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Gastrointestinal Complications of Prescription and Over-the-Counter Nonsteroidal Anti-inflammatory Drugs: A View from the ARAMIS Database

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More than 30 million people worldwide consume prescription nonsteroidal anti-inflammatory drugs (NSAIDs) on a daily basis. Gastrointestinal (GI) toxicity owing to the use of NSAIDs is a well-recognized clinical problem, with approximately 25% of all reported adverse drug reactions being attributed to prescription NSAID use. In addition to prescription NSAIDs, the use of over-the-counter (OTC) formulations of these products is common. Although it has been suggested that OTC doses of NSAIDs may not lead to significant GI toxicity, the data confirming this have been lacking. Data on the GI risks of OTC doses of aspirin, ibuprofen, naproxen, paracetamol, and no drug from 4164 consecutively diagnosed patients with rheumatoid arthritis from eight ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) centers in North America are presented. Serious GI events were defined as GI bleeds and other clinically significant GI events requiring hospitalization. Relative risks were standardized for potential demographic confounders using Cox proportional hazard models. Although the relative risk of OTC doses of NSAIDs (3 to 4) is less than the previously published risk of prescription doses (6 to 7), it remains clinically significant and a matter of serious concern because of the widespread use of these medications and an underappreciation of the true risk. Paracetamol was not associated with increased risk of GI complications and should be considered first-line therapy.

Keywords: paracetamol, acetaminophen, gastrointestinal toxicity, over-the-counter dose, nonsteroidal anti-inflammatory drug.

INTRODUCTION

Aspirin and the other nonsteroidal anti-inflammatory drugs (NSAIDs) are considered to be one of the most frequently used class of drugs, with more than 30 million people using them on a daily basis. Despite their popularity, these drugs do carry risks. It is now well recognized that they are associated with significant adverse effects on the gastrointestinal (GI) tract, that these are the most prevalent category of adverse drug reactions,[1] and that they lead to significant morbidity and mortality.[2] In recent years, there has been much research interest in the area of GI-related complications. The aim of this paper is to put these GI complications into clinical perspective using information gained from the studies of the ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) database. To this end, we briefly review the literature and update previously published ARAMIS information from the prescription setting as well as new information relating to the use of over-the-counter (OTC) analgesics.

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THE ARAMIS DATABASE

ARAMIS is a prospective observational noninterventional cohort study that has systematically collected data on individuals with chronic rheumatic diseases. It provides a means with which physician- and pa-

tient-reported data can be systematically collected and analyzed. Funded primarily by grants from the National Institutes of Health, the ARAMIS database has now amassed detailed clinical outcome information on more than 36,000 patients with rheumatic diseases from 17 centers in the United States and Canada who have been followed for more than 300,000 patient-years. The ARAMIS Post-Marketing Surveillance (PMS) Program has prospectively followed patient outcome status, drug side effects, and economic impact of illness in a cohort of more than 12,000 consecutively enrolled osteoarthritis (OA) and rheumatoid arthritis (RA) patients from eight patient populations (Stanford, CA; Santa Clara County, CA; Wichita, KS; Phoenix, AZ; Cincinnati, OH; Baltimore, MD; Saskatoon, Saskatchewan, Canada; and Montreal, Quebec, Canada).[3] These data provide a large body of information that can be used to evaluate various aspects of the epidemiology of NSAID-related GI side effects. Patient characteristics, study design, and data collection methods are described in detail elsewhere.[4–6]

NSAID-RELATED GASTROINTESTINAL COMPLICATIONS

NSAID-related GI complications cover a number of different disorders that can be divided into three main categories ranging from nuisance symptoms to endoscopically determined mucosal lesions and serious GI complications.[3]

Nuisance symptoms, including dyspepsia

Nuisance symptoms, such as heartburn, nausea, dyspepsia, and abdominal pain, affect approximately 10% to 20% of patients after taking an NSAID,[6–8] although this may range from 5% to 50%, depending on factors such as study design, patient populations, drugs, dosages, and duration of use.[8] Such symptoms can have a great impact on NSAID compliance. Indeed, it has been noted that, among patients with OA on NSAID treatment after 1 year, only 15% to 20% were still taking the same drug.[9]

Endoscopically determined mucosal lesions

NSAID-induced mucosal lesions can range from minor gastroduodenal lesions to serious GI complications such as bleeding and perforation. Acute hemorrhages and erosions occur within several hours to minutes of taking NSAIDs and can be seen in as many as 80% of patients treated with NSAIDs.[10] These ulcers are usually asymptomatic and will heal and redevelop over time. Endoscopic evidence of mucosal damage can be seen without the patient reporting any symptoms; similarly a patient may report symptoms without any evidence of mucosal damage; and serious GI complications can occur without the patient reporting any symptoms or there being any endoscopic evidence of mucosal damage.[11]

Serious gastrointestinal complications

Serious GI complications resulting in hospitalization occur annually in 1% to 2% of individuals taking NSAIDs regularly.[12] We recently reported the data on the incidence of serious GI complications resulting in hospitalization among patients with RA and OA (Table 1),[3] showing that, when compared with previously published data,[6,13–15] the rate of hospitalization for NSAID-related serious GI complications may have decreased in recent years. This decline may be accounted for by two factors, namely, the establishment of more stringent criteria for hospitalization in a managed-care setting and physician-education campaigns, which emphasize increased use of newer, less GI-toxic

Table 1. Gastrointestinal complications in osteoarthritis and rheumatoid arthritis.

