**Nonsteroidal Anti-inflammatory Drug-related Gastrointestinal Bleeding in the Elderly**

Shou-Chuan Shih\(^1\,2,3,\ast\), Chen-Wang Chang\(^1\)

\(^1\)Division of Gastroenterology, Department of Internal Medicine, \(^2\)Health Evaluation Center, Mackay Memorial Hospital and \(^3\)Mackay Medicine, Nursing and Management College, Taipei, Taiwan.

**SUMMARY**

Nonsteroidal anti-inflammatory drug (NSAID) could induce gastrointestinal (GI) injury by way of topical (mucus, gastric acid and drug interaction) and systemic mechanism (decreased prostaglandin synthesis). Compared with non-NSAID users, elderly taking NSAID or aspirin have a higher chance than younger people of developing GI bleeding (5.5-fold vs. 1.65-fold). Endoscopy is the best tool to identify the source and severity of ulcer with bleeding. The use of NSAID or aspirin should be weighed carefully in elderly who have a history of peptic ulcer. If necessary, it is better to choose cyclooxygenase-2 inhibitor since it has been reported that the drug has less than half the risk of non-selective NSAID to ignite GI complications. Eradication of *Helicobacter pylori* might reduce ulcer risk in new NSAID users, but not in patients with long-term therapy. Proton pump inhibitor is the drug of choice that is effective for both treatment and prevention (taken together with NSAID) of NSAID-related GI bleeding. [International Journal of Gerontology 2007; 1(1): 40–45]

**Key Words:** elderly, GI bleeding, NSAID

**Introduction**

By the year 2020, it is predicted that more than 16% of people in the United States will be 65 years of age or older\(^1\). In Taiwan, people in that age range were more than 7% of the population in 1993 and are expected to occupy 10% of the population by 2011 and 20% by 2030.

Not unusually, older individuals have a number of diseases such as cardiovascular disorders and arthritis that are treated with antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs)\(^1\). Although the overall incidence of spontaneous bleeding and perforation of peptic ulcers has decreased, those complications are on the rise among people who use NSAIDs\(^2\). These agents are associated not only with an increased risk of peptic ulcer disease and its complications but also with higher expenses for the prescription of gastroprotective drugs and for hospitalization for gastrointestinal (GI) hemorrhage\(^3\,5\,6\). Several risk factors may identify patients prone to adverse effects of NSAID therapy, with advanced age consistently found to be one of them\(^7\).

Health care professionals must thus be conversant with the problem of NSAID-related GI bleeding in the elderly, as they will likely see more and more older patients with this complication. We reviewed the English-language literature on this topic using the search terms “elderly”, “GI bleeding”, and “NSAID”.

**Age-related Physiologic Changes in the GI Tract**

With aging, various changes occur in the GI tract. The esophageal sphincter pressure decreases, and hiatal hernia is not uncommon in the elderly who are therefore frequently subject to gastroesophageal reflux. In the stomach, atrophy of mucosa and achlorhydria...
are not unusual and may induce gastritis, hypergastrinemia, decreased gastric emptying, and bacterial overgrowth. In the US population above 60 years of age, the prevalence of *Helicobacter pylori* is approximately 50%, compared with approximately 10% in those less than 20 years of age. This increasing prevalence of *H. pylori* infection in the elderly may also increase the risk of Type B chronic gastritis, gastric atrophy, peptic ulcer disease, and neoplasm. *H. pylori* infection and NSAIDs are independent and synergistic risk factors for both uncomplicated and bleeding peptic ulcer. Finally, diverticulae are more common in the elderly, are a possible source of obscure GI bleeding, and thus may further confuse the situation.

**Pathogenesis of NSAID-related Peptic Ulcer Disease**

NSAIDs induce GI mucosal injury, which may then result in ulcers and bleeding. Pathogenesis of NSAID-induced mucosal injury can generally be divided into topical and systemic effects.

**Topical injury**

By creating a near-neutral pH at the epithelial surfaces in the stomach and the duodenum, secretion of bicarbonate from the duodenum into the mucus gel layer provides the first line of protection against luminal acid. The acidic properties of aspirin or NSAIDs are responsible for initiation of mucosal injury. NSAIDs can cause topical damage by decreasing the hydrophobic properties of gastric mucus, allowing endogenous gastric acid and pepsin to injure the surface epithelium. Indirect mechanisms may also contribute to topical injury, such as duodenogastric reflux of active NSAID metabolites or bile.

