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NSAIDs and Peptic Ulcer Disease

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1. Introduction

In 1897 Felix Hoffman, a 29-year-old scientist working for the Bayer Company patented a chemical procedure that enabled the acetylation of salicylic acid with the enough purity to be used commercially (Wallace, 1997). The new product was evaluated by Dreser Heinrich, head of marketing at Bayer, who - despite some initial misgivings - gave his approval for marketing acetylsalicylic acid under the name "Aspirin" in 1899. The new compound was commercialized by Bayer as an effective therapy for fever and aches, one that, unlike its source molecule (salicylic acid), had no gastric side effects. For over six decades aspirin remained the mainstay of non-narcotic analgesic treatment and nonsteroidal anti-inflammatory drug (*NSAIDs*) therapy. Beginning with the sale of indomethacin in 1963, used for the treatment of rheumatoid arthritis, at least twenty other *NSAIDs* with aspirin-like actions have been developed over the past half-century. Although aspirin's preeminence as an over-the-counter analgesic has been progressively displaced by new *NSAIDs*, new studies exploring its antiplatelet effect led to aspirin's development as a major antithrombotic agent (Patrono et al., 2005). Today, *NSAIDs* are popular because of their versatile effectiveness as analgesics, antipyretics, and as anti-inflammatory agents, and they remain among the most frequently prescribed medications worldwide.

The long-standing confidence in the gastric safety of aspirin went unchallenged for 40 years until 1938 when two researchers at Guy's Hospital in London, Douthwaite and Lintott, showed unquestionably that it had a major gastro-erosive activity (Douthwaite & Lintott 1938). Unfortunately, most of the *NSAIDs* currently available on the market can injure the gastric and duodenal mucosa (Cryer & Feldman, 1992; Soll et al., 1991), much like aspirin, with considerable rates of morbidity and mortality. The standard evolution of peptic ulcers resulting from *NSAIDs* ranges from resolution without intervention to the development of complications, such as bleeding and perforation. To variable degrees aspirin and *NSAIDs* inhibit the cyclooxygenase (COX) enzymes COX-1 and COX-2, which synthesize the inflammatory mediators known as prostaglandins and thromboxane. Prostaglandin inhibition plays a critical role in the pathogenesis of *NSAIDs*-induced gastric injury. Beginning ten years ago new specific inhibitors of COX-2 became available, compounds that have significantly reduced gastrointestinal (GI) side effects compared with COX-1 inhibitors (Bombardier et al., 2000; Laine et al., 2007; Silverstein et al., 2000).

Peptic ulcers are defects in the GI mucosa that extend throughout the muscularis mucosae, and which are often associated with *Helicobacter pylori* (*H. pylori*) infection or with

consumption of *NSAIDs*. As the prevalence of *H. pylori* infection has declined in Western countries, gastric ulcers have increasingly been linked to *NSAID* use, with acetylsalicylic acid (Yuan et al., 2006) being an important cause of morbidity and rising health care costs related to work loss, hospitalization, and outpatient care (Ramakrishnan & Salinas, 2007). Management of peptic ulcer disease has improved radically during the past few decades, culminating in the widespread use of proton pump inhibitor (PPI)-based triple therapy for *H. pylori* eradication. However, prescriptions for drugs such as aspirin and *NSAIDs* have also increased over this same time period and adherence to gastroprotection protocols to prevent *NSAID*-induced peptic ulcer disease still seem to be far from optimal (Jones, 2001).

2. Epidemiology

2.1 Ulcers and NSAIDs. Incidence and prevalence

In the United States alone sales of over-the-counter analgesics approach 3 billion dollars annually, with *NSAIDs* accounting for about 60% of sales (the other 40% is attributed to acetaminophen) (Laine, 2001). An estimated 14 million patients use *NSAIDs* for the relief of symptoms associated with arthritis alone (Wolfe, 1996), and among patients older that 65, as many as 70% take NSAIDs at least once a week, with at least 34% of this population taking a *NSAID* tablet daily (Talley et al., 1995).

A systematic review of the worldwide literature estimated that the annual incidence of peptic ulcer disease ranged from 0.1 to 0.19 percent for physician-diagnosed and 0.01 to 0.17 percent when based upon hospitalized patients (Sung et al., 2009). Upper GI symptoms, such as dyspepsia, occur in 15% to 60% of NSAID users, twice as often as in individuals not taking NSAIDs. The prevalence of gastric or duodenal ulcers in patients taking NSAIDs regularly is approximately 15% to 30%. The annual incidence of NSAID-related clinical upper GI events (complicated and symptomatic ulcers) is approximately 2.5% to 4.5%, with the annual incidence of serious complications (severe bleeding, perforation, and obstruction) running about 1% to 1.5% (Laine, 2002).