	OA	RA	
	Hospitalizations	Hospitalizations	Deaths
Number of patients	1283	3883	2921
Person—years of observation	3234	19,961	12,224
Person—years taking NSAIDs	2199	15,638	8471
Number of GI events	19	228	25
Number of GI events while taking NSAIDs	16	205	19
Rate per year while taking NSAIDs (%)	0.73	1.31	0.22
Rate per year while **not** taking NSAIDs (%)	0.29	0.19	0.05
Relative risk while taking NSAIDs	2.51	6.77	4.21

Adapted from ref. 3.

NSAIDs and non-NSAID analgesics, such as paracetamol, in high-risk populations.[2,3]

THE BURDEN OF NSAID-RELATED GASTROINTESTINAL COMPLICATIONS

Approximately 10% to 15% of cases of hospitalizations for upper GI bleeding results in death.[16] In our previously published ARAMIS data, we reported 26 GI deaths in 12,224 patient-years of exposure to NSAIDs.[3] Of these deaths, 19 could be attributed to NSAIDs, giving a GI death rate of 0.22% per year, and a relative risk of 4.21.

It could be argued that this may not seem significant. However, given the high usage of these products, often on a chronic basis, the lifetime risk and health care burden may be substantial. Based on these conservative figures and ARAMIS data, the number of hospitalizations for serious GI complications per year is estimated to be 103,000, which, at a conservative estimated cost of US$15,000 to 20,000 per hospitalization, amounts to an annual cost in excess of US$2 billion.[3]

Among RA and OA patients, data are even more startling. It has been conservatively estimated that 16,500 NSAID-related deaths occur in these patients every year in the United States (Fig. 1). When compared with some other common causes of death in the United States during 1997,[17] it becomes apparent that NSAIDs may be responsible for almost as many deaths as AIDS and significantly more deaths than asthma, cervical cancer, and Hodgkin's disease.[3]

MANY CONSUMERS DO NOT RECOGNIZE THE SERIOUSNESS OF THE PROBLEM

A survey conducted in 1998 by Roper-Starch, the American Gastroenterological Association, and G.D. Searle & Co. revealed that limited consumer knowledge plus a lack of concern contribute to the problem of NSAID-related GI complications. Some 807 individuals were included in the analysis, which revealed that almost half (45%) took NSAIDs for 5 days or longer at least once a month.[3] Furthermore, nearly 40% of individuals combined OTC and prescription NSAIDs. Of great concern was the revelation that of those consumers who regularly used NSAIDs, nearly 75% did not know about or were unconcerned about NSAID-related GI complications (Fig. 2). In addition, almost two thirds believed they would get warning signs in advance of a serious NSAID-induced complication (Fig. 3). Yet other studies showed that only 20% of people who have a serious GI complication will have any warning sign.[6]

ARE THERE WARNING SIGNS FOR SERIOUS GASTROINTESTINAL COMPLICATIONS?

Whereas dyspeptic symptoms are common in patients on NSAIDs, there is little correlation between these symptoms and serious GI complications. For example, we previously reported that in a prospective cohort evaluation of 1921 patients, the overall incidence of

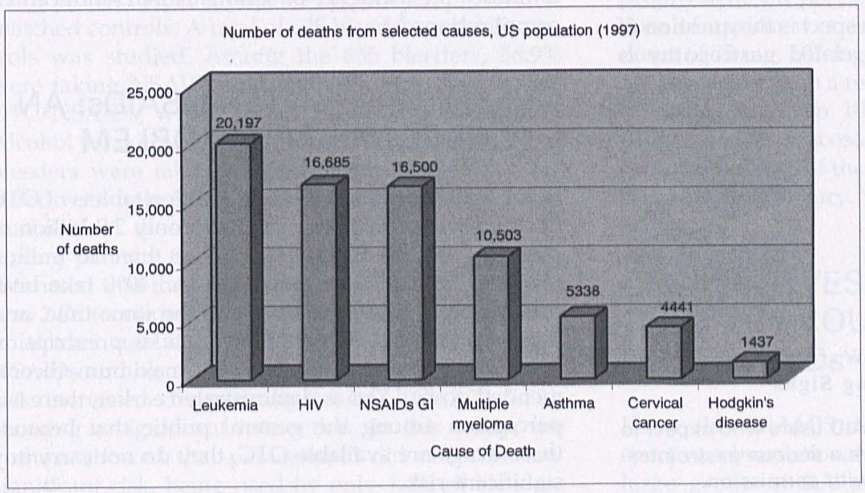

Fig. 1. Number of deaths associated with NSAID-induced gastrointestinal damage compared with other causes (U.S. population).[17] From ref. 3, with permission.

