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Gastrointestinal lesions and complications of low-dose aspirin in the gastrointestinal tract

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Low dose aspirin (ASA) use has been associated with a wide range of adverse side effects in the upper gastrointestinal (GI) tract, which range from troublesome symptoms without mucosal lesions to more serious toxicity, including ulcers, GI bleeding, perforation and even death. Upper GI symptoms in low dose ASA users are common but often careless or misinterpreted and they are not always related to the presence of mucosal injury. Usually, low dose ASA related ulcers are reasonably small and asymptomatic, and probably heal over a period of weeks to a few months. But, the real clinical problem occurs when the ulcer results in a GI complication (mostly bleeding). The estimated average excess risk of symptomatic or complicated ulcer related to low dose ASA is five cases per 1000 ASA users per year. Death is the worst outcome of GI complications in low dose ASA users, but data about this aspect are scarce. Current evidence indicates that low dose ASA can damage the lower GI tract also, but the real size of the problem is still unknown.

Introduction

Low dose ASA, commonly defined as 75–325 mg daily, is one of the most widely used drugs in the world and the mainstay of therapy for cardiovascular disease [1]. One survey suggested that over one-third of the US adult population (including 80% of those with known cardiovascular disease) use low dose ASA regularly [2]. In England in 2007, over 30 million primary care prescriptions were issued

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for ASA [3]. Low dose ASA is associated with GI injury, and this damage may be different according to dose, concomitant medication use and patient risk profiles. Guidance from the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents state that low dose ASA is associated with a two to four fold increase in GI events, increasing with concomitant medication use [4–6]. In this review we are going to summarize the most important points about GI symptoms and complications derived from the use of low dose ASA.

Upper gastrointestinal symptoms

Low dose ASA use has been associated with a wide range of adverse side effects in the upper GI tract, range from troublesome symptoms without mucosal lesions to more serious toxicity, including ulcers, GI bleeding, perforation and even death. [Fig. 1] [7]. Upper GI symptoms in low dose ASA users are common but often careless or misinterpreted. Gastro-oesophageal reflux (regurgitation and/or heartburn) and dyspeptic symptoms (including bloating, belching, epigastric discomfort, early satiety and postprandial nauseas) seem to be the most frequent and can be present in up to 15–20% of low dose ASA takers [5,8]. The study called "The UGLA survey" showed that 15.4% of low dose ASA users quoted upper GI symptoms, 70% gastroesophageal reflux, and that these symptoms had a negative impact on treatment compliance in 12% of patients. In addition, they also reported that a prior history of dyspeptic symptoms was predictive of low dose ASA related upper GI symptoms onset.

The onset of these symptoms is important because it may lead to poor adherence or even discontinuation of low dose ASA treatment. Despite the strong evidence supporting the protective effects of low dose ASA, discontinuation rates of around 50% have been reported in patients who have been taking this medication for several years [9]; this is disturbing as interruption is associated with increased risk of major cardiovascular events including cardiovascular mortality [Fig. 2]. Cessation of treatment with oral antiplatelet agents (including aspirin and thienopyridines) has been shown to be an independent predictor of an increase in mortality after acute coronary syndromes [10], and multivariate analysis has shown an increased risk of transient ischaemic attack in the four weeks after discontinuation of ASA [11]. A systematic review of actual literature to date showed that withdrawal of low dose ASA is associated with a threefold increase in the risk of adverse cardiovascular events [12].

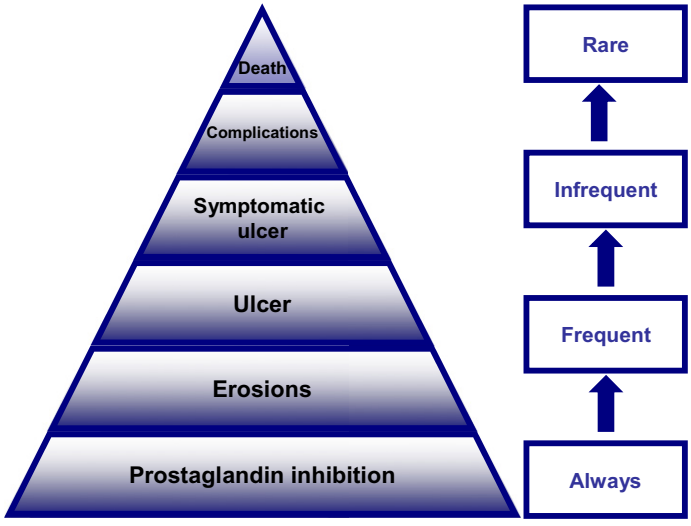

Fig. 1. Biologic progression of gastrointestinal damage associated with low dose aspirin [7].