2.2 Trends

The epidemiology of peptic ulcer disease largely reflects environmental factors, primarily *H. pylori* infection, but also *NSAID* use and smoking. The incidence of *H. pylori* below age 50 is falling dramatically in developed countries due, in part, to improved hygiene and socioeconomic conditions; however, the prevalence of *H. pylori* infection remains high for older individuals and in certain predisposed subpopulations. The epidemiology of peptic ulcer disease has changed in the past decade due to the enormous efforts made to eradicate *H. pylori* infection, which is the single largest cause of peptic ulcers. As the prevalence of *H. pylori* infection has declined, the proportion (and actual numbers) of patients with *H. pylori*-negative idiopathic ulcers, and with ulcers attributed to the use of NSAIDs, has risen (Chow & Sung, 2007). A prospective cohort study in Hong Kong (Chan et al., 2001; Hung et al., 2005) demonstrated that the number and proportion of *H. pylori*-associated ulcers decreased from 50.3% in 1997–1998 and to 33.4% in 2000–2001. This study also showed that there was a 4.5-fold increase in the absolute number of idiopathic ulcers, from 4.1% to 18.8% during that same time period. By contrast, the relative proportion of *NSAID*-associated ulcers remained constant (45.5% in 1997–1998 versus 47.8% in 2000–2001). On the basis of these data, the incidence of non-*H. pylori*, non-*NSAID* peptic ulcer bleeding is thought to be on the rise in Asia. Similar prospective studies are awaited in the West; however, it is clear that the global

prevalence of idiopathic ulcers is on increasing. Although *H. pylori* is the predominant cause of peptic ulcer disease worldwide, it appears that there are regional differences in prevalence that cannot be explained by this infection per se. Patterns of *NSAID* use and smoking are likely to be important, too.

At a minimum, smoking clearly exacerbates *H. pylori*-associated ulcer disease. The decline in smoking in younger individuals, particularly in males, and the concomitant increase in women, may be a factor in the declining male/female ratio of ulcer disease. Smoking does not appear to be a factor in the ulcerative complications found in older women or in *NSAID*-related ulcers. It should also be borne in mind that *NSAID* use increases as a function of age and is an independent risk factor for ulcers. In addition, older subjects are more likely not only to develop complications from *NSAID*-related ulcers, but also to suffer increased morbidity and mortality from these complications because of co-morbidities.

3. Mechanisms of therapeutic action of NSAIDs

Based on their chemical structure, there are now at least 20 different *NSAIDs* from six major groups available for use in humans (Table 1). All of them are absorbed completely, have negligible first-pass hepatic metabolism, are tightly bound to albumin, and have small volumes of distribution. The half-lives of *NSAIDs* vary, though in general can be divided into "short" (less than six hours) and "long" (more than six hours) lasting drugs. These compounds differ in their doses, interaction with other drugs, and some specific side effects. The inhibition of prostaglandin synthesis via the blockade of cyclooxygenase (COX) has been widely accepted as the main mechanism of action and toxicity utilized by these compounds (Moncada et al., 1973). However, during the last decade, many groups have described a number of non-prostaglandin-mediated anti-inflammatory effects from NSAIDs, suggesting that COX inhibition is not the only explanation for either the anti-inflammatory action or the gastric toxicity observed with this group of therapeutic agents (Abramson & Weissmann, 1989; Amin et al., 1995; Kopp & Ghosh, 1994; Mahmud et al., 1996).

Non-selective nonsteroidal anti-inflammatory (NSAID) agents
  Salicylate (acetylated): Aspirin
  Salicylates (non-acetylated): Diflunisal, Choline magnesium trisalicylate, Salsalate
  Propionic acids: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen, Oxaprozin
  Acetic acids: Diclofenac, Etodolac, Tolmetin, Sulindac, Ketorolac, Indomethacin
  Oxicams (enolic acids): Meloxicam, Piroxicam
  Fenamates (anthranilic acids): Meclofenamic acid, Mefenamic acid
  Non-acidic (naphthylalkanone): Nabumetone

Selective COX-2 inhibitors:
  Celecoxib, Eterocoxib, Parecoxib

Table 1. NSAID families

3.1 COX inhibition
As stated above, NSAIDs target COX, and hence the synthesis of prostaglandins, particularly prostaglandin E2 (PGE2). This inflammatory molecule lowers pain thresholds,

and the primary goal of NSAIDs is to reduce pain. Tissue prostaglandins are produced from membrane arachidonic acid via two pathways: cyclooxygenase-1 (COX-1) and COX-2. The COX-1 pathway is the predominant constitutive pathway; prostaglandins derived from this enzyme mediate many effects, most notably they facilitate gastroduodenal cytoprotection, renal perfusion, and platelet activity. In contrast, the COX-2 pathway is inducible by inflammatory stimuli and mediates effects through prostaglandins, which results in inflammation, pain, and fever. COX-2 induces at least two orders of magnitude more PGE2 than COX-1. Specific inhibitors of COX-2 represent a major advance in the treatment of pain, particularly in patients with osteoarthritis or rheumatoid arthritis. For the most part, COX-2 inhibitors have significantly reduced gastrointestinal side effects compared with COX-1 inhibitors (Rostom et al., 2007).