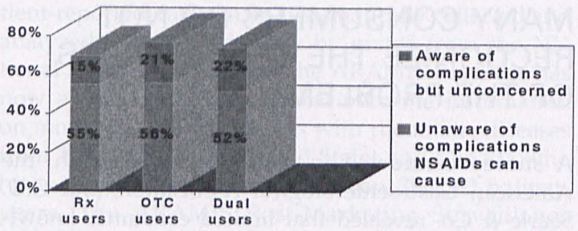

Fig. 2. Percentage of people who are unaware of NSAID-related complications in a cohort of regular NSAID users. Rx, prescription. From ref. 3, with permission.

NSAID-related GI side effects was 15%, with a 2.2% incidence of serious GI complications requiring hospitalization[3] and that as many as 81% of patients who had serious GI complications had no prior GI symptoms.[6]

WHO IS AT GREATEST RISK FOR SERIOUS GASTROINTESTINAL COMPLICATIONS?

Owing to the largely asymptomatic nature of GI side effects, determining risk factors is important. Data from many studies established a variety of risk factors including advanced age,[18–22] higher NSAID doses,[22,23] history of GI problems (eg, peptic ulcer and GI bleeding),[24–26] concomitant corticosteroid use,[24,27,28] duration of therapy,[13,23,29] and concomitant anticoagulant use.[24,30] Despite the consistent results from these studies, many are based on univariate analyses and do not take into account the interaction among multiple factors (eg, an older patient is also likely to have a longer duration of disease and is perhaps sicker with more comorbidities).

One important issue in this respect is the question of whether the risk for NSAID-related gastropathy is constant over time. Some believe that if patients are going to bleed, they will do so early in the course of therapy. Therefore, it is postulated that those patients who continue with NSAID therapy may have become tolerant and thus will have a reduced risk of developing serious GI complications. Our studies, which have followed cohorts for as long as 15 years, suggest that the risk of GI bleed (the hazard function) remains constant.[3] One of the ways of understanding this is to use the analogy of a game of darts. The probability of hitting the center of a dartboard is dependent on the number of darts thrown—the more darts that are thrown, the greater the odds. Similarly, the longer a patient takes NSAIDs, the greater the odds of a GI bleed. But, based on chance alone, the first dart can hit the center, or the second one can, or the third one can and similarly, a patient can bleed from just one tablet, or the second tablet, or the third one.

The single most important risk factor for an NSAID-related bleed is the duration of NSAID therapy; however, currently available risk factor models do not consider this exposure. Through ARAMIS it has been possible to develop Cox proportional hazard models based on life-table analysis that enable us to estimate the true risks associated with various patient characteristics. These have now evolved into a simple point-based, risk-factor algorithm called the GI SCORE (Standardized Calculator of Risks for Events) that may be used to assess a patient's risks from NSAID therapy.[3] The SCORE program has been well validated and is available from the author should more information be needed.[13,31] It is hoped that this simple scoring system will aid physicians in making informed decisions regarding the prescription of NSAID therapy, the use of prophylactic therapy, and the frequency of patient monitoring, all of which would help to reduce the incidence of serious NSAID-induced GI complications.[3]

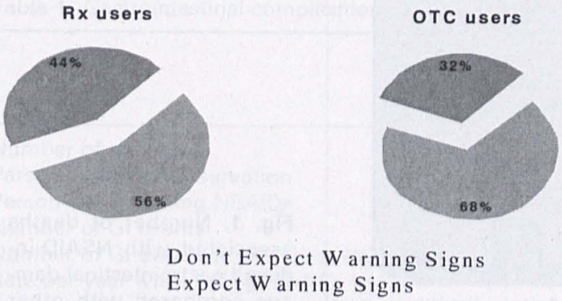

Fig. 3. Percentage of regular NSAID users who expect to experience a warning sign before a serious gastrointestinal complication. From ref. 3, with permission.

OVER-THE-COUNTER NSAIDs: AN UNDERESTIMATED PROBLEM

In the United States in 1998, 16.1 billion tablets of OTC NSAIDs were sold compared with only 2.9 billion of prescription NSAIDs. Of the more than 30 million people who regularly take NSAIDs, 40% take both prescription and OTC NSAIDs at the same time, and nearly one third of people who take prescription NSAIDs consume more than the maximum recommended doses.[3] Yet, as demonstrated earlier, there is a perception among the general public that because these drugs are available OTC, they do not carry any significant risk.

