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Mechanisms of the Development of Aspirin-Induced Gastroduodenopathies in Patients with Ischemic Heart Disease during Acetylsalicylic Acid Therapy

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Resume: Aspirin (acetylsalicylic acid, ASA) remains the cornerstone of antiplatelet therapy for secondary prevention in ischemic heart disease (IHD); however, its chronic use is frequently associated with gastrointestinal (GI) complications, collectively known as aspirin-induced gastroduodenopathies. The ulcerogenic effect of ASA is multifactorial and primarily determined by inhibition of cyclooxygenase-1 (COX-1) with subsequent suppression of protective prostaglandins (PGE_2, PGI_2), direct topical mucosal injury, and activation of inflammatory and oxidative pathways. ASA disrupts the balance between mucosal protective and aggressive factors at all levels of the intestinal barrier, leading to epithelial injury, increased permeability, microvascular ischemia, and impaired mucosal repair. Experimental data demonstrate that ASA shifts arachidonic acid metabolism toward the lipoxygenase pathway, resulting in elevated leukotriene B4 and tumor necrosis factor-alpha (TNF-α), promoting neutrophil adhesion, oxidative stress, and epithelial apoptosis. In patients with IHD, pre-existing endothelial dysfunction, reduced mucosal perfusion, and concomitant risk factors (advanced age, H. pylori infection, use of anticoagulants or corticosteroids) exacerbate mucosal vulnerability. Preventive strategies include acid suppression with proton pump inhibitors, mucoprotective agents, eradication of H. pylori, and cautious selection of antiplatelet regimens. Understanding the underlying mechanisms of ASA-induced mucosal injury in IHD patients is essential for balancing cardiovascular protection and gastrointestinal safety.

Keywords: Aspirin-induced gastropathy, ischemic heart disease, cyclooxygenase inhibition, prostaglandins, mucosal defense, lipoxygenase pathway, TNF-alpha.

The **ulcerogenic effect of acetylsalicylic acid (ASA)** is determined by three main mechanisms: inhibition of COX-1 and gastroprotective prostaglandins, increased permeability of gastrointestinal (GI) mucosal membranes, and stimulation of additional proinflammatory mediators [1]. The specific contribution of each mechanism to the overall pattern of damage remains incompletely understood. A crucial role in the formation of NSAID-induced gastropathies is attributed to the imbalance between mucosal protective and aggressive factors. ASA and other NSAIDs affect all levels of the intestinal barrier — pre-epithelial, epithelial, and post-epithelial [2]. Dyspeptic symptoms primarily arise from the local action of ASA on the GI mucosa. The topical effect of ASA on the gastrointestinal lining manifests as local irritation during absorption. Being weak acids, ASA molecules directly irritate the gastric and intestinal mucosa, leading to hydrogen ion back-diffusion, sodium ion and infectious agent penetration into the submucosal layer, and local inhibition of prostaglandin synthesis . This causes a decrease in pH within the submucosal layer, which stimulates pain receptors. ASA and other NSAIDs can also accelerate gastrointestinal motility [3]. In addition, active ASA metabolites re-enter the duodenum and stomach with bile as a result of hepatic excretion.

The principal damaging mechanism of ASA involves **irreversible inhibition of cyclooxygenase (COX)** through covalent binding of the acetyl group of ASA to the hydroxyl group of a serine residue at the N-terminal region of the enzyme . COX is a constitutive human enzyme that exists in two isoforms — COX-1 and COX-2. These isoforms differ slightly in their amino acid sequence. COX-1 is the predominant, structural form synthesized under physiological conditions and present in most cells and tissues . COX-1 mediates the synthesis of **thromboxane A_2 (TXA_2),** a potent platelet aggregation inducer and vasoconstrictor released during platelet activation. Moreover, COX-1 is responsible for the synthesis of **prostaglandins PGE_2 and PGI_2,** which exert a protective role throughout the GI mucosa. Under the influence of PGE_2 and PGI_2, mucus and bicarbonate production is stimulated, mucosal microcirculation is enhanced, and the damaging effects of pepsin, bile acids, and hydrochloric acid are neutralized [4].

