Telomerase activity, cellular senescence, increased lipid peroxidation, impaired hypoxia sensor in endothelial (and epithelial?) cells
↑ Reactive oxygen species
Downregulated or mutated Klotho protein and dysregulated mitochondrial-nuclear communication
↓ Importin-α expression in endothelial cells of gastric mucosa → ↓activation and ↓expression of vascular endothelial growth factor (VEGF), which is a pro-angiogenic factor and protects gastric endothelial cells; imbalance between VEGF and endostatin
↓ Expression of nerve growth factor in gastric mucosal endothelial cells → reduced endothelial cell viability, impaired angiogenesis and gastric ulcer healing

Revised from *World J Gastroenterol* 2014[29] and updated based on our previous publications[24-29].

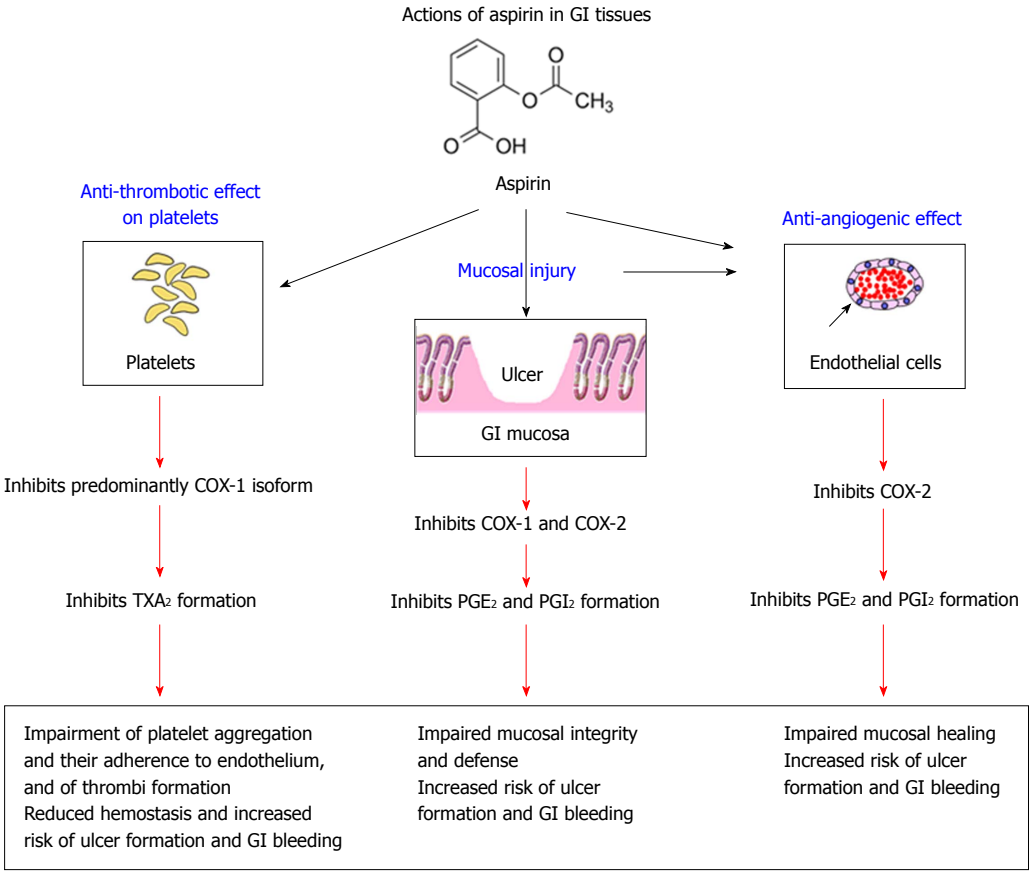

Figure 1 Actions of aspirin in gastrointestinal tissues. Aspirin low dose has an anti-thrombotic effect on platelets - it mainly inhibits cyclooxygenase (COX)-1 enzyme resulting in inhibition of thromboxane A_2 formation, and impairment of platelet aggregation and their adherence to endothelium, and of thrombi formation. Aspirin induced impaired thrombi formation reduces hemostasis and therefore, increases the risk of gastrointestinal (GI) ulcers and bleeding. Aspirin increases GI mucosal injury and has an anti-angiogenic effect since it inhibits COX-1 and COX-2 enzymes in the GI mucosa and in endothelial cells resulting in the reduction of the cytoprotective prostaglandin E_2 and prostacyclin. This causes impaired mucosal integrity and defense, thus increasing the risk of GI ulcers and bleeding and impaired mucosal healing. GI: Gastrointestinal; COX: Cyclooxygenase; TXA_2: Thromboxane A_2; PGE_2: Prostaglandin E_2; PGI_2: Prostacyclin.

injection of NGF significantly increases angiogenesis, accelerates ulcer healing and improves the quality of mucosal regeneration[26].