The association of prescription NSAIDs with serious GI complications has been established primarily from case-control studies. Most of these studies are based on analysis of computer databases of Medicare, Medicaid, or managed care records. Although these retrospective studies document that prescriptions have been dispensed, actual consumption cannot be determined, and the prevalence of OTC NSAID use cannot be assessed.

There are several case series demonstrating the association of prescription NSAIDs with upper GI hemorrhage, but few have specifically looked at OTC NSAIDs. In a prospective study, Wilcox and colleagues showed that in a large U.S. county hospital, 56% of 421 upper GI bleeds during 1990 to 1992 were associated with the use of NSAIDs.[32] Of the NSAID-related bleeds, 63% were associated with OTC aspirin use and 16% with OTC nonaspirin NSAID use. They state:

> In our experience, when a patient is asked generically concerning medication use, consumption of OTC preparations is often not volunteered as patients consider these OTC agents as not a drug *per se*. In addition, some patients consume non-aspirin NSAIDs as an "aspirin substitute" but are unaware of their potential gastrointestinal toxicity. Given the apparent frequency with which these OTC NSAIDs are used, these products may represent an important health hazard, particularly in patients with ulcer disease.

How important the health hazard is was brought out clearly in a recent study conducted by the American College of Gastroenterology (ACG)[33] to assess demographics, management strategies, and outcomes for patients with GI bleeding. All ACG members and Fellows were requested to send information on as many as ten bleeding patients and for ten procedure-matched controls. A total of 635 bleeders and 600 controls was studied. Among the 635 bleeders, 56.9% were taking NSAIDs and of these, 84% were taking OTC NSAIDs, with the vast majority using aspirin. Alcohol intake was also recorded. Overall, 47.6% of bleeders were taking OTC aspirin or NSAIDs compared with only 19.4% of controls. Of note is the fact that 84% of the NSAID-related GI bleeds occurred among patients taking OTC NSAIDs. These authors estimated that the odds ratio for use of OTC NSAIDs was 2.76 (confidence interval [CI] 2.03–3.74) and that of alcohol use was 2.07 (CI 1.48–2.88). When OTC NSAIDs and alcohol were used together, the relative risk increased dramatically to 4.47 (CI 2.73–7.32), showing a significant interaction. In this study, the authors showed that paracetamol did not have any significant risk, being used by only 4.4% of bleeders and 6.2% of controls, nor was there an increased GI risk for those using paracetamol and alcohol.

Blot and McLaughlin recently presented a detailed analysis of the ACG bleed registry and association with OTC NSAIDs.[34] Overall, 27% of bleeders were taking OTC dose aspirin compared with 12.0% of controls. The corresponding numbers with OTC dose ibuprofen were 10.1% and 5.8%, respectively, and those with OTC dose paracetamol were 4.5% and 6.3%, respectively. The odds ratios for a serious GI bleed with OTC dose aspirin and ibuprofen were 2.7 and 2.3—both representing a statistically significant increase in risk. The odds ratio for paracetamol was 0.9, representing a risk not statistically different from background. The odds ratios were related to the dose: ibuprofen doses of <600 mg/day had a ratio of 1.7. This increased to 3.4 in patients who took 600 to 1200 mg/day, and to 3.5 in those who took >1200 mg/day. There was a strong interaction between alcohol consumption and OTC NSAID use. Although alcohol use doubled the risk for a GI bleed, when alcohol was combined with aspirin, the risk increased to fourfold. In patients who took OTC ibuprofen and alcohol together, the risk increased to 7.1.

There are several studies on the risk of aspirin, although many do not differentiate between prescription and OTC use. In a case-control study, Levy and colleagues reported that the relative risk of occasional aspirin use (presumably OTC) in causing major upper GI bleeds was 5.6 (CI 2.7–12.0).[35] There was no increased risk with the use of paracetamol. Weil and colleagues estimate that approximately two thirds of the 10,000 episodes of ulcer bleeding in people aged 60 years and older every year in England and Wales are related to the use of NSAIDs.[36] Of these, 46% are related to aspirin use, two thirds of which is given for prophylactic purposes. According to the authors, no dose of aspirin was safe: the relative risks for daily doses of 75 mg, 105 mg, and 300 mg were 2.3, 3.2, and 3.9, respectively. In a recent study, Cryer and Feldman reported that even 10 mg aspirin substantially reduced gastric mucosal prostaglandin levels to approximately 40% of the baseline value and caused significant gastric injury.[37]

ARAMIS INVESTIGATION OF OVER-THE-COUNTER DOSE NSAIDs

Using the ARAMIS database, we conducted a prospective observational noninterventional study in a large group of RA patients taking OTC doses of

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