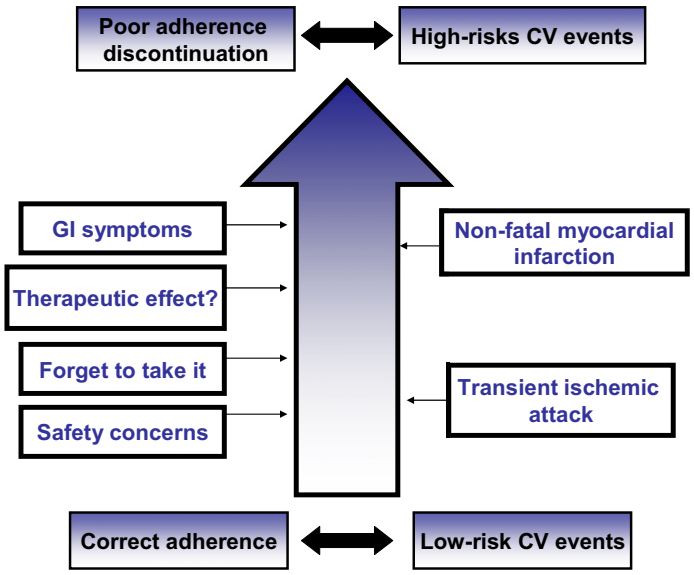

Fig. 2. Main causes and effects of low-dose aspirin poor adherence or discontinuation [13].

Patients might not adhere to treatment because they forget to take it, because they do not perceive that it has therapeutic benefit, or because of adverse events not well discussed with their physician [13].

On the other hand, and unfortunately, symptoms are not clearly predictive of the presence of mucosal injury. Holtmann et al have shown in their study that asymptomatic patients taking low dose ASA elevate their gastric sensory and they do not experience dyspepsia although acute mucosal injury was present [14].

Reducing the number of low dose ASA users who discontinue treatment could therefore have a major impact on the benefit obtained with low dose ASA in the general population. New studies with this objective are now needed to evaluate whether efforts to encourage patients to continue prophylactic treatment with low dose ASA will result in a decrease in non-fatal myocardial infarction.

Low dose aspirin related upper gastrointestinal injury

Patients who take ASA could develop acute mucosal injury, and even at very low dose (10 mg daily). The whole gut tract can be damaged, but low dose ASA related mucosal lesions developed especially in upper GI tract. Antrum and particularly the pre-pyloric area are the most frequent locations. This harm includes petechiaes, ecchymosis, erosions and ulcers [15]. Damage may be different according to dose, concomitant medication use and patient risk profiles. Geall et al demonstrated for years that every dose of ASA causes some superficial loss of cells from the gastric mucosa in most people [16]. Much of this superficial damage is not visible macroscopically but, in areas where the repair process fails, luminal acid and pepsin aggravate and deep the damage. Thus, deeper lesions still confined to the mucosa develop focally and are visible endoscopically as acute erosions.

Mechanisms of low dose ASA gastrointestinal damage

Injury to the GI tract attributable to NSAIDs occurs on a nearly daily basis in patients who are taking these drugs [18]. The mechanisms responsible for ASA-induced ulcerative lesions of the GI tract are not yet completely understood, particularly with respect to lesions in the small and large intestine [17,18]. However, it is known that aspirin damages the gut by causing topical injury to the mucosa and by the systemic effect associated with mucosal prostaglandin depletion as a result of (cyclooxygenase) COX inhibition. Whether a low dose ASA also has a systemic damaging effect in the GI tract that is

based on inhibition of COX1 is uncertain, as most of the antiplatelet effects seen with low dose ASA occur in the portal system, and the amount of drug and the time available in the systemic circulation is rather limited [19].