All of the non-salicylate, non-COX-2 selective *NSAIDs* including aspirin can interfere with platelet aggregation and secretion (McQueen et al., 1986; O'Brien, 1968) through the inactivation of platelet COX-1. In platelets, this enzyme is a rate-limiting step in the transformation of arachidonic acid into thromboxane A2, a potent platelet-aggregating agent. However, aspirin inhibits platelet COX-1 in an irreversible manner and thus has proven beneficial in reducing the risk of secondary thrombotic cardiovascular events (Berger et al., 2008). These properties may be important enough to warrant its continued use in those patients also needing common *NSAIDs*. Thus, if needed, such patients can be continued on low dose aspirin. Administration of some *NSAIDs* may interfere with the desirable antiplatelet effects of aspirin (Catella-Lawson et al., 2001).

3.2 Nonprostaglandin-mediated effects

Although *NSAIDs'* degree of potency as inhibitors of prostaglandin synthesis *in vitro* tends to reflect their anti-inflammatory potency *in vivo*, several experimental and clinical studies suggest that prostaglandin inhibition is only part of the story. The necessary dose of any given *NSAID*, notably aspirin, which is essential for suppressing inflammation, may well exceed that required to substantially inhibit prostaglandin synthesis, at least in plasma. In this regard, salicylate, which is a weak inhibitor of COX activity, appears to be as effective as aspirin, a potent inhibitor of COX activity, in controlling inflammation in patients with rheumatoid arthritis (Brooks & Day, 1991). These and other data have led to the suggestion that these drugs are driven by prostaglandin-independent mechanistic actions, particularly in terms of their anti-inflammatory properties.

Therefore, several non-prostaglandin-mediated *NSAID*-induced mechanisms of action may also be important. These mechanisms are generally related to the ability of *NSAIDs* to insert themselves into biological membranes and disrupt a wide range of cell functions and cell-cell interactions. For example, *NSAIDs* might interfere with neutrophil-endothelial cell adherence by decreasing the availability of L-selectins in the membranes of neutrophils, thereby removing a critical step in the migration of granulocytes to sites of inflammation (Diaz-Gonzalez et al., 1995). *NSAIDs* also inhibit nuclear factor *kappa B (NF-kB)*-dependent transcription *in vitro*, resulting in a decrease in available nitric oxide synthetase (Amin et al., 1995). This enzyme produces nitric oxide in large amounts, thereby causing vasodilation, cytotoxicity, and increased vascular permeability (Hawkey, 1995). The anti-nociceptive actions of some *NSAIDs*, though not all, appear to involve L-arginine-NO-cyclic GMP-potassium channel pathways (Ortiz et al., 2003).

The role and importance of these non-prostaglandin-mediated processes in clinical inflammation remains unclear. Also unknown is whether any of these potential

mechanisms of action might explain the great variability in individual patient response to *NSAIDs*.

4. Mechanisms underlying NSAID-induced gastrointestinal toxicity

NSAIDs damage gastrointestinal mucosa by causing both local injuries and by systemically inhibiting prostaglandin production. However, current consensus on the pathogenesis of symptomatic peptic ulcer disease resulting from exposure to *NSAIDs* holds that it is mainly a consequence of systemic (post-absorptive) inhibition of GI mucosal COX activity rather than a local effect (van Oijen et al., 2008).

4.1 COX inhibition

NSAIDs induce gastrointestinal cytotoxicity through the inhibition of COX enzyme activity, a correlation which has been well established (Warner et al., 1999). In addition, while it is now known that certain prostaglandins such as *PGE2* reduce gastric acid secretion, the onset of hypochlorhydria does not entirely explain the mucosal protection observed with PGE2. This has led to the notion that prostaglandins have antisecretory-independent effects that have been collectively referred to as "cytoprotection". Some of the cytoprotective mechanisms employed by prostaglandins include stimulation of glycoprotein (mucin), bicarbonate and phospholipid production by epithelial cells, enhancement of mucosal blood flow and oxygen delivery to epithelial cells via local vasodilation, increased epithelial cell migration towards the luminal surface (restitution), and enhanced epithelial cell proliferation (Robert et al., 1979). Inhibition of the COX-1 pathway blocks production of prostaglandins in epithelial cells and, consequently, these compounds impair any protective capabilities, resulting in a gastric environment that is more susceptible to topical attack by endogenous factors, such as acid, pepsin, and bile salts. Many *NSAIDs* block COX-1 and COX-2 more or less equally (i.e., are non-selective) and thus they may impair gastric prostaglandin production even at low concentrations. Since prostaglandins are essential to both the maintenance of intact GI defenses and normal platelet function, *NSAIDs* promote ulcer formation as well as bleeding. Drugs that more selectively inhibit COX-2 than COX-1 have less suppressive effects on gastric prostaglandin synthesis. As a result, selective inhibitors of COX-2 preserve prostaglandin-mediated GI mucosal protection. However, COX-2 selective inhibitors may still block COX-1 at clinically recommended doses, and thus have the potential to also block COX-1 in the stomach and duodenum and thereby cause damage.

