Review Article

Medical Progress

Gastrointestinal Toxicity of Nonsteroidal Antiinflammatory Drugs

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ONE hundred years have passed since Felix Hoffman, working at Bayer Industries, reported the successful synthesis of acetylsalicylic acid as the first nonsteroidal antiinflammatory drug (NSAID).[1,2] At the suggestion of Hermann Dreser, Bayer's chief pharmacologist at the time,[3] the compound was called "aspirin" and was purported to represent a convenient mechanism for the delivery of salicylic acid in the treatment of rheumatic diseases, menstrual pain, and fever.[2] Approximately 40 years elapsed before Douthwaite and Lintott[4] provided endoscopic evidence that aspirin could cause gastric mucosal damage. Numerous reports have corroborated this observation,[5-8] and the introduction of more potent agents with an even greater propensity for toxic effects has increased the awareness of NSAID-induced gastroduodenal ulcer and provided impetus for the development of effective NSAIDs with a more favorable safety profile.

Starting in the early 1970s, numerous new NSAIDs were developed that were initially believed to be devoid of gastrointestinal toxicity, but few, if any, are entirely harmless. These agents constitute one of the most widely used classes of drugs, with more than 70 million prescriptions and more than 30 billion over-the-counter tablets sold annually in the United States.[9] Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients, resulting in substantial morbidity and mortality.

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EPIDEMIOLOGY OF GASTROINTESTINAL COMPLICATIONS

Because of the broad and nonspecific definitions of gastrointestinal disorders caused by the use of NSAIDs, as well as differences in patient populations, drugs, dosages, and periods of use, estimates of the prevalence of adverse effects vary greatly. In general, at least 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent.[10,11] Within a six-month period of treatment, 5 to 15 percent of patients with rheumatoid arthritis can be expected to discontinue NSAID therapy because of dyspepsia.[11]

According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication. The risk in patients with osteoarthritis is somewhat lower (7.3 per 1000 patients per year).[12]

The rate of NSAID-related serious gastrointestinal complications requiring hospitalization has decreased in recent years. The decrease may be due, at least in part, to extensive medical-education campaigns that have persuaded physicians to use newer, less toxic NSAIDs and non-NSAID analgesics in populations at high risk.[12]

The mortality rate among patients who are hospitalized for NSAID-induced upper gastrointestinal bleeding is about 5 to 10 percent.[13] An analysis of data from ARAMIS has shown that the mortality rate attributed to NSAID-related gastrointestinal toxic effects is 0.22 percent per year, with an annual relative risk of 4.21 as compared with the risk for persons not using NSAIDs.[12] Although the annual mortality rate is low, it must be emphasized that because a large number of patients are exposed to NSAIDs, often for extended periods of time, the risk over a lifetime is substantial. In the United States, for instance, it is estimated that NSAIDs are used regularly by at least 13 million people with various arthritides. On the basis of these conservative figures and ARAMIS data, the annual number of hospitalizations in the United States for serious gastrointestinal complications is estimated to be at least 103,000. At an estimated cost of $15,000 to $20,000 per hospitalization, the annual direct costs of such complications exceed $2 billion.[14]

It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States. This figure is similar to the number of deaths from the acquired immunodeficiency

syndrome and considerably greater than the number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease (Fig. 1).[12,15] If deaths from gastrointestinal toxic effects of NSAIDs were tabulated separately in the National Vital Statistics reports, these effects would constitute the 15th most common cause of death in the United States. Yet these toxic effects remain largely a "silent epidemic," with many physicians and most patients unaware of the magnitude of the problem.[12] Furthermore, the mortality statistics do not include deaths ascribed to the use of over-the-counter NSAIDs.

In a recent survey of 4799 Americans, 807 were identified who had taken NSAIDs (prescribed or over-the-counter drugs) at least twice in the past year for five or more consecutive days.[12] Approximately 45 percent of the group took NSAIDs for five or more consecutive days at least once per month, and 40 percent took both over-the-counter and prescribed NSAIDs. Nearly 75 percent of those who used NSAIDs regularly were either unaware of or unconcerned about possible gastrointestinal complications. In addition, almost two thirds of the regular users indicated that they would expect warning signs before the development of serious NSAID-induced complications. Only a minority of patients who have serious gastrointestinal complications report any antecedent dyspepsia.[11,13] In a study of patients with serious gastrointestinal complications, Singh et al.[11] found that although the proportion of patients with prior symptoms was only slightly higher than the proportion with no prior symptoms (2.7 percent vs. 2.0 percent), 81 percent of the patients reported no antecedent dyspepsia.