NSAIDs can be grouped on the basis of their pharmacodynamic features, for example COX1 or COX2 selectivity [20]. ASA has >10 times greater selectivity for COX1 than COX2 [21]. By inhibiting both COX isoforms, ASA, as with other NSAIDs, is an effective pain reliever at doses >325 mg. At low doses (75–325 mg daily), ASA predominantly inhibits the COX1 isoform, thereby inhibiting the synthesis of platelet thromboxane A2.

Topical injury: Direct contact of ASA with the gastroduodenal mucosa can induce damage by disrupting the gastric epithelial cell barrier [22]. However, clinical experience, including meta-analysis, with enteric-coated versus 'uncoated' ASA formulations, does not support the notion that ASA has predominantly local effects in causing gastroduodenal injury [23–27]. ASA is weakly acidic (pKa 3.5) and, therefore, is retained in its nonionized form in the aqueous, low-pH environment of the gastric lumen [23]. The pKa of ASA is among the lowest of the NSAIDs and, therefore, it confers a high propensity for gastroduodenal injury. ASA is able to penetrate the phospholipid membrane of gastric epithelial cells because of its lipophilicity ($\log P = 1.15$) [28]. The ability of ASA to decrease epithelial surface hydrophobicity [29] probably increases the susceptibility of the gastric mucus–bicarbonate barrier to injury [30].

Systemic effects: Indirect toxicity via systemic inhibition of cyclooxygenase (COX)-1-mediated prostaglandin synthesis may be the main mechanism by which ASA causes damage to the upper GI mucosa [29,31,32]. However, the inhibition of COX-1 is not the only cause of gastric injury, since ASA induces gastric damage both in COX-1-deficient and COX-2-deficient mice [29]. COX-1 is expressed in many cells throughout the body and the activity of ASA at cells in the gastric mucosa, where prostaglandins play an important role in maintenance of the gastric mucus–bicarbonate barrier, can result in gastroduodenal toxicity [33,34].

The main difference between ASA and other NSAIDs in terms of systemic activity lies in the irreversible nature of ASA–COX-1 binding in platelets [31], the effects of which are maintained for the duration of the platelet life-span (i.e. eight to ten days). It is important because the prevalence of gastroduodenal erosions with long-term ASA therapy is relatively high [5,35,36], and therefore bleeding may develop even when the dose of ASA is low or when the lesion is small or superficial. The differential effects of ASA versus other NSAIDs might have relevant implications in clinical practice, because in concomitant administration of non-ASA NSAIDs can interfere with the cardioprotection conferred by low dose ASA [37]. The platelet COX-1 binding site is temporarily occupied by the non-ASA NSAID [38,39] thereby preventing ASA binding. For example, ibuprofen administered before low dose ASA may block its antiplatelet effect [40].

Endoscopically-controlled studies have shown that the prevalence of erosions in gastroduodenal mucosa in low dose ASA users is about 60% [41,42]. Hart et al in their study examined the potential risk factors for development of these lesions in patients taking low dose ASA [43]. They concluded that *Helicobacter pylori* infection may be a protector factor for gastric erosions and age is not an important risk factor, in contrast to the known increased risk for NSAID induced gastric ulcer with advancing age. Presumably, the aged mucosa is not more susceptible to ASA injury, but is less capable of healing the erosions that result from initial damage. Some erosions might progress into ulcers and/or associated complications.

The most important lesion, of course, is a frank ulcer by definition, a lesion that extends through the whole thickness of the mucosa into the submucosa or deeper layers. One recent study of 187 patients taking low dose ASA without gastroprotective drugs showed that ulcer prevalence was 11% (95% confidence interval 6.3–15.1%) and ulcer incidence in patients followed for 3 months was 7% (95% CI 2.4–11.8%) [5], that is identical to ulcer incidence found by Laine et al in patients who were taking enteric-coated low dose ASA [44]. If we assumed a linear rate of ulcer development, this translates to an annual ulcer incidence of 28%. In this study only 20% of patients with endoscopic evidence of an ulcer had epigastric symptoms [5], that is similar to the incidence of dyspeptic symptoms reported by patients without ulcer.

