CME CREDIT

Minimizing the risk of NSAID-induced GI bleeding

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ABSTRACT

Although nonsteroidal anti-inflammatory drugs (NSAIDs) have definite indications and can offer relief for many conditions, many patients have severe gastrointestinal problems after taking them. Physicians should prescribe these drugs more selectively and advise patients to limit their use of over-the-counter NSAIDs. For patients at high risk who need an NSAID, a prophylactic drug or a cyclooxygenase 2-selective NSAID can decrease the risk.

USE OF nonsteroidal anti-inflammatory drugs (NSAIDs) accounts for a considerable number of patients admitted to the hospital for gastrointestinal (GI) bleeding. Although the risk of GI bleeding is low for any individual patient taking an NSAID, so many people take these drugs that NSAID-induced GI toxicity is the 15th most common cause of death in the United States. Even if we count only patients with rheumatoid arthritis or osteoarthritis, the number of deaths each year due to NSAID-induced bleeding rivals that from AIDS—16,500 per year.[1] And our own research indicates that NSAID use and abuse is often underreported in patients treated for GI bleeding.

The implications for physicians are that we should:

- Inquire about NSAID use in patients presenting with GI bleeding, and perhaps even order a test of cyclooxygenase inhibition in refractory cases in which the patient denies NSAID use.
- Prescribe NSAIDs more selectively, and discourage patients from inappropriately using over-the-counter NSAID products.
- For high-risk patients who absolutely need an NSAID, consider prescribing a prophylactic drug such as omeprazole, lansoprazole, or misoprostol, or consider a cyclooxygenase-2-selective NSAID.

HOW COMMON IS NSAID USE AND GI BLEEDING?

Physicians write an estimated 100 million prescriptions for NSAIDs each year. Of these, 40% are for people over the age of 65, a group at high risk. Several times as many people probably use over-the-counter NSAIDs compared with prescription NSAIDs, and overall use is expected to increase as the population ages.

From 20% to 25% of patients who take prescription NSAIDs have some GI side effects (TABLE 1), and 10% have to discontinue taking the drug because of them.

Bleeding is much less common, and deaths less common still. In patients with rheumatoid arthritis, Singh and Triadafilopoulos[1] calculated the incidence of NSAID-related deaths due to GI toxicity at 0.22% per year. Keep in mind however that millions of people take NSAIDs, often for many years.

NSAID use appears to increase the risk of GI bleeding approximately fourfold. For example, in a study in our clinic,[2] when we tested for platelet cyclooxygenase inhibition (which can detect NSAID use within the previous 120 hours), we found that 80% of patients admitted for GI bleeding had been taking an NSAID, compared with 24.3% of a group of controls matched for age and sex ($P < .0001$). Aspirin accounted for 89% of the NSAIDs taken.

NSAID use often underreported

Of the patients with bleeding who tested positive for NSAID use in this study,[2] 15% denied taking an NSAID or were uncertain, illustrating the value of obtaining an objective test.

A remarkable finding in this study was that approximately one third of the patients with bleeding had bleeding from the lower GI tract, and that 86% of them had taken an NSAID. This finding indicates that patients need not have a peptic ulcer to have NSAID-induced GI bleeding. (NSAID-induced gastroduodenal lesions can be grouped into four grades; see TABLE 2 and FIGURES 1 and 2.)

WHO IS AT RISK?

According to Wolf and colleagues,[3] established risk factors for development of NSAID-associated gastroduodenal ulcers are:

- Advanced age
- History of ulcer
- Concomitant use of corticosteroids
- Higher doses of NSAIDs
- Use of more than one NSAID
- Concomitant use of anticoagulants
- Serious systemic disorders

In addition, less well-established risk factors are concomitant infection with *Helicobacter pylori*, cigarette smoking, and consumption of alcohol.

ASPIRIN AND INTRACTABLE ULCERS

Aspirin deserves special mention because it is so widely used, both by itself and in combination preparations. Yet it causes intractable and implacable ulcers of the upper GI tract, which are difficult to treat and will not heal unless aspirin is stopped. The ulcers are atypical and frequently multicentric, ie, occurring in two different locations or multiples in any one location, often complicated by stenosis.

Aspirin use may be the cause of many cases of ulcers that persist despite surgery to cure them. Here again, use may be surreptitious. We recently reported 30 cases of intractable ulcers in patients who had undergone surgery for ulcers.[4] Although all the patients in the series had blood salicylate levels of at least 3 mg/dL, indicating they had taken at least 1 g of aspirin in the previous 18 hours, half denied taking aspirin. In those who reported taking aspirin, intake ranged from 1 to 3.5 g/day.