4.2 Nonprostaglandin-mediated effects

Most *NSAIDs* are carboxylic acid derivatives. As a result, they are not ionized at the acidic pH levels found in the gastric lumen and can thus be absorbed across the gastric mucosa. Once the drug moves from the acidic environment of the gastric lumen into the pH–neutral mucosa, the drug ionizes and is trapped temporarily in epithelial cells where it may inflict damage.

The ability to uncouple mitochondrial oxidative phosphorylation is a common characteristic of NSAIDs containing an ionizable group. NSAIDs are able to interfere with mitochondrial oxidative phosphorylation (Krause et al., 2003), reducing intracellular ATP synthesis *in vivo* (Mingatto et al., 1996), an effect that has been postulated as representing an early pathogenic event in NSAID-mediated enteropathy (Mahmud et al., 1996; Rainsford, 1980). Recently,

novel pathways, independent of COX inhibition, have been identified for some NSAIDs, as has their ability to bind and disrupt cell membranes. *In vitro* exposure of gastric epithelial cells to different concentrations of NSAIDs can result in altered cell-membrane permeability. This can lead to profound and rapid changes in cell morphology, suggesting that the cytotoxicity and biological actions of NSAIDs are mediated by the cell membrane and are not dependent upon COX (Zhou et al.).

4.3 Role of Helicobacter pylori infection

Until recently, data analysis on the role of *H. pylori* infection as a risk factor for GI bleeding in *NSAID* users was complicated by a failure, in many studies, to account for the variable influence of multiple, co-existing risk factors. Not surprisingly, therefore, these studies have yielded conflicting results (Graham et al., 1992).

A comprehensive meta-analysis of 16 case–controlled studies demonstrated that the risk of peptic ulcer bleeding was increased by a factor of 1.79 with *H. pylori* infection, by 4.85 with *NSAID* usage, and by 6.13 in the presence of both *NSAID* use and *H. pylori* infection, strongly suggesting the possibility of an additive effect (Huang et al., 2002). Further evidence of *H. pylori* infection's additive role in the context of *NSAID* use comes from trials measuring the impact of *H. pylori* eradication. Indeed, the eradication of *H. pylori* in high-risk patients prior to the initiation of *NSAID* therapy has been shown to significantly reduce the risk of subsequent ulceration (Bazzoli et al., 2001; Malfertheiner et al., 2002). Two systematic reviews have clearly shown that eradication of *H. pylori* is superior to placebo therapy in the primary prevention of peptic ulcers among *NSAID* users (risk ratio (95 % CI) 0.35 (0.20 – 0.61)) (Leontiadis et al., 2007). Using a Markov model, Leontiadis *et al*. (Leontiadis et al., 2007) showed that the most cost-effective strategy for primary prevention of *NSAID*-associated ulcers was *H. pylori* eradication in patients over age 50. Interestingly, sensitivity analysis showed that eradication therapy remained cost-effective even when the *H. pylori* prevalence was as low as 5%. However, eradication seems less effective than treatment with a maintenance PPI for preventing non-steroidal anti-inflammatory drug-associated ulcers (Vergara et al., 2005).

It must be added that many patients take *NSAIDs* intermittently and often for only short periods at a time. Whether a "test-and-treat" strategy would be cost effective for such a large population group is unknown. Furthermore, it has also been noted that eradication of *H. pylori* infection alone is not sufficient for the secondary prevention of peptic ulcer bleeding in chronic *NSAID* users (Vergara et al., 2005).

5. Risk of GI complications in patients taking different NSAIDs

Recent studies suggest that the risk of GI complications may be lower with the use of some *NSAIDs*, including ibuprofen, nabumetone, meloxicam, and etodolac, but higher with others such as sulindac, piroxicam, and ketorolac (de Abajo & Garcia Rodriguez, 2001; Garcia Rodriguez & Hernandez-Diaz, 2001; Hernandez-Diaz & Rodriguez, 2000). In the case of ibuprofen, this may be due to the use, in general, of lower analgesic doses, especially in relation to ibuprofen preparations that are available over-the-counter. Nabumetone, meloxicam, and etodolac may possess some degree of COX-2 selectivity, whereas sulindac, piroxicam, and ketorolac may owe their increased toxicity to the presence of relatively long plasma half-lives, which would thereby result in more prolonged mucosal exposure (Simon & Mills, 1980). With respect to aspirin, its use at low doses alone, in the absence of other risk

factors, is also associated with an increased risk for both GI bleeding and death from GI complications. Numerous studies in patients taking low-dose aspirin alone have shown a relative risk of 2–4 for GI bleeding (Lanas et al., 2005). Furthermore, a large percentage of patients on low-dose aspirin are elderly, have multiple co-morbidities, and cardiovascular disease, in particular, and are likely to be concurrently taking anticoagulants, *NSAIDs* and corticosteroids, any one of which will elevate their relative risk for GI events to several times that of low-dose aspirin alone. It is important to emphasize that physicians are often unaware that patients are self-medicating with low-dose aspirin when they prescribe *NSAIDs* for pain relief or anti-inflammatory effects.