COX-2, on the other hand, is an inducible isoform that is markedly upregulated during inflammatory processes. It catalyzes the formation of prostaglandins involved in inflammation and pain, as well as prostacyclin synthesis in endothelial cells [5]. **Prostacyclin** inhibits platelet aggregation and induces vasodilation . The **antiplatelet effect of ASA** is primarily due to irreversible inhibition of platelet COX-1, resulting in decreased thromboxane A_2 production. At cardioprotective doses (75–81 mg), COX-2 is virtually insensitive to ASA, which explains the use of higher doses for anti-inflammatory purposes. Thus, it is generally accepted that the main mechanism underlying ASA-induced gastroenteropathy is **inhibition of COX-1 activity and the resulting reduction of prostaglandin levels in the gastric and intestinal mucosa** [6]. Overall, all NSAIDs exhibit similar efficacy and toxicity at equivalent doses; however, interindividual differences in adverse reactions exist. It is hypothesized that mucosal alterations depend on each patient's individual prostaglandin baseline. Evidence suggests that patients with inherently low prostaglandin synthesis are at higher risk of developing gastropathies when taking NSAIDs or ASA.

Adverse effects of long-term ASA therapy occur throughout the GI tract, but lesions are most frequently found in the **antral region of the stomach,** where the density of prostaglandin receptors is highest. Overall, the pathogenesis of ASA-induced gastrointestinal injury during prolonged administration remains **incompletely understood.** Experimental studies have shown that acetylsalicylic acid (ASA) alters the metabolic pathway of arachidonic acid, shifting it from the prostaglandin to the lipoxygenase pathway. Under the influence of lipoxygenase, pro-inflammatory cytokines and leukotriene B4 are formed. This leads to the adhesion of neutrophils to the vascular endothelium, which exert toxic effects on the gastrointestinal tract (GIT) and can induce inflammation and tissue ischemia [7]. The enhanced adhesion of neutrophils with the formation of white thrombi is associated with the possible influence of cytokines. However, the exact role of pro-inflammatory cytokines in this cascade of mucosal injury has not been fully elucidated. It is assumed that the damaging effect may be induced by tumor necrosis factor-alpha (TNF-α) .

It has been observed that, subsequently, there is an increase in the production of hydrochloric acid and pepsinogen, enhanced generation of free radicals, changes in intracellular calcium levels, uncoupling of oxidative phosphorylation in epithelial cell mitochondria, disturbances in gastroduodenal motility, and intensification of necrosis, apoptosis, and desquamation of epithelial cells [8]. In addition, inhibition of cyclooxygenase-1 (COX-1), by reducing platelet aggregation, contributes to the development of bleeding from the damaged mucosal surface . Despite these findings, the intimate mechanisms of gastrointestinal injury during long-term ASA administration in patients with ischemic heart disease remain insufficiently understood.

The primary pharmacologic action of ASA is the irreversible acetylation of the cyclooxygenase enzyme(s) (COX-1 and, at higher doses, COX-2). COX-1 is constitutively expressed in many tissues, including the gastric and duodenal mucosa, and regulates the synthesis of protective prostaglandins (PGs) such as PGE_2 and PGI_2. These PGs serve multiple protective functions: stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, enhancing microcirculation, and neutralising aggressive luminal factors (acid, pepsin, bile salts). When ASA inhibits COX-1 in the gastrointestinal mucosa, the net result is a reduction in mucosal PG levels,

which in turn compromises the mucosal barrier [9]. The mucus–bicarbonate layer is weakened, microcirculatory resistance is reduced, and the ability to neutralize luminal acid and pepsin is diminished. This state renders the mucosa more vulnerable to injury from acid, bile, and other luminal aggressors. Furthermore, some studies suggest that combined inhibition of COX-1 and COX-2 amplifies mucosal susceptibility. While ASA at low cardioprotective doses primarily targets COX-1, oral ASA exerts local effects that may influence COX-2 expression or downstream inflammatory responses, contributing to mucosal injury. In addition to decreased PG synthesis, ASA therapy also affects platelet function (via decreased thromboxane A_2) and thus influences mucosal haemostasis. The impaired platelet aggregation reduces the mucosa's ability to respond to micro-injury, increasing bleeding risk.

In addition to systemic COX inhibition, ASA exerts direct local (topical) injurious effects on the gastrointestinal mucosa. ASA is a weak acid; in the gastric lumen it remains partially non-ionised, facilitating its penetration into epithelial cells and disruption of the mucosal phospholipid bilayer [9]. Within the mucosal cells, ASA and its salicylate metabolite may dissipate proton gradients, reduce intracellular ATP levels, initiate sodium ion back-diffusion, and increase epithelial cell permeability. These changes disrupt the integrity of the mucosal barrier, allowing luminal aggressors (acid, pepsin, bile salts, bacteria) and toxic ions to access the submucosa and microvasculature. In parallel, ASA may accelerate gastrointestinal motility, reducing contact time for protective mucus or bicarbonate layers and exacerbating mechanical stress on vulnerable mucosa. Thus, synergy arises: local epithelial injury + systemic defence impairment = enhanced mucosal susceptibility.