**Systemic effects**

The systemic effects of NSAIDs are mediated by decreased synthesis of mucosal prostaglandins. Prostaglandins are derived from arachidonic acid, a substance derived from cell-membrane phospholipids through the action of phospholipase A. The metabolism of arachidonic acid to prostaglandins is catalyzed by cyclooxygenase (COX), an enzyme with two distinct forms, COX-1 and COX-2. Although structurally similar, these two isoenzymes have different properties. COX-1 is produced in virtually all body tissues, including the GI tract, platelets, endothelial cells, renal medullary collecting ducts, and interstitium. It is essential for maintaining GI integrity, platelet aggregation, and sodium and water balance. Mucosal prostaglandins defend the gastric and duodenal mucosa against injury and ulceration by stimulating several factors that contribute to normal mucosal integrity. These factors include mucus synthesis and secretion, mucosal bicarbonate secretion, mucosal blood flow, and cellular repair. COX-2, normally present in the brain and kidney cells, is expressed in high concentrations at sites of inflammation and carcinogenesis. Traditional NSAIDs are nonselective inhibitors of both COX-1 and COX-2 isoenzymes. The anti-inflammatory properties of NSAIDs are mediated through inhibition of COX-2, whereas adverse effects, such as gastroduodenal ulceration, occur as a result of suppression of constitutively expressed COX-1. By inhibiting prostaglandin synthesis, NSAIDs compromise the gastroduodenal defense mechanism including blood flow and secretion of mucus and bicarbonate. Because these agents are used so frequently and so commonly cause mucosal damage, NSAIDs are the most widely reported drugs causing adverse events.

Attempts have been made to reduce the topical damage induced by NSAIDs by using enteric-coated preparations or parenteral or rectal administration. However, the systemic effects cannot be avoided, so ulcers may still develop. Doses of aspirin as low as 30 mg are sufficient to suppress prostaglandin synthesis in the gastric mucosa.

**NSAID-related GI Bleeding in the Elderly**

Choudari et al. compared the outcome in patients with bleeding from NSAID-related and non-NSAID-related peptic ulcers. Seventy-six patients with NSAID-related disease were older and more likely to have cardiorespiratory disease than the 112 patients with non-NSAID-related ulcers. The outcome of the bleeding itself did not differ significantly between the 2 groups. However, those with NSAID-related disease were hospitalized for significantly longer, most likely because of their other conditions. While NSAIDs may be prescribed for a variety of reasons in the elderly, 1 prominent indication is to provide antiplatelet activity to reduce cardiovascular mortality. It is ironic that a medication given to reduce cardiovascular risk may lead to bleeding—a potential contributing factor to increased cardiovascular risk.
morbidity and mortality. A series of 991 patients with coronary artery disease on low-dose aspirin followed in Hong Kong for 2 years found a relatively low incidence of GI bleeding—1.5% per year. They had no deaths related to the bleeding in this series, but the morbidity associated with bleeding was significant. The risks and benefits of prophylactic low-dose aspirin in the elderly must therefore be weighed very carefully.

Overall, the reported incidence of clinically apparent upper GI events is 3–4.5% of patients taking NSAIDs, with serious complications developing in approximately 1.5% of patients. The mortality among patients who are hospitalized for NSAID-induced upper GI bleeding is about 5–10%. Compared with nonusers of NSAIDs, elderly people taking these agents have a 5.5-fold increased risk of gastric ulcer and a 4.3-fold higher risk of duodenal ulcer. In people below 65 years of age, NSAIDs increase the risk of GI bleeding 1.65-fold, but in those 65 years and above, the risk is approximately 5.5-fold higher than in people not taking NSAIDs, a risk that increases linearly with age. Therefore, a history of peptic ulcer in an elderly patient should generally be regarded as a relative contraindication to NSAIDs. It should also be noted that NSAIDs or aspirin may also increase the risk of diverticular bleeding in the elderly.

Diagnosis of NSAID-related GI Bleeding

The clinical diagnosis of ulcer disease is often difficult. Pain may be masked for a number of reasons, perhaps even by the analgesic property of NSAIDs themselves. On the other hand, indigestion and upper abdominal pain are quite common but may have a variety of causes, of which ulcer is only 1 possibility.

Fecal occult blood testing can be used to look for GI bleeding, but its utility is limited because of insufficient sensitivity and specificity. Certainly, any patient using NSAIDs who has a positive stool test ought to undergo esophagogastrroduodenoscopy (EGD) or, if that cannot be tolerated, a barium study. EGD is clearly the most reliable tool for the diagnosis of ulceration of the upper GI tract. However, ulcerations may be present beyond the duodenum. In the event that neither EGD nor colonoscopy demonstrates an obvious lesion, the source of occult bleeding may be further sought by using push-enteroscopy, capsule endoscopy, or double-balloon enteroscopy, all of which are means of evaluating the small bowel. Other than capsule endoscopy, however, these studies may be uncomfortable and not well tolerated by the elderly. A sucrose permeability test has been suggested as a test for NSAID-induced GI damage, but it is only of limited usefulness since it cannot define the location or severity of a lesion.

Treatment and Prevention

Other than avoiding unnecessary use of NSAIDs, there are several strategies to manage elderly patients who must take the drugs but who are prone to or have already experienced GI bleeding.