In regards to COX-2 inhibitors, there have been several large randomized, controlled, outcome trials comparing COX-2 inhibitors to traditional NSAIDs. The CLASS study (Silverstein et al., 2000) compared celecoxib 400 mg b.i.d. with ibuprofen 800 mg t.i.d., or diclofenac 75 mg b.i.d., in osteoarthritis or rheumatoid arthritis patients. A non-significant 50% reduction in ulcer complications was observed in the celecoxib group compared with those who received the conventional *NSAID* after 6 months of therapy. After 1 year, however, there was little or no difference between the three groups. Another large trial, the VIGOR study (Bombardier et al., 2000), compared outcomes in rheumatoid arthritis patients taking either 500 mg of naproxen b.i.d. or 50 mg of rofecoxib daily. At 6 months, rofecoxib was associated with a significantly lower incidence of GI events (2.1 *vs.* 4.5%, $P < 0.001$), and GI complications (0.6 *vs.* 1.42 %, $P = 0.005$). The TARGET study (Schnitzer et al., 2004) compared lumiracoxib with traditional *NSAIDs* in patients with osteoarthritis. After 1 year, a significant reduction in ulcer complication rates was noted for lumiracoxib among the entire study population (0.3 *vs.* 0.9%), as well as among those who were not taking aspirin (0.2 *vs.* 0.9%), but not in those taking aspirin. In a report summarizing the results of eterocoxib, based on three prospective randomized, double-blind trials (Laine et al., 2007), 34,701 arthritic patients were treated with 60 or 90 mg of etoricoxib or 150 mg of diclofenac daily. This study included patients on low-dose aspirin and/or PPI therapy. It was found that the overall incidence of uncomplicated GI events was significantly less with etoricoxib than with diclofenac (Hazard ratio 0.69, 95 % CI; 0.57 – 0.83) ($P < 0.001$). There were no differences between the groups for complicated events (bleeding, perforation, and/or obstruction).

A Cochrane systematic review of GI safety revealed that COX-2 inhibitors produced significantly fewer gastroduodenal ulcers (relative risk, 0.26; 95 % confidence interval, 0.23 – 0.30) and ulcer complications (relative risk, 0.39; 95 % confidence interval, 0.31–0.50), as well as fewer withdrawals caused by GI symptoms when compared with nonselective *NSAIDs* (Rostom et al., 2007).

6. Clinical spectrum of gastroduodenal mucosal injury by NSAIDs

NSAIDs are valuable agents in the treatment of arthritis and many other musculoskeletal disorders, and as analgesics in a wide variety of clinical scenarios. However, as stated above, their use has been limited mainly by their association with mucosal injury to the upper gastrointestinal tract, including the development of peptic ulcer disease and its complications, most notably upper gastrointestinal hemorrhage and perforation (Cryer & Feldman, 1992; Soll et al., 1991).

6.1 Gastric damage

Upper GI symptoms, such as dyspepsia, occur in 15% to 60% of *NSAID* users, twice as often as in individuals not taking *NSAIDs*. Dyspepsia occurs in three common patterns: ulcer-like

or acid dyspepsia (e.g., burning, epigastric hunger pain with food, antacid, and antisecretory agent relief); indigestion (also called functional dyspepsia or dysmotility-like dyspepsia, with postprandial belching, bloating, epigastric fullness, anorexia, early satiety, nausea, and occasional vomiting); and reflux-like dyspepsia. These patterns overlap considerably. Although poorly correlated with endoscopic lesions and clinical events, dyspepsia and other GI symptoms limit the use of *NSAIDs*, affect quality of life, and frequently require medical co-therapy with H2-receptor antagonists or PPIs. For example, it has been estimated that 5% to 15% of patients with rheumatoid arthritis can expect to discontinue *NSAID* therapy because of dyspepsia (Singh & Triadafilopoulos, 1999).

Endoscopically visible lesions associated with *NSAID* use include subepithelial hemorrhages, erosions, and ulcers. Subepithelial hemorrhages appear as bright red areas without any clear break in the mucosa. Microscopically, they appear as large numbers of red blood cells in the superficial portion of the mucosa, beneath the epithelium. Erosions are breaks in the mucosa that remain confined therein. Subepithelial hemorrhages occur in virtually 100% of people within 15 to 30 minutes after ingestion of a single 650-mg dose of aspirin. Repeated dosing of aspirin (650 mg 4 times daily) leads to development of gastric erosions within 24 hours in virtually all patients (Laine, 1996). With longer-term therapy, adaptation may occur, although gastric erosions are still found in approximately 40% to 60% of patients taking regular doses of *NSAIDs*.