TABLE 1

Gastrointestinal (GI) side effects of nonsteroidal anti-inflammatory drugs (NSAIDs)

Indigestion, nausea, and dyspepsia, often not related to definable lesions
Gastric or duodenal ulcers, varying from shallow erosions, which are insignificant, to deep chronic ulcers
GI bleeding, which is related to both ulcer and non-ulcer lesions, including upper and lower GI tract
Stenosis of the pylorus, or of the gastroenterostomy stoma after gastric surgery for ulcer
Perforation of ulcers or of any part of the GI tract
Delayed healing of ulcers or resistance to therapy
Esophagitis
Small and large bowel problems, including chronic GI blood loss, inflammations, ulcerations, strictures (especially acute bleeding from colonic diverticula), and acute exacerbation of colitis

OTHER NSAIDS AND RISK OF BLEEDING ULCERS

However, aspirin does not carry the greatest risk. Langman et al[5] performed a case-control study to examine the risk of bleeding peptic ulcer associated with various NSAIDs. They found that ibuprofen was the safest, followed, in increasing order of risk, by aspirin, diclofenac, naproxen, ketoprofen, indomethacin, piroxicam, and azapropazone. Risks also increased with drug dose for all the drugs combined.

More than half of all prescriptions for NSAIDs are inappropriate

PREVENTING GI SIDE EFFECTS

Prescribe NSAIDs selectively

The best prophylaxis is to avoid the use of NSAIDs except for solid indications. Recent studies show that more than half of all

TABLE 2

Grades of NSAID-induced gastroduodenal lesions

Grade 1	Petechiae; these often appear in the antrum of the stomach after a single dose of an NSAID, are irrelevant and common, and disappear very quickly
Grade 2	Erosions, such as aphthous erosions in the mouth; these, too, are not serious, and do not progress to chronic lesions
Grade 3	Chronic gastric and duodenal ulcers
Grade 4	Bleeding, perforation, and stenosis

NSAID-induced lesions can be grouped into four grades

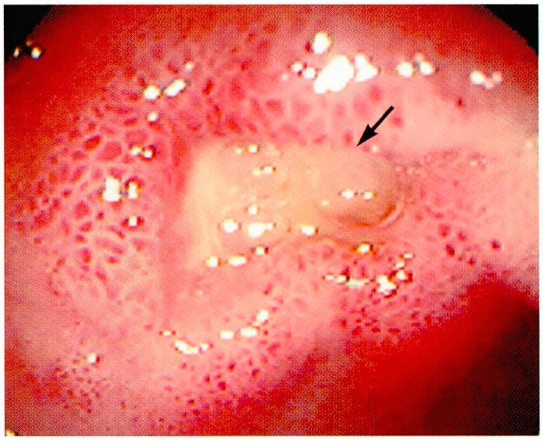

FIGURE 1. An NSAID-induced duodenal ulcer (arrow) that is characterized as a grade 3 lesion.

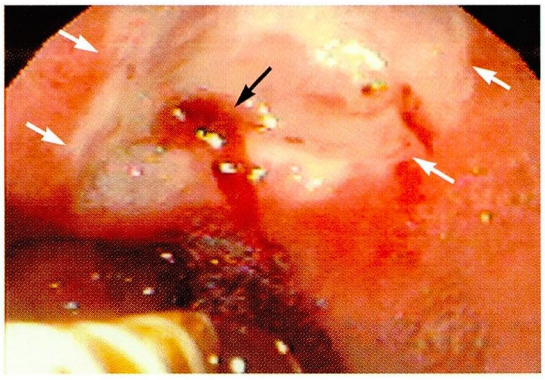

FIGURE 2. An NSAID-induced duodenal ulcer, with ulcer border indicated by white arrows. The bleeding vessel in the center of the ulcer (black arrow) makes this a grade 4 lesion.

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NSAIDs are prescribed inappropriately.[6] For example, 62% of patients with osteoarthritis are given NSAIDs. However, these patients need pain relief only, not the inflammatory and antithrombotic action that NSAIDs also provide. For such patients, a simple analgesic may be better, particularly if the patient is at high risk of NSAID side effects.

As for over-the-counter NSAIDs or aspirin, the best advice to patients is to avoid using them regularly except on the advice of their physicians, who must assess the risks and benefits of regular NSAID use.

Are COX-2-selective NSAIDs safer? A new class of NSAIDs has been developed that selectively inhibit cyclooxygenase 2 (COX-2) but not COX-1. In clinical trials these produced a much lower incidence of bleeding than did nonselective NSAIDs. However, it would be simplistic to assume that these drugs will be completely without side effects.[7]

Consider a prophylactic drug

Several drugs have been shown to prevent NSAID-induced ulcers.[8–10] Misoprostol is effective against duodenal and gastric ulcer and bleeding, but 32% of patients report diarrhea. Omeprazole will prevent both gastric and duodenal ulcers. Histamine$_2$-receptor antagonists will prevent duodenal but not gastric ulcers, and may reduce ulcer bleeding. However, none of these drugs will prevent non-ulcer bleeding.

WHEN A PATIENT HAS AN NSAID-RELATED ULCER

To treat an NSAID-related ulcer, the NSAID should be stopped, if possible, and an alternative drug used for pain relief. Once the NSAID has been stopped, conventional therapy for ulcer usually works very well. If *H pylori* is present, it should be treated as well. If an NSAID must be used, omeprazole or lansoprazole should be prescribed as prophylactic therapy. After the ulcer is healed, the patient should undergo surveillance. If the patient has stopped taking NSAIDs, the ulcer heals like any other and does not generally need follow-up. If it has bled, one endoscopy to confirm healing at 8 weeks should suffice.

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