Switch to COX-2 selective inhibitor

The COX-2-selective NSAIDs were specifically designed to provide pain relief comparable to that of traditional NSAIDs while reducing the incidence of adverse GI events in the elderly. These agents are less likely to suppress mucosal prostaglandin secretion than the traditional nonselective NSAIDs. The incidence of acid-related GI disorders in the elderly is reportedly less than half as great with COX-2-selective than with traditional NSAIDs (6% vs. 13%). However, rofecoxib and valdecoxib were recently withdrawn from the market because of serious cardiovascular adverse events. Surveillance of the safety of the other COX-2 inhibitors is currently ongoing.

Misoprostol

A different approach to mucosal protection but still focusing on preserving the protective effect of prostaglandins is the administration of misoprostol, a prostaglandin analog, along with NSAIDs. Although effective, its utility is frequently limited by side effects. In addition, in patients with a history of peptic ulcer, misoprostol has no significant protective effect against the risk of rebleeding. Although prostaglandins are useful in preventing NSAID-induced gastroduodenal mucosal injury, their role in the treatment of already established NSAID-associated ulcers is unclear.

Mucosal protective agents

Sucralfate, a basic aluminum salt of sucrose octasulfate, is effective in the treatment of both NSAID- and non-NSAID-related duodenal ulcers. It appears to be as effective as H2-receptor antagonists in the healing of non-NSAID-related gastric ulcers. Long-term sucralfate
therapy may reduce GI symptoms and therefore improve compliance with NSAID treatment of any type\textsuperscript{32}. In 1 study, sucralfate reportedly reduced the incidence of NSAID-related ulcers from 28\% to 8\%\textsuperscript{33}.

**Histamine H\textsubscript{2}-receptor antagonists**

Treatment of peptic ulcer disease with conventional doses of H\textsubscript{2}-receptor antagonists for 6–12 weeks results in the healing of approximately 75\% of gastric and 87\% of duodenal ulcers, despite the continued use of NSAIDs. However, continuation of NSAIDs appears to result in delayed healing, and the final outcome is largely dependent on the initial size of the ulcer\textsuperscript{7}. H\textsubscript{2}-receptor antagonists are relatively safe drugs that are widely available over the counter without a doctor’s prescription. However, drug metabolism in the elderly differs from that of younger people. In general, renal function decreases with age, and it may be even worse in elderly with comorbid illnesses. Dosages of the renally cleared H\textsubscript{2}-receptor antagonists should, therefore, be adjusted accordingly. In addition, cimetidine is known to inhibit cytochrome p450, thereby increasing the serum concentration of drugs normally metabolized by that enzyme, such as calcium channel blockers, benzodiazepines, and lovastatin. Cimetidine should be replaced with other H\textsubscript{2}-receptor antagonists, which do not have the same effect on hepatic drug metabolism, particularly in elderly individuals who are quite likely to be on such drugs\textsuperscript{34}.

**Proton pump inhibitors (PPIs)**

PPIs have a demonstrated role in the treatment and prevention of both aspirin and nonselective NSAID-related upper GI damage\textsuperscript{29,35}. Even patients on COX-2-selective NSAIDs may benefit from PPI cotherapy\textsuperscript{36}. In the treatment of NSAID-related peptic ulcer disease, PPIs are much more effective than H\textsubscript{2}-receptor blockers. In 1 study, PPI was associated with a significantly better risk reduction for peptic ulcers in both acute and chronic NSAID users than were H\textsubscript{2}-receptor blockers\textsuperscript{37}.

**Eradication of H. pylori**

In addition to its importance in treating ulcers, eradication of *H. pylori* is considered necessary to prevent GI bleeding in patients on low-dose aspirin or NSAIDs\textsuperscript{38–40}. However, routine testing for and eradication of *H. pylori* infection have not been recommended for patients at no or low risk of peptic ulcer disease\textsuperscript{41}. Current evidence suggests that *H. pylori* eradication reduces the ulcer risk for patients who are being started on NSAIDs but not for those already on long-term NSAID therapy\textsuperscript{42}.

**Conclusion**

Aging is inevitable, and the elderly are often subject to chronic diseases. In these patients, NSAIDs are a 2-edged sword. They may well be useful for treatment or secondary prevention of the diseases to which these patients are susceptible. However, they also clearly pose a risk of bleeding, to which the elderly are more prone. Proper patient selection is important. A history of peptic ulcer should be regarded as a relative contraindication to the use of NSAIDs. When they must be given, however, the use of gastroprotective agents will probably reduce the incidence of bleeding associated with them\textsuperscript{22}. Weighing of the benefit-risk ratio, however, goes beyond the decision for any 1 patient. In Taiwan, H\textsubscript{2}-receptor blockers and PPIs are relatively expensive drugs, and the National Health Insurance Bureau does not cover their routine prescription for elderly patients taking NSAIDs. This policy should be carefully examined in light of the following question. In the long run, which will cost more: covering the cost of drugs that may help protect against NSAID-induced GI bleeding or caring for elderly patients who develop this complication?

**References**