There is some controversy about if ulcers develop in low dose ASA users who do not have other risk factor (such a *H. pylori* infection or concomitant use with NSAIDS). It seems that *H. pylori* infection

increases the risk of duodenal ulcer in ASA users, but the relationship with gastric ulcer has been highly controversial [5,45].

The clinical significance of these endoscopic findings is unclear, as the incidence of detected ulcers is higher that actual incidence of upper GI complications in clinical practice and the correlation between symptoms and mucosal damage is scarce. A recent review of available literature suggested, however, that endoscopic ulcers could be a possibly surrogate endpoint for upper GI harm [46].

Low dose aspirin related lower gastrointestinal injury

It was generally believed that low dose ASA did not cause any small bowel damage since the drug is largely absorbed before reaching the intestine, and this would limit the topical action on the intestinal mucosa. Growing evidence indicates that ASA can damage the GI tract below the angle of Treitz. Long-term ASA users can suffer small bowel bleeding and protein loss that might contribute to iron deficiency anaemia and hypoalbuminemia [47]. The mechanisms of damage and the real clinical impact of most observations are, however, far from being completely understood. GI injury by ASA therapy is the result of both topical and systemic effects produced by a decrease in mucosal COX-1 derived prostaglandins. Prostaglandin inhibition attributable to inhibition of COX by ASA use is present in all segments of the digestive tract. Very little evidence on this issue it is available so far.

A systematic review found a small increase of fecal blood loss (0.5–1.5 ml per day) in low dose ASA users (<325 mg) [48]. This amount increased up to 10 ml per day in some individuals, especially in those taking 1800 mg daily. A recent study by Smecuol et al has evaluated the effect of low-dose enteric-coated ASA on the small bowel. Twenty healthy volunteers underwent videocapsule endoscopy (VCE), fecal calprotectin and permeability tests before and after ingestion of 100 mg of enteric-coated ASA daily for 14 days. Half of the healthy volunteers showed some degree of mucosal damage in the VCE studies, including erosions and two ulcers in one patient [49]. The median baseline of permeability test increased after ASA use and the post-ASA ratio was above the upper end of normal in 10 out of 20 volunteers. The median baseline fecal calprotectin concentration also increased significantly after ASA use, although only three patients had values above the cutoff (>50 μg/g). These data should be taken with care since the clinical significance of this is uncertain. It must be remembered that low dose ASA is associated with acute gastric damage, but very few patients develop serious adverse events. However, the data show that low dose enteric-coated ASA may induce damage to the small bowel and could well be the responsible agent in some patients with anaemia or GI obscure bleeding. Further studies should validate these data and determine the clinic relevance of them.

Gastrointestinal complications (GI bleeding, ulcer perforation and obstruction)

Upper GI tract complications

Most of ulcers are asymptomatic and reasonably small, and probably heal over a period of weeks to a few months. The real clinical problem occurs when an ulcer erodes a vessel or, less commonly, perforates.

American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents state that low dose ASA is associated with a 2–4 fold increase in symptomatic or complicated ulcer, increasing with concomitant medication use [4–6]. The estimated average excess risk of symptomatic or complicated ulcer related to low dose ASA is five cases per 1000 ASA users per year [50].

There are some factors that put patients on low dose ASA treatment at increased risk of upper GI complications. These risk factors that are thought to be important include a history of an ulcer, a history of a bleeding ulcer, age >70 years, *H. pylori* infection and concomitant drug therapy with NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, other antiplatelet agents (clopidogrel) or anticoagulants [51,52]. Multiple risk factors have a cumulative effect on complications; not all patients who take ASA are at the same risk of upper GI bleeding [Table 1].

A recent meta-analysis of 61controlled-randomized trial [53] estimated that the risk of major GI bleeding increases in patients treated with low dose ASA alone (OR, 1.55; 95% CI, 1.27–1.90), compared with inert control reagents. The risk increased further when ASA was combined with clopidogrel or anticoagulants, compared with ASA alone (OR, 1.86; 95% CI, 1.49–2.31 and OR, 1.93; 95% CI, 1.42–2.61,

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