Beyond COX inhibition and barrier disruption, several additional pathways contribute to ASA-induced gastroduodenal injury. Experimental studies have shown that ASA shifts arachidonic acid metabolism toward the lipoxygenase pathway, increasing leukotriene B4 and pro-inflammatory cytokines (for example TNF-α, IL-6). This promotes neutrophil adhesion to the endothelium of mucosal microvasculature, leading to microcirculatory ischemia, oxidative stress, and further mucosal damage [10]. In animal models of ASA (and other NSAIDs) exposure, increased expression of endothelial adhesion molecules, increased neutrophil-endothelial interactions, mitochondrial dysfunction (uncoupling of oxidative phosphorylation), changes in intracellular calcium, elevated reactive oxygen species and altered epithelial apoptosis/necrosis have been documented. Reduced mucosal blood flow due to microvascular compromise, along with diminished nitric oxide production, further undermines mucosal defence. In IHD patients, these mechanisms may be potentiated: underlying atherosclerosis and endothelial dysfunction may impair mucosal microcirculation, while the requirement for antiplatelet therapy (e.g., ASA) means that the protective haemostatic capacity is reduced. Furthermore, many IHD patients have comorbid hypertension, diabetes or renal impairment which further compromise mucosal defence.

In patients with ischemic heart disease on ASA therapy [11], certain additional factors may amplify gastroduodenal injury risk:

- Age (particularly > 60 or > 75 years) – associated with reduced mucosal regenerative capacity and increased comorbidities.
- Concomitant medications: other NSAIDs, anticoagulants, corticosteroids, antiplatelet agents — each adds further mucosal or bleeding risk.
- Helicobacter pylori infection – impaired mucosal integrity.
- Hypertension and vascular disease – microvascular dysfunction in the gut mucosa analogous to that in coronary circulation.
- Genetic predisposition – e.g., SLCO1B1 polymorphisms have been associated with increased ASA-related gastric mucosal erosion.

In this context, the long-term ASA therapy needed for secondary prevention in IHD becomes a double-edged sword: essential for cardiovascular risk reduction, yet increasing GI mucosal risk [12]. Understanding the mechanistic overlap helps tailor preventive strategies.

From a mechanistic perspective, several interventions are justified:

- Proton pump inhibitors (PPIs) or other acid suppressants: by reducing gastric acidity, these help lessen the local irritant burden and may support mucosal healing.
- Mucoprotective agents (for example rebamipide) that enhance mucus or bicarbonate secretion and improve mucosal microcirculation. One retrospective Japanese study found that co-administration of rebamipide and PPI/H_2 antagonists significantly reduced mucosal injury incidence in low-dose ASA users.
- Eradication of *H. pylori* and screening for other risk factors (older age, comorbidities, concomitant medications) to reduce additional mucosal vulnerability.
- Minimisation of other ulcerogenic medications (NSAIDs, corticosteroids) where possible.
- Enteric-coated or buffered formulations of ASA may reduce direct epithelial exposure, though the benefit in IHD patients requires further study.
- Attention to microvascular disease and mucosal perfusion: in IHD patients with comorbid vascular disease, ensuring optimal control of hypertension or diabetes may indirectly protect the gastrointestinal mucosa.

Conclusion. Aspirin-induced gastroduodenopathies arise from the complex interplay between systemic cyclooxygenase inhibition, local epithelial injury, and inflammatory microvascular mechanisms. The central pathogenic factor is the suppression of COX-1-derived prostaglandins, which weakens the mucosal barrier and predisposes to acid-induced injury. Additional pathways—such as increased leukotriene synthesis, cytokine release, oxidative stress, and endothelial dysfunction—amplify mucosal damage, especially in patients with ischemic heart disease. These patients possess pre-existing vascular impairment that further reduces mucosal perfusion and healing potential. To mitigate these adverse effects, clinicians should adopt individualized preventive strategies including proton pump inhibitor co-therapy, mucosal protective agents, eradication of *H. pylori*, and optimization of comorbid conditions. Future research should focus on molecular targets that preserve mucosal integrity without compromising aspirin's cardioprotective efficacy.

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