In the recent issue of the *World Journal of Gastroenterology* [2018; 24(34): 3908-3918], Fukushi *et al*[33]. published the interesting paper: Gastroduodenal ulcer bleeding in elderly patients on low dose aspirin therapy. That study addresses an important issue - aging gastric mucosa and its ulceration and bleeding induced by antiplatelet therapy with LDA alone or in combination with other anticoagulants. In that retrospective study, 1105 patients with bleeding gastroduodenal ulcers (GDU) treated between 2000-2016 were analyzed for age and medications used, length of hospital stay, hemoglobin

decrease, blood transfusion, and presence of underlying disease. In the elderly patients (≥ 70 years of age), GDU bleeding and its severity and impact were significantly higher in patients receiving LDA combination therapies with either: Other antiplatelet drugs (*e.g.*, clopidogrel, ticlopidine, or prasugrel), and/or anticoagulation drugs than in patients receiving LDA monotherapy. In the latter group, the authors did not find significant differences in the length of hospital stay nor the percentage of severe conditions between elderly and non-elderly patients except increased transfusion requirement in the former group. This conclusion is in a stark contrast to a recent study from the Oxford University, which demonstrated in a prospective population-based study that included 3166 patients (approximately 50% aged ≥ 75 years) that the long-term risks and severity of bleeding in patients receiving LDA long term treatment for secondary CVE prevention was increased dramatically with age (≥ 75 years hazard ratio 3.10, 95%CI: 2.27-4.24; $P < 0.0001$)[34]. The risks of major bleeding in patients older than 75 years were higher and more sustained than those in younger patients (hazard ratio 4.13, 2.60-6.57; $P < 0.0001$) and the risk of disabling or fatal GDU bleeding was also increased (hazard ratio 10.26, 4.37-24.13; $P < 0.0001$). These apparently conflicting results between Fukushi *et al*[33] study and the Oxford University study may be explained by differences in study design, age threshold of 70 *vs* 75 years of age, and statistical power (relatively small number of patients = 113 on LDA alone treatment in Fukushi *et al*[33] study), different environmental factors, or by the possibility that GI mucosa in Japanese patients has different genetic and biochemical features compared to British patients. In the research arena, further study is necessary. It would be particularly interesting to compare Japanese and Western European data directly and perhaps the biology of the mucosa directly. Increased power with similar study design would help address the issue.

Iwamoto *et al*[18] extensively reviewed the clinical and endoscopic features, incidence, risk factors and mechanisms of gastroduodenal injury and bleeding induced by long-term LDA treatment. They listed the following as risks factors for aspirin-induced increased GI complications: prior history of ulcer and/or GI bleeding, age ≥ 70 years, concurrent use of non-aspirin NSAIDs and *H. pylori* infection. They also pointed out preventive efficacy not only proton pump inhibitors but also H2 receptor antagonists *e.g.*, famotidine[18]. Aging itself increases GI injury and complications. In patients aged under 60 years, 70-79 years and those over 80 years, the incidence rate of upper GI complications per 1,000 male subjects was 20, 90, and 150, respectively[35]. Aspirin use increased these rates of GI complications within each age group by 2-fold resulting in dramatically higher incidence of complications[35]. The absolute increase in complications with aspirin use is significantly higher in the aging population due to their higher baseline risk of aging gastropathy.

CLINICAL IMPLICATIONS

Aging gastropathy and its complications are important and clinically relevant issues for at least three reasons. First, in many countries *e.g.*, Japan, some European countries and the United States, the population is aging. Second, older patients have much greater risk for both CVE and gastroduodenal ulcers and bleeding gastrointestinal complications of LDA-induced gastric injury than younger patients. Third, increased susceptibility of aging gastric mucosa to injury can be potentially reduced or reversed pharmacologically.

CONCLUSION

While the overall cardioprotective benefits of LDA therapy outweighs the risk of LDA- induced GI ulcers and bleeding (reviewed in[36]) from a gastroenterologist's perspective, it is very important to prevent LDA-induced GI ulcers and bleeding, especially in patients 70 years of age or older. The decision regarding initiation of a long-term LDA therapy should be made after careful consideration of both cardiovascular and gastrointestinal risk factors. The latter include previous history of gastroduodenal bleeding and/or ulcers, age ≥ 70, male gender, concurrent use of other NSAIDs, alcohol consumption, and *H. pylori* infection. The recommendations for these patients are as follows: (1) Test for and eradicate *H. pylori* if present; (2) Avoid the non-aspirin NSAIDs, including COX-2-selective NSAIDs, and alcohol consumption; (3) Use proton pump inhibitors that reduce the risk of bleeding GI ulcers, or alternatively use histamine H2-receptor antagonists (recommended by some studies to be effective in prevention of LDA-induced gastroduodenal ulcers). The eradication of *H. pylori* is as effective as treatment with omeprazole in preventing recurrent bleeding in patients on LDA therapy. Clinicians should also recognize that potential new drugs being developed may change the balance between heart health and mucosal protection. For instance, aspirin associated with phosphatidylcholine (PL2200) retains all the properties of aspirin but reduces LDA-induced GI ulcerations by approximately 50%[37].

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