RISK FACTORS FOR GASTROINTESTINAL COMPLICATIONS

Because dyspeptic symptoms are not a reliable warning sign, it is important to identify factors that increase the risk of serious gastrointestinal complications and to determine methods for reducing this risk. A number of studies have been designed to identify patients who are most likely to have adverse effects of NSAID therapy (Table 1).

Advanced age has been consistently found to be a primary risk factor for adverse gastrointestinal events. The risk increases linearly with age.[15-20] Although previous reports suggested that the risk diminishes over time, a recent study indicates that the risk of NSAID-associated gastrointestinal hemorrhage remains constant over an extended period of observation.[12] Other risk factors that have been identified in multiple studies are higher doses of NSAIDs (including the use of two or more NSAIDs), a history of gastroduodenal ulcer or gastrointestinal bleeding, concomitant use of corticosteroids, serious coexisting conditions, and concomitant use of anticoagulants.[20-27] However, many of these studies are based on univariate analysis and do not consider the interactions among multiple factors and coexisting conditions.

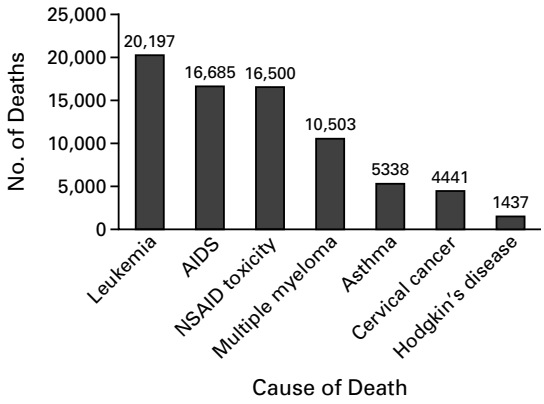

Figure 1. U.S. Mortality Data for Seven Selected Disorders in 1997. A total of 16,500 patients with rheumatoid arthritis or osteoarthritis died from the gastrointestinal toxic effects of NSAIDs. Data are from the National Center for Health Statistics and the Arthritis, Rheumatism, and Aging Medical Information System.[12]

TABLE 1. RISK FACTORS FOR THE DEVELOPMENT OF NSAID-ASSOCIATED GASTRODUODENAL ULCERS.*

Established risk factors
Advanced age (linear increase in risk)
History of ulcer
Concomitant use of corticosteroids
Higher doses of NSAIDs, including the use of more than one NSAID
Concomitant administration of anticoagulants
Serious systemic disorder
Possible risk factors
Concomitant infection with *Helicobacter pylori*
Cigarette smoking
Consumption of alcohol

*Information on risk factors is from Singh and Triadafilopoulus,[12] Bjorkman,[16] Longstreth,[17] Greene and Winickoff,[18] Gabriel et al.,[19] Griffin et al.,[20] Langman et al.,[21] Garcia Rodriguez and Jick,[22] Hallas et al.,[23] Silverstein et al.,[24] Hochain et al.,[25] Piper et al.,[26] Shorr et al.,[27] and Barkin.[28]

The identification of *Helicobacter pylori* infection as a factor in the development of peptic ulcer has raised the question of a possible synergistic relation between the presence of *H. pylori* infection and NSAID use. Although several studies[29-32] have found these two factors to be independent, two prospective studies have suggested a synergistic relation. Bianchi Porro et al.[33] used the combination of amoxicillin and omeprazole to treat NSAID users infected

with *H. pylori*. They found that the eradication of *H. pylori* did not affect the rate of ulcer healing. However, six months after the end of combination therapy, the cumulative rate of recurrent ulcers was 31 percent among the patients in whom *H. pylori* had been eradicated and 46 percent among those who were still infected. This difference was not statistically significant.

Chan et al.[34] found that the use of a regimen that included bismuth subcitrate to eradicate *H. pylori* significantly decreased the rate of ulcer development associated with the use of naproxen. In this study, gastroduodenal ulcers developed in 26 percent of *H. pylori*–infected persons, but in only 7 percent of those in whom the organism had been eradicated. The inclusion of bismuth in the drug regimen, however, makes the findings somewhat ambiguous, because bismuth can accumulate in the gastric mucosa and stimulate prostaglandin synthesis.[28] Most recently, Hawkey et al.[35] randomly assigned 285 patients with current ulcers or a history of ulcers who were using NSAIDs to combined treatment with omeprazole, clarithromycin, and amoxicillin or to treatment with omeprazole alone. They found that the eradication of *H. pylori* did not affect the rate of recurrent ulcer; in addition, ulcer healing was impaired even in the patients who were successfully treated with antibiotics for *H. pylori* infection. It thus appears that infection with *H. pylori* increases the risk of gastroduodenal mucosal injury associated with NSAID use only minimally, if at all.[28]

