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EDITORIALS

NSAIDs Without a Prescription: Over-the-Counter Access, Under-Counted Risks

The introduction of anti-inflammatory agents with a lower propensity for GI injury (coxibs) has focused attention on the well-recognized association between prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and GI adverse events. Although over-the-counter (OTC) NSAIDs—including aspirin—are used far more frequently that their prescription counterparts, similar notice has not been paid to their potential health hazards. The Food and Drug Administration approval of low-dose NSAIDs to be sold without a prescription, the long-standing availability of aspirin, and aggressive direct-to-consumer marketing contribute to the lay public's perception of the safety of these drugs. Although data on the GI risks of OTC NSAIDs are emerging, most regular NSAID users lack awareness of their potential side effects (1). The sheer numbers of individuals exposed to OTC agents raise concern regarding their appropriate use.

Published case series have implicated OTC NSAIDs in over one third of patients admitted for GI hemorrhage (2). However, there is a dearth of information regarding the effects of less serious GI adverse events attributable to these drugs as they occur in the "real world." Thomas *et al.*, in this issue of the *Journal* (3), report the results of a nationwide telephone survey undertaken to evaluate indications for regular OTC NSAID use, the impact of NSAID use on GI symptoms, and treatment patterns for these GI complaints. The principal findings, that individuals who regularly use OTC NSAIDs are twice as likely to report GI symptoms and use OTC GI medications than matched controls who did not use these drugs, are important contributions. These results demonstrate that the well-described, "shadow costs" of treating drug-related GI effects of prescription NSAIDs (4) extends to the OTC sector. More importantly, it exposes the fact that *the OTC GI medications used by the study population for their GI symptoms may effectively treat symptoms, but do not reduce the risk of clinically meaningful adverse events*.

Antacids and histamine-2 receptor antagonists at OTC doses may reduce dyspepsia, but have not been demonstrated to reduce serious ulcer risk (5). Interestingly, despite a 2-fold increased risk of symptoms and the use of GI OTC medications by the survey respondents using OTC NSAIDs, there was no increase in provider visits and/or GI prescription medications compared with nonusers. These observations provide insight into the seemingly paradoxical observations from the ARAMIS database that found that rheumatoid arthritis patients receiving prescription histamine-2 receptor antagonists had increased rates of NSAID-related ulcer disease (6). The use of medications that reduce symptoms but do not lower ulcer risk, coupled with the fact that these patients may not present to a clinician, may explain this unexpected rise in adverse events in the cohort of patients taking histamine-2 receptor antagonists.

The Thomas *et al.* (3) study found that aspirin or aspirin-containing products were the predominant OTC NSAID product used (55% of users). Low-dose aspirin, which provides unequivocal benefit for the secondary prevention of cardiovascular (CV) disease, has been associated with a 2–4-fold increased risk of GI bleeding (7). Other studies have established that neither enteric coating nor the use of buffering alters this risk (8). Although the dose of aspirin for secondary prevention of CV events varies by indication, the dose required for most atherosclerotic complications is likely 81 mg daily or less. Although it appears that dose reduction is unlikely to reduce the CV protective effect of aspirin, the evidence suggests that bleeding complications (including GI bleeding) increase with aspirin dose (9).

These well-documented GI safety concerns of aspirin led the U.S. Preventative Services Task Force to recommend a risk-benefit calculation be performed before the recommendation of low-dose aspirin for primary prevention of CV events (10). They concluded that the balance of risk and benefit of aspirin was strongly tied to cardiac risk, explicitly recommending prophylactic aspirin only to those with a 5-yr risk of CV events $\geq$3%. Given this narrow therapeutic window, it is clear that a clinician's input is warranted before beginning aspirin for primary CV prophylaxis.