An ulcer is defined histologically as a break that extends into the submucosa or deeper, and endoscopically as a break in the mucosa of >3 mm in diameter with unequivocal depth. For this reason, only ulcers can cause serious GI complications, such as bleeding, perforation, and obstruction. Subepithelial hemorrhages and erosions do not cause major GI bleeding because they are confined to the mucosal layer, where there are no blood vessels of significant size. Furthermore, they cannot cause the most dreaded of GI complications, perforation, since perforation requires an extension of the break in the mucosa through all 4 layers of the GI tract (mucosa, submucosa, musclaris propria, and serosa) (Laine, 2002). Ulcers may be formed in healthy subjects within 1 week of regular *NSAID* use. The prevalence of ulcers in patients taking *NSAIDs* regularly is approximately 15% to 30% (Laine, 1996; Larkai et al., 1987). The cumulative incidence of *NSAID*-associated ulcers in recent double-blind trials has been as high as 45% after 6 months. Most ulcers do not cause clinically important GI events. In fact, large outcome studies of arthritis patients indicate that the annual incidence of *NSAID*-related clinical upper GI events (complicated and symptomatic ulcers) is approximately 2.5% to 4.5%, while the annual incidence of serious complications (severe bleeding, perforation, and obstruction) is about 1% to 1.5%(Bombardier et al., 2000; Silverstein et al., 2000). Although these percentages are relatively small, the consumption of *NSAIDs* is so extensive that a large number of GI events are caused by *NSAIDs*, making GI complications the most important concern limiting use of *NSAIDs*.

6.2 Duodenal damage

In contrast to the stomach, damage to the duodenal mucosa by aspirin and *NSAIDs* seems to largely depend upon gastric acid. The "classic" symptoms of a duodenal ulcer occur when acid is secreted in the absence of a food buffer. Food is usually well emptied by two to three hours after meals, although food-stimulated acid secretion can persist for three to five hours; thus, classic duodenal ulcer symptoms occur two to five hours after meals or on an empty stomach. Symptoms also occur at night when the circadian stimulation of acid secretion is maximal. The ability of alkali, food, and antisecretory agents to produce relief suggests that

acid plays a role in this process. Thus, "acid dyspepsia" is a fitting term. Symptomatic periods lasting a few weeks, followed by symptom-free periods of weeks or months, is a pattern characteristic of classic duodenal ulcers.

Numerous findings suggest that *NSAIDs* represent the most relevant factor in duodenal ulcers not associated with *H. pylori* infection. The history of *NSAID* use is more common in duodenal ulcer patients who have a normal, non-infected stomach than in those in whom the ulcer is associated with *H. pylori* gastritis. Several studies have found either that *NSAID* intake is present in 25–75% of the *H. pylori*-negative duodenal ulcer patients or that *NSAIDs* are the most frequently identifiable cause in non-infected duodenal ulcers (Gisbert & Calvet, 2009).

6.3 Death rates associated with NSAIDs

A very large study carried out by the Spanish National Health System reported a death rate of 15.3 persons per 100,000 *NSAID* users, including aspirin. Approximately 50% of the patients who died in the Spanish study had a prior history of one, or more, of the following risk factors: peptic ulceration, GI bleeding, dyspepsia, cardiac disease, or hypertension. The average age of patients dying from *NSAID* complications was 70±13.5 years and 89.7% of those who died were above age 60 (Lanas et al., 2005). In the United States the reported death rate associated with *NSAIDs* is three times higher than in Spain (Singh & Triadafilopoulos, 1999), probably because this figure was extrapolated from a small sample of rheumatoid arthritis patients and it is well-known that rheumatoid arthritis alone has been associated with increased mortality, independent of *NSAID* use.

7. Risk factors for NSAID-related GI complications

Risk factors for GI complications associated with *NSAIDs* have been identified through a series of case–control and cohort studies that compared outcomes for patients taking these agents with those of control groups. A series of nested case–control studies based on incidence rates for hospitalization for GI bleeding in patients above age 65 showed an increased risk not only for this population group (odds ratio 4.7), but also for those on higher doses of *NSAIDs* (odds ratio 8.0), those who had a relatively short-term history of *NSAID* use (less than 1 month; odds ratio 7.2), and those concurrently taking corticosteroids (odds ratio 4.4) or anticoagulants (odds ratio 12.7) (Griffin et al., 1991; Griffin et al., 1988; Piper et al., 1991; Shorr et al., 1993) . In a large study series based on autopsy findings on patients with a history of *NSAID* use, gastric and duodenal ulcers were found to be more common among those who had consumed *NSAIDs* for less than 3 months (Allison et al., 1992). Although the risk of ulcer complications decreases after the first few months of *NSAID* use, it does not disappear with long-term therapy. One approach to risk stratification has been proposed (Table 2) (Lanza et al., 2009). Gastrointestinal risk is arbitrarily stratified into low (i.e., no risk factors), moderate (presence of one or two risk factors), and high-risk groups (multiple risk factors, a history of ulcer complications, or concomitant use of corticosteroids or anticoagulants).

8. Treatment and prevention of NSAID-related GI complications

If a patient develops an ulcer while on *NSAIDs*, the relevant *NSAID(s)* should be stopped if at all possible and traditional ulcer therapy with a PPI or an H2 antagonist started. PPIs are

generally preferred as they are associated with more rapid healing. As in all patients with peptic ulcers, the individual's *H. pylori* status should also be assessed; if positive, appropriate therapy should be instituted. For patients who must remain on *NSAID* therapy or on low-dose aspirin, randomized trials have shown that ulcer healing occurs more rapidly with a PPI rather than with an H2 antagonist (Agrawal et al., 2000; Yeomans et al., 1998), misoprostol (Hawkey et al., 1998), or sucralfate (Bianchi Porro et al., 1998).