Singh et al.[36] recently proposed a simple, point-based algorithm that patients and their physicians can use to estimate the risk of an NSAID-related gastrointestinal complication. If confirmed by other investigators, this tool may help guide decisions about prescriptions for specific NSAIDs, the use of prophylactic agents, and the need for and frequency of patient monitoring.[36]

PATHOGENESIS OF NSAID-INDUCED GASTRODUODENAL MUCOSAL INJURY

Gastroduodenal mucosal injury develops when the deleterious effect of gastric acid overwhelms the normal defensive properties of the mucosa. Concepts about NSAID-induced gastroduodenal mucosal injury have evolved from a simple notion of topical injury to theories involving multiple mechanisms with both local and systemic effects (Fig. 2). The systemic effects are largely the result of the inhibition of endogenous prostaglandin synthesis.[37] Prostaglandin inhibition, in turn, leads to decreases in epithelial mucus, secretion of bicarbonate, mucosal blood flow, epithelial proliferation, and mucosal resistance to injury.[38,39] The impairment in mucosal resistance permits injury by endogenous factors, including acid, pepsin, and bile salts, as well as by exogenous factors such as NSAIDs and possibly ethanol and other noxious agents.

Topical Injury

Mucosal injury is initiated topically by the acidic properties of aspirin and many other NSAIDs. Because of a low dissociation constant, which varies according to the particular agent, these weak acids remain in their nonionized lipophilic form in the highly acidic gastric lumen. Such conditions favor migration through the gastric mucus across plasma membranes and into surface epithelial cells, where NSAIDs are dissociated into the ionized form, resulting in trapping of hydrogen ions.[37] NSAIDs can also cause topical mucosal damage by diminishing the hydrophobicity of gastric mucus, thereby allowing endogenous gastric acid and pepsin to injure the surface epithelium.[39] In addition, topical mucosal injury may occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.[40,41] For example, although sulindac is administered as a nontoxic prodrug, its active metabolite, sulindac sulfide, is excreted into the bile. On entry into the duodenum, sulindac sulfide causes topical injury to the mucosa by virtue of its acidic properties.

The Role of Prostaglandins

Topical injury caused by NSAIDs contributes to the development of gastroduodenal mucosal injury. However, the systemic effects of these agents appear to have the predominant role,[37,42,43] largely through the decreased synthesis of mucosal prostaglandins.[44] The use of enteric-coated aspirin preparations[44] and parenteral[45] or rectal[46] administration of NSAIDs in order to prevent topical mucosal injury has also failed to prevent the development of ulcers. Moreover, doses of aspirin as low as 30 mg are sufficient to suppress prostaglandin synthesis in the gastric mucosa.[47]

Prostaglandins are derived from arachidonic acid, which originates from cell-membrane phospholipids through the action of phospholipase A_2 (Fig. 3). The metabolism of arachidonic acid to prostaglandins and leukotrienes is catalyzed by the cyclooxygenase pathway and the 5-lipoxygenase pathway, respectively.[1,37] Two related but unique isoforms of cyclooxygenase, designated cyclooxygenase-1 and cyclooxygenase-2, have been demonstrated in mammalian cells.[48,49] Despite their structural similarities, they are encoded by distinct genes and differ with regard to their distribution and expression in tissues.[50,51] The cyclooxygenase-1 gene contains a promoter region without a TATA sequence and is primarily expressed constitutively. In contrast, the cyclooxygenase-2 gene is thought to be the inducible form that is nearly undetectable in most (but not all) tissues under normal physiologic conditions.