Nearly half (43%) of the regular NSAID users in the Thomas *et al.* (3) study reported they were taking the drugs for CV protection. The specific agents used for this indication were not provided in the manuscript. *It is essential to determine which agent(s) is being taken for cardioprotection and whether other NSAIDs are being used concurrently.* This inquiry is critical for several reasons. First, there is no definitive evidence that nonaspirin NSAIDs (as a class) reduce CV events (11). Until controlled investigations determine that specific traditional NSAIDs reduce the risk of CV events to the same extent as aspirin, low-dose aspirin—not nonaspirin NSAIDs—should be used for this indication. Second, the risk of GI events rises substantially when more than one NSAID is used (12). Last, it has been recently reported that certain NSAIDs can block the antiplatelet action of aspirin and potentially abrogate its cardioprotective properties (13). In light of these issues, we strongly concur with the authors' recommendation that clinicians aggressively solicit OTC medication use and consider this information when prescribing therapy (3).

One additional reason to query for regular aspirin use is fueled by the ongoing debate whether the GI safety advan-

tage of coxibs (compared with traditional NSAIDs) is reduced or eliminated in the setting of concomitant low-dose aspirin. *Post hoc* analyses of the 21% of patients enrolled in the CLASS trial (14) who used low-dose aspirin suggest that the GI safety advantage of celecoxib was nearly eliminated in the setting of aspirin cotherapy. These analyses—although not appropriately powered to make a statistical infererence—call into question the incremental value of coxibs when low-dose aspirin is concomitantly prescribed (14). In response to these data (in part), the Department of Veterans Affairs has restricted coxib use for patients taking aspirin (15). Ironically, the highly publicized finding that coxib users may have an enhanced risk of prothrombotic events has led to an increase in the use of aspirin by individuals using coxibs for whom cardioprophylaxis is indicated (16). This unexpected turn of events mandates the performance of a well-designed GI safety study of coxibs and aspirin before coxib use is inappropriately curtailed (mainly because of economic concerns) in large populations who may benefit from less GI toxic NSAID therapy.

Aspirin and NSAIDs have received attention in the lay press as a potential preventive agent for certain types of cancer and Alzheimer's disease. These interesting yet unproven hypotheses may further stimulate patients to use these agents without consulting a physician. In the case of colon cancer prevention, the use of aspirin as either a substitute or adjunct to current screening practices cannot be advocated either on clinical or economic grounds (17). Thus, the decision to use these agents for chemoprevention, as for CV prophylaxis, should be guided by a careful consideration of all the risks and benefits, as well as examination of available alternative strategies.

One important missing piece of the puzzle is whether OTC NSAID use leads to increased rates of clinically significant adverse events. This hypothesis, although not proven by the Thomas *et al.* (3) study, is supported in the literature by case-control studies implicating OTC NSAID doses as important risk factors for serious GI events (18). Mechanistically, the finding of a dose-dependent relationship would not be surprising because NSAID GI toxicity is linked to inhibition of both cycloxygenase isoforms important in maintaining upper GI mucosal defense and repair. Preliminary data from the American College of Gastroenterology GI bleeding registry demonstrated OTC NSAID use was nearly three times more common among patients who bled when compared with controls (19).

Although the lower doses of OTC NSAIDs may be perceived as safer than their prescription counterparts, their unregulated nature does not allow control over who uses these drugs, how much they use, and with which other drugs. It is apparent that the clinical and economic attractiveness of available NSAID treatment options is determined by the particular NSAID used, other medications used simultaneously, and the patients' underlying risk for adverse events (20). Outcomes studies that quantify the risks and benefits of these easily accessed and widely used drugs in different patient populations are clearly needed.

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Where Next With Endoscopic Ulcer Hemostasis?

Severe upper GI (UGI) bleeding is a relatively frequent reason for hospital admission in adult patients (1). In most major medical centers, peptic ulcers are still the most common etiology for UGI hemorrhage (2, 3). However, in North America and some European countries, ulcers are becoming less prevalent as the cause of UGI hemorrhage than varices, tumors, Mallory Weiss tears, and angiomas. This may relate to primary prophylaxis (such as eradication of *Helicobacter pylori*) or secondary prophylaxis in high-risk patients such as those with a prior history of ulcer hemorrhage or those taking nonsteroidal anti-inflammatory drugs or aspirin (4).

