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EDITORIAL

NSAID-Associated Deaths: The Rise and Fall of NSAID-Associated GI Mortality

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Although gastrointestinal (GI) morbidity and mortality from NSAIDs continues to be a significant problem, this study by Lanas *et al*. indicates that the magnitude of the concern is declining. Explanations for this reduction are more likely related to the increased use of proton pump inhibitors (PPIs) than to the introduction of COX-2 inhibitors. This study further reveals that one-third of NSAIDs' GI mortality comes from low-dose, daily aspirin. Another important contribution derived from this report is a more reliable estimate of NSAIDs' lower GI clinical consequences than previously available.

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Most physicians readily acknowledge that NSAIDs are an important cause of gastrointestinal (GI) morbidity. This problem is largely a consequence of NSAIDs' regular use by more than 60 million Americans (1) resulting in clinically significant upper GI events in 1–2% of users (2). Not widely appreciated, however, is that NSAIDs use also results in death. Few studies have estimated mortality resulting from GI complications of NSAIDs. Among the available reports, estimates attributable to NSAIDs have widely varied from 3,200 to higher than 16,500 deaths per yr in the United States (3, 4).

A few studies have recently indicated that NSAIDs also cause significant lower GI tract morbidity (5–7). In contrast to the widespread appreciation of NSAIDs' upper GI effects, lower GI events attributable to NSAIDs have been a concept that the medical community has been less willing to accept. Moreover, the quantitative degree of NSAIDs' lower GI effects has been uncertain as observations have ranged from trivial small intestinal and colonic lesions (5, 6) to reports that as many as 40% of major GI events with NSAIDs occur in the lower tract (7).

Low daily doses of aspirin clearly have the potential to cause GI injury as 10 mg of aspirin daily causes gastric ulcers (8). Less well understood, however, is the prevalence of clinically significant GI consequences attributable to low doses of aspirin. Despite of all the knowledge acquired from the vast body of investigations of NSAIDs, it seems somewhat surprising that in 2005 we cannot confidently quantify as a consequence of NSAID use: deaths, clinically significant lower GI tract effects nor GI complications due to low-dose, daily aspirin.

The lack of good estimates regarding these problems with NSAIDs is largely a reflection of the inadequate surveillance systems to capture rare events. The current preapproval process for drugs is better designed and powered to detect efficacy rather than safety. If a drug has a dangerous but rare side effect, such as death, that effect will generally not be recognized in prospectively conducted trials of several weeks' duration as part of a clinical developmental program. Consequently, about half the drugs that enter the U.S. market have serious adverse effects that are detected only after approval (9). Only after a medication is being widely used in clinical practice, typically in millions of patients, can low rates of adverse events usually be noticed. Moreover, conventional postmarketing surveillance schemes, which mainly rely on physicians to inform pharmaceutical companies of adverse events and companies, in turn, informing regulators have also not been successful. Consequently, reliable estimates of rare adverse effects of drugs such as NSAIDs are best derived from population-based studies of patients taking medications in clinical practice. In these types of studies, researchers are directed by cues from clinical trials or case reports suggesting potential problems. Study population databases containing millions of patient records can then be specifically queried to evaluate information on medicines prescribed, hospitalizations, complications, and deaths.

In the current issue of the *American Journal of Gastroenterology*, Lanas and colleagues present a population-based study from Spain in which they use pharmacoepidemiologic tools to better quantify some of the current uncertainties regarding NSAIDs' clinically important GI toxicity (10). They conducted an observational study of NSAID-related GI complications and deaths evaluated throughout more than 200 hospitals in the Spanish National Health System, a healthcare system, which provides care for 80% of the country. They calculated a frequency of 15.3 deaths per 100,000 NSAID users, occurring in 5% of all patients hospitalized with GI complications secondary to NSAIDs. Of note, mortality rates in the current study are only 30% of the widely popularized death rate from NSAIDs reported in the United States. Also important, and somewhat surprising, is that one-third of NSAID-associated GI mortality occurred in patients whose only NSAID taken was low-dose aspirin.

The most widely quoted NSAID mortality estimates of 16,500 annual NSAID-related U.S. deaths come from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database, a surveillance program of 4,258

rheumatoid arthritis patients whose health-care outcomes have been followed for several years (4). This high mortality rate, however, is imprecise as it was calculated by extrapolation from a small number of actual deaths in the ARAMIS cohort. Also, the imprecision in ARAMIS is further magnified as it was extrapolated to a non-age-adjusted rheumatoid arthritis patient population, a disease cohort, which has higher all cause mortality than the overall population.

While some previous reports overstated the problem of NSAID-associated GI mortality, alternative explanations for lower current death rates in Spain, as well as worldwide, can be largely attributed to declining hospitalizations over the last decade for complicated NSAID ulcers (11). This phenomenon has been attributed to implementation of strategies such as proton pump inhibitors (PPIs) and COX-2 inhibitors, which can reduce NSAIDs' deleterious GI effects (11). One major variable which may explain differences in NSAID complications between Spain and the United States is variability in prevalence of PPI use. In the United States, approximately 29% of NSAID users take PPIs compared to greater than 50% of Spanish NSAID users (10). COX-2 inhibitors are taken by only 1% of Spain's NSAID-taking patients. In Spain, where PPIs are taken by one-half of NSAID users and COX-2 inhibitor use is almost nonexistent, NSAID complication rates are one-third of U.S. rates leading one to wonder whether the PPI plus NSAID strategy is a more effective means than COX-2 inhibitors to reduce NSAIDs' GI complications in actual clinical practice. In support of this concept is the fact that the majority of the decline in NSAID-associated GI hospitalizations and deaths in the United States occurred during the 1990s when PPI utilization was increasing and prior to introduction of COX-2 inhibitors.

Another highlight of Dr. Lanas' study is that clinically significant lower GI events attributable to NSAIDs comprised 14% of total GI complications, an estimate that is probably more accurate than previously reported (5–7). A venerability of the PPI strategy for NSAID-GI risk reduction is that this approach does not cover the proportion of events occurring in the lower GI tract, a limitation consistent with the GI pharmacologic targets of PPIs. On the other hand, if Lanas' report is accurate, that 86% of NSAIDs' GI effects are in the upper tract (10), then the PPI approach should effectively cover the overwhelming majority of NSAIDs' GI effects.

In summary, Dr. Lanas and colleagues have provided us a well-considered and methodical assessment of NSAIDs' GI morbidity and mortality. The study is also a nice example of a scenario where observational studies are preferable to moderately sized, prospective randomized controlled trials, specifically, in situations where rare adverse events are being queried. Although clinically significant GI events with NSAIDs are uncommon, as a result of the vast numbers of patients who take these medications, when assessed by percentages these complications remain a significant public health concern. Consequently, we continue to be reminded that NSAIDs can be harmful and, unfortunately, lethal and we must be persistently vigilant in our efforts to reduce complications in our patients who take these agents.

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