Cyclooxygenase-1 appears to function as a "housekeeping" enzyme in most tissues, including the gastric mucosa, the kidneys, and the platelets, whereas the expression of cyclooxygenase-2 can be induced

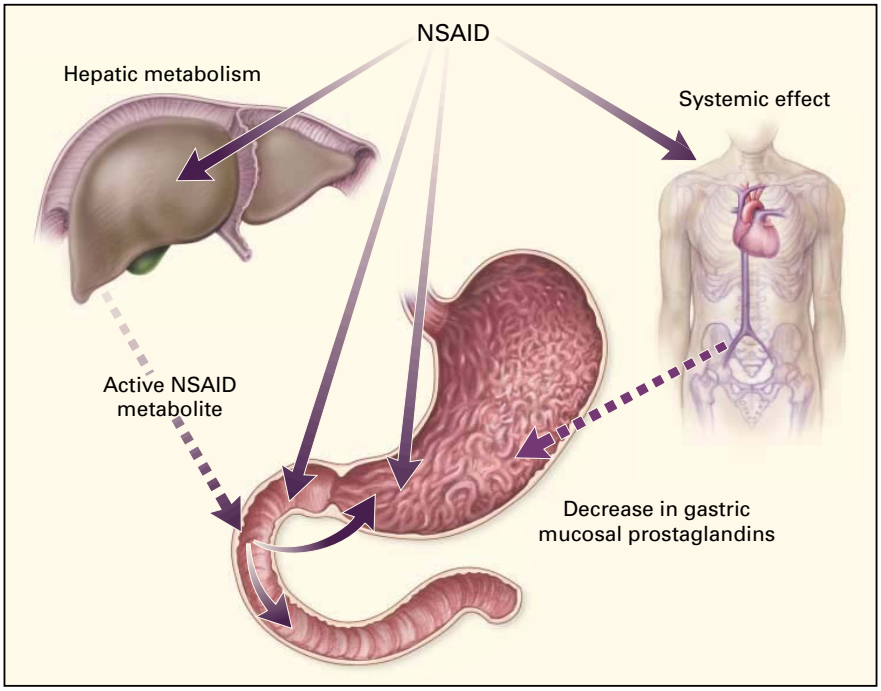

Figure 2. Mechanisms by Which NSAIDs Induce Gastroduodenal Mucosal Injury.
According to the dual-injury hypothesis of Schoen and Vender,[37] NSAIDs have direct toxic effects on the gastroduodenal mucosa (solid arrows) and indirect effects through active hepatic metabolites and decreases in mucosal prostaglandins (broken arrows). Hepatic metabolites are excreted into the bile and subsequently into the duodenum, where they cause mucosal damage to the stomach by duodenogastric reflux and mucosal damage to the small intestine by antegrade passage through the gastrointestinal tract. Adapted from Schoen and Vender.[37]

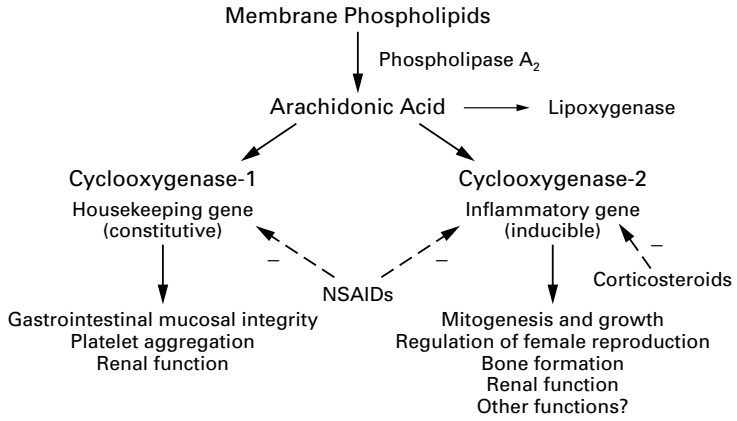

Figure 3. Biosynthesis of Prostaglandins through the Cyclooxygenase Pathways.
The immediate precursor of prostaglandins, arachidonic acid, is derived from membrane phospholipids and is catalyzed by the two cyclooxygenase isoenzymes (also designated as prostaglandin H synthase), cyclooxygenase-1 and cyclooxygenase-2. The gene for cyclooxygenase-1, the housekeeping enzyme, is expressed constitutively and maintains the homeostasis of organs, including gastric mucosal integrity. In contrast, the gene for cyclooxygenase-2, the inflammatory enzyme, is inducible. Although both pathways can be variably inhibited by different NSAIDs, only the gene for cyclooxygenase-2 contains a corticosteroid-responsive repressor element in its promoter region. The broken arrows indicate the inhibitory effects of pharmacologic agents.

by inflammatory stimuli and mitogens in many different types of tissue, including macrophages and synovial cells.[43] It has thus been suggested that the antiinflammatory properties of NSAIDs are mediated through the inhibition of cyclooxygenase-2, whereas adverse effects, such as gastroduodenal ulceration, occur as a result of effects on the constitutively expressed cyclooxygenase-1.[43,49] As discussed below, current strategies for developing NSAIDs with an improved safety profile include the selective inhibition of cyclooxygenase-2, with the sparing of cyclooxygenase-1.