8.1 Prevention

Most experts in the field agree that patients with a recent complicated peptic ulcer are at very high risk and it is best in such cases to avoid *NSAID* treatment entirely; however, if anti-inflammatory treatment must be undertaken, a COX-2 inhibitor plus misoprostol or a PPI therapy should be employed. Patients with a history of peptic ulcer disease, with or without complications, at any time in the past, and concurrent use of aspirin (including low

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High risk

1. History of a previously complicated ulcer, especially if recent

2. Multiple (>2) risk factors

Moderate risk (1-2)

1. Age > 65

2. High-dose NSAID therapy

3. A previous history of an uncomplicated ulcer

4. Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants

Low risk

1. No risk factors

H. pylori is an independent and additive risk factor and needs to be addressed separately

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Table 2. Patients at increased risk for NSAID GI toxicity (Guidelines for the Prevention of NSAID-related Ulcer Complications) (Lanza et al., 2009)

dose), antiplatelet drugs (e.g., clopidrogel), anticoagulants (e.g., warfarin), or corticosteroids, or two or more risk factors also fall in the high-risk categories; here, treatment should consist of a COX-2 inhibitor and either misoprostol or PPI therapy (Lanza et al., 2009). As shown in Table 2, patients considered to be at moderate risk must be treated with a COX-2 inhibitor alone or with an *NSAID* plus misoprostol or a PPI. Patients without risk factors are at low risk for *NSAID*-related peptic ulcer complications and no protective measures are required (Lanza et al., 2009) (Table 3).

As mentioned above, multiple studies have evaluated the relationship between *H. pylori* and the risk of gastric ulcers in *NSAID* users. Based upon the available evidence, patients with a history of uncomplicated or complicated peptic ulcers (gastric, duodenal) should be tested for *H. pylori* prior to beginning a course of *NSAIDs* or low-dose aspirin therapy. If present,

Gastrointestinal risk level		
Low	Moderate	High
NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID + PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol

Table 3. Treatment recommendations (Guidelines for the Prevention of NSAID-related Ulcer Complications) (Lanza et al., 2009)

H. pylori should be treated with the appropriate therapy, even if it is believed that the prior ulcer was due to *NSAIDs*. In asymptomatic patients who have no history of ulcers and who are not currently taking a *NSAID*, physicians can consider *H. pylori* testing prior to beginning long-term therapy with a *NSAID*. One review of this topic found that eradication of *H. pylori* was beneficial in patients who were naïve to *NSAIDs*, while little benefit was observed in patients already taking and tolerating *NSAIDs* (Kiltz et al., 2008). This "test-and-treat" approach may be more useful in populations with a relatively high prevalence of *H. pylori* infection.

8.2 Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog that replaces the protective prostaglandins ingested during prostaglandin-inhibiting therapies. It was the first agent approved for the prevention of *NSAID*-related ulceration. Early studies in normal volunteers showed a marked reduction in the primary prevention of gastroduodenal lesion in patients receiving *NSAIDs* in combination with misoprostol, compared with those who received *NSAIDs* and a placebo (Lanza et al., 1989). A more recent meta-analysis revealed that co-therapy with misoprostol reduced the incidence of duodenal ulcers by 53% and gastric ulcers by 74%, when compared with placebo therapy (Rostom et al., 2002). Another study that compared a standard dose of misoprostol (200 mcg q.i.d.) with the PPI lansoprazole (in doses of 15 and 30 mg daily) in long-term *NSAID* users showed that 93% of patients taking misoprostol were protected from developing a gastric ulcer compared with 80% and 82% in the two lansoprazole groups, respectively, over 12 weeks, and without any statistical significance among treated groups. Patients who were ulcer free after 12 weeks of therapy were kept on the same regimen for another 12 weeks, and at the end of that time 43% of those on placebo, 83% on misoprostol, 83% on lansoprazole 30 mg, and 89% on lansoprazole 15 mg were still ulcer free (Graham et al., 2002) .
Although misoprostol has proven to be effective in the prevention of GI complications induced by *NSAIDs*, it should be noted that its usefulness is limited in clinical settings by the occurrence of GI side effects, primarily cramping and diarrhea, and by compliance problems related to multiple dosage.

8.3 Proton pump inhibitors (PPIs)

PPIs have been utilized extensively as a co-therapy for the prevention of *NSAID*-induced peptic ulcers. Two large randomized controlled trials (Hawkey et al., 1998; Yeomans et al., 1998) have been performed in osteoarthritis and rheumatoid arthritis patients comparing omeprazole with placebo therapy, misoprostol, and ranitidine in the secondary prevention

and healing of gastric and duodenal ulcers. In the first study, omeprazole (20 mg or 40 mg daily) co-therapy resulted in a significant reduction in the total number of *NSAID*-related ulcers when compared to ranitidine (150 mg orally twice a day). In the second study, omeprazol (20 mg daily) was more effective than misoprostol (800 mg daily) in preventing duodenal ulcers and in reducing gastric ulcers.