After initial resuscitation of patients with severe UGI bleeding and initiation of medical therapy for those with suspected ulcer hemorrhage, urgent endoscopy is the standard of care for diagnosis and, along with clinical history and laboratory tests, for triaging patients by low and high risk. Also, endoscopic treatment of those with major stigmata of ulcer hemorrhage (active bleeding, nonbleeding visible vessel [NBVV], or an adherent clot) is highly recommended because outcomes improve (1–3). Oozing bleeding without another stigmata (such as a NBVV or clot) is often self-limited and does not usually require endoscopic therapy, although some endoscopists report rebleeding rates on medical therapy alone of up to 28% and recommend endoscopic hemostasis for this stigma (5). Endoscopic treatment of minor stigmata of ulcer hemorrhage (flat spots or gray slough) or clean ulcer bases is not recommended because outcomes do not improve and may worsen (1–6). For all patients with ulcer hemorrhage, biopsy for *H. pylori* and subsequent eradication of infection, early refeeding, treatment with high-dose proton pump inhibitors (PPIs) to heal ulcers, and counseling about the dangers of subsequent nonsteroidal anti-inflammatory drugs or aspirin ingestion are highly recommended also (4).

Many types of endoscopic hemostasis techniques for treatment of nonvariceal bleeding lesions have been developed and studied over the last 25 yr (1). The major thermal types include lasers, monopolar electrocoagulation, argon plasma coagulator, bipolar probes, and heater probe. The former two are now rarely used for emergency hemostasis because of inconvenience, efficacy, or safety concerns. The argon plasma coagulator does not coagulate through blood well and has superficial coagulation, which renders treatment of ulcers with larger underlying vessels impractical. Injection techniques are with epinephrine (usually 1:10,000), sclerosants, clotting factors, or cyanoacrylate. Worldwide, emergency hemostasis with epinephrine (alone or in combination with sclerosants, thermal, or mechanical therapy) is probably the most common technique for emergency ulcer hemostasis. Topical methods such as spraying of vasoactive drugs, tissue glues, clotting factors, or ferromagnetic tamponade onto ulcers are safe but not effective for arterial hemostasis and therefore rarely used to treat ulcers with major stigmata of hemorrhage. Mechanical techniques such as hemoclips, endoloops, rubber bands, or sutures have been applied to both variceal and nonvariceal lesions (1). For emergency endoscopic hemostasis of ulcers with major stigmata of hemorrhage, most endoscopists rely upon their own training and experience, using techniques that are available on their emergency hemostasis carts, and catheters or probes that are easily applied, effective, and safe (1–8).

Thermal contact probes such as the heater probe or multipolar probes have been marketed in most countries for more than 20 yr (1, 3, 9). These can be applied en face or tangentially in almost all peptic ulcers with major stigmata of hemorrhage. Target irrigation, suctioning, and tamponade of the bleeding point help the endoscopist localize the stigmata in the ulcer and facilitate endoscopic treatment (1, 9). In the laboratory, coaptive coagulation or welding the walls of the vessel together can be achieved for arteries up to 2 mm in diameter, when blood flow is first interrupted by firm tamponade and then at least 150 J of thermal energy (or W/s) are applied (1, 2, 7). Large diameter probes and slow coagulation give the most consistent results in the laboratory and clinically for coaptation of lesions with arterial bleeding (1, 2, 7, 9). Based upon the histopathological studies of Swain *et al.* (8) and others (1), most peptic ulcers with major stigmata of hemorrhage have arteries smaller than 2 mm in diameter, and therefore are amenable to coaptive coagulation with large heater or multipolar probes.