Although there is substantial evidence that the suppression of gastric prostaglandins is the fundamental mechanism responsible for the gastrointestinal toxicity of NSAIDs, some studies suggest that other mechanisms may be involved. For example, ulcers do not develop spontaneously in mice with a disrupted cyclooxygenase-1 gene,[52] and Wallace et al.[53,54] reported that NSAID-induced injury occurred in association with enhanced adherence of neutrophils to the gastric vascular endothelium, as the result of an increase in the expression of intercellular adhesion molecule 1 in the basal endothelium.[55-58] Neutrophil adherence, in turn, causes mucosal injury through the release of oxygen-derived free radicals and proteases.[1]

CLINICAL SPECTRUM OF INJURY

In the majority of patients, NSAID-induced gastroduodenal mucosal injury is superficial and self-limited. However, peptic ulcers develop in some patients, and they may lead to gastroduodenal hemorrhage, perforation, and death. Serious complications of NSAID use that are less commonly recognized include pill esophagitis, small-bowel ulceration, small-bowel strictures, colonic strictures, diverticular disease, and exacerbations of inflammatory bowel disease.[9]

The spectrum of NSAID-related gastroduodenal injury includes a combination of subepithelial hemorrhages, erosions, and ulcerations that is often referred to as NSAID gastropathy. The distinction between erosions and ulcerations depends on pathological definitions, with ulcers defined as lesions that penetrate to the level of the submucosa and erosions defined as lesions confined to the mucosa. For practical purposes, an endoscopic definition is used, which is based on a subjective assessment of the size, shape, and depth of the lesion. Erosions are likely to be small and superficial, whereas ulcers tend to be larger (more than 5 mm in diameter) and deeper.[9]

After ingestion of an NSAID, ultrastructural damage to the gastric surface epithelium occurs within minutes, and gross, endoscopically detectable hemorrhages and erosions in the gastroduodenal epithelium occur within several hours.[59] However, mucosal adaptation appears to occur in response to long-term administration of aspirin in most persons.[60,61] No area of the stomach is resistant to NSAID-induced mucosal injury; the most frequently and severely affected site is the gastric antrum.[59] Although the prevalence and severity of acute injury vary according to the drug formulation,[62-64] the acute injury commonly observed during short-term administration of NSAIDs is not closely correlated with the subsequent development of the more clinically relevant process of mucosal ulceration[20,21,65,66] or with serious complications.[10,67,68] Duodenal mucosal injury occurs less commonly than gastric damage; however, ulcer complications associated with NSAIDs occur with nearly equal frequency in these two sites.[51,66] Prospective, cross-sectional endoscopic studies have shown that the combined prevalence of gastric and duodenal ulcers is 10 to 25 percent in patients with chronic arthritis treated with NSAIDs,[10,67] which is 5 to 15 times the expected prevalence in an age-matched healthy population.

TREATMENT OF NSAID-RELATED DYSPEPSIA

At least 10 to 20 percent of patients have dyspeptic symptoms during NSAID therapy.[10,11] However, such symptoms are poorly correlated with the endoscopic appearance and severity of mucosal injury, since up to 40 percent of persons with endoscopic evidence of erosive gastritis are asymptomatic,[10,68] and conversely, as many as 50 percent of patients with dyspepsia have normal-appearing mucosa.[10]

Histamine H_2–Receptor Antagonists

Several studies using different methods have shown an improvement in dyspeptic symptoms when histamine H_2–receptor antagonists are given to patients taking NSAIDs.[69-73] A recent prospective, observational cohort study by Singh et al.,[11] however, found that asymptomatic patients with rheumatoid arthritis who were taking H_2-receptor antagonists had a significantly higher risk of gastrointestinal complications than those not taking these drugs. The explanation for this surprising observation is unknown, but it might be due to the masking of dyspeptic symptoms associated with mucosal injury. Therefore, although H_2-receptor antagonists are effective in reducing NSAID-related dyspepsia, their routine use in asymptomatic patients taking NSAIDs cannot be recommended. Patients receiving H_2-receptor antagonists for the treatment of dyspepsia must be monitored carefully for the development of serious complications. The initial dose should generally be low (e.g., 400 mg of cimetidine, 150 mg of ranitidine or nizatidine, or 20 mg of famotidine, administered twice daily in each case), and the dose should be tailored to the needs of each patient.

Proton-Pump Inhibitors

In two recent studies, the proton-pump inhibitor omeprazole was compared with ranitidine[74] or mi-

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