The results of two similar multicenter randomized controlled trials have recently been published jointly (Scheiman et al., 2006). They compared esomeprazole 20 or 40 mg/daily with placebo therapy in preventing ulcers in patients taking *NSAIDs* or COX-2 inhibitors over a 6-month period. In the first study, which involved 844 patients, ulcer rates were 20.4%, 5.3%, and 4.7% for placebo, esomeprazole 20 mg, and esomeprazole 40 mg, respectively. In the second study, which involved 585 patients, the respective ulcer rates were 12.3%, 5.2%, and 4.4 %. Patients in both studies were *H. pylori*-negative and were considered at-risk on the basis of age (above 60), or due to a history of documented gastric or duodenal ulcerations within 5 years of entry into the study. Both studies concluded that in at-risk patients, esomeprazole was effective at preventing ulcers in long-term users of *NSAIDs*, including COX-2 inhibitors.

Thus, although full-dose misoprostol (200 mcg q.i.d.) is very effective in preventing *NSAID*-related ulcers and their complications, as stated above, GI side effects limit its clinical use. Lower doses of misoprostol are not associated with cramps or diarrhea, but appear to be no more effective than standard PPI therapy. For all of these reasons, PPIs have assumed a dominant role in *NSAID*-related upper GI injury prophylaxis and therapy. A randomized trial of *NSAID* users who had *H. pylori* infection and prior ulcer bleeding (Chan et al., 2001) demonstrated that co-therapy with omeprazole was effective at preventing recurrent ulcer bleeding. Data from observational studies and secondary analyses of a large-scale randomized trial also indicate that PPIs reduce the risk of *NSAID*-associated ulcer bleeding. Maintenance therapy is indicated in patients who remain on or who resume *NSAID* treatment.

There is no data suggesting that any of the available PPIs is more effective than another in treating NSAID-related GI damage.

8.4 H2 receptor antagonists

In most reports, standard doses of H2 receptor antagonists have shown no effectiveness in preventing NSAID-induced gastric ulcers. Systematic reviews have shown that double-dose (e.g., famotidine 40 mg two times daily) but not single-dose H2 receptor antagonists are effective at reducing the risk of NSAID-induced endoscopic gastric ulcers (Leontiadis et al., 2007; Rostom et al., 2002). In patients taking low-dose aspirin, famotidine 20 mg twice daily can reduce the development of oesophagitis, gastric and duodenal ulcers by 80% in an average-risk population, when compared with placebo therapy (Taha et al., 2009). In contrast, a separate study from Hong Kong showed that high-dose famotidine (40 mg twice daily) was inferior to pantoprazole (20mg daily) in the prevention of gastroduodenal ulcers in patients at high risk of aspirin-related ulcers. Recurrent symptomatic or bleeding ulcers (20% versus 0%) and gastrointestinal bleeding (7.7% versus 0%) were more common in patients on famotidine than in those on pantoprazole (Ng et al., 2010). However, economic modeling suggests that co-therapy with H2 receptor antagonists may be a cost-effective strategy for the prevention of ulcer bleeding in *NSAID* users (Brown et al., 2006). Like PPIs, there have not been any randomized, clinical outcome trials that evaluate the efficacy of H2 receptor antagonists in chronic *NSAID* users.

9. Conclusions

In high-risk patients, gastrointestinal complications associated with the use of NSAIDs are often caused by the concomitant use of aspirin or multiple NSAIDs, a failure to properly identify a patient's risk factors, and the underutilization of gastroprotective agents. The latter includes the use of PPIs in patients at high risk of gastrointestinal bleeding and the eradication of *H. pylori* in patients with a prior history of ulcers. PPIs have been shown to significantly reduce both gastric and duodenal ulcers and their attendant complications in patients taking not only NSAIDs, but also COX-2 inhibitors. Misoprostol, when given at full doses (800 mg/day) is very effective in preventing ulcers, and ulcer complications, in patients taking NSAIDs. However, its usefulness is limited in clinical practice due to its GI side effects. COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when compared to traditional NSAIDs. However, these beneficial effects are abrogated when the patient is concomitantly taking low-dose aspirin.

10. References

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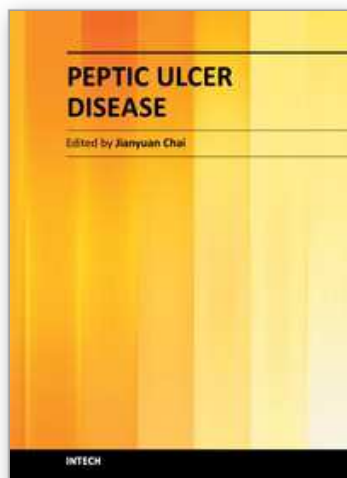
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Peptic Ulcer Disease

Edited by Dr. Jianyuan Chai

Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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