

Nonsteroidal Anti-Inflammatory Drug-Associated Gastropathy: Incidence and Risk Factor Models

JAMES F. FRIES, M.D., CATHERINE A. WILLIAMS, M.A., DANIEL A. BLOCH, Ph.D.,
BEAT A. MICHEL, M.D., *Stanford, California*

PURPOSE: The most prevalent serious drug toxicity in the United States is increasingly recognized as gastrointestinal (GI) pathology associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The incidence of serious GI events (hospitalization or death) associated with NSAID use was therefore prospectively analyzed in patients with rheumatoid arthritis (RA) and patients with osteoarthritis.

PATIENTS, METHODS, AND RESULTS: The study consisted of 2,747 patients with RA and 1,091 patients with osteoarthritis. The yearly hospitalization incidence during NSAID treatment was 1.58% in RA patients and was similar in all five populations studied. The hazard ratio of patients taking NSAIDs to those not taking NSAIDs was 5.2. The incidence in osteoarthritis may be less. The risk of GI-related death in RA patients was 0.19% per year with NSAIDs. Multivariate analyses assessing risk factors for serious GI events were performed in the 1,694 (98 with an event) RA patients taking NSAIDs at the predictive visit. The main risk factors were higher age, use of prednisone, previous NSAID GI side effects, prior GI hospitalization, level of disability, and NSAID dose. A rule is presented that allows estimation of the risk for the individual patient with RA.

CONCLUSION: Knowledge of the risk factors for NSAID-associated gastropathy and their interrelationships provides a tool for identification of the patient at high risk and for initiation of appropriate therapeutic action.

From the Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, California. This work was supported by a grant from the National Institutes of Health (AR21393) to ARAMIS (the Arthritis, Rheumatism, and Aging Medical Information System) and in part by a grant from Searle Laboratories.

Requests for reprints should be addressed to James F. Fries, M.D., 1000 Welch Road, Suite 203, Palo Alto, California 94304.

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Gastrointestinal (GI) pathology associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is increasingly recognized as the most prevalent serious drug toxicity in the United States, resulting in an estimated 2,600 deaths and 24,000 hospitalizations annually in patients with rheumatoid arthritis (RA) alone [1,2]. The predominant syndrome consists of antral prepyloric ulcers, which may eventuate in GI hemorrhage or perforation, although events in the duodenum, small bowel, and the large bowel are also seen. Ulcerations visible on endoscopy have a point prevalence of 10% to 25%, and severe erosions are seen in additional patients [3-5]. The risk of GI hospitalization has been estimated at 1% to 1.5% per year in persons taking NSAIDs [1], and the risk of death is approximately 0.13% per year in individuals treated with NSAIDs [1,6,7]. The importance of the syndrome has been emphasized by gastroenterologists [3,8,9], rheumatologists [2,5,10], and the Food and Drug Administration (FDA) [11].

Important information required for estimation of the magnitude of the problem and for development of strategies for resolution, however, has been lacking. For example, the prevalence of complications in conditions other than RA, such as osteoarthritis, has not been established. Generalizability of the observations to different practice sites has not been presented. Quantitation of likely risk factors such as prior bleeding has not been reported, and the frequency of deaths has not been confirmed by prospective study. Most importantly, while individual risk factors have been suggested by a number of investigators [1,12,13], no multivariate risk factor model that permits estimation of risk in the individual patient has been presented.

This report addresses these issues in two steps: (1) with descriptive analyses of 2,747 patients with RA followed prospectively for an average of 4 years at five ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) data bank centers [14,15] and 1,091 patients with osteoarthritis, and (2) with risk factor analyses based on the 1,694 of these RA patients taking NSAIDs at the predictive visit.

TABLE I
Rheumatoid Arthritis Gastrointestinal (GI) Hospitalization by Center

	Center					
	All Centers	Santa Clara	Saskatoon	Phoenix	Stanford	Wichita
Number of patients	2,747	302	679	307	379	1,080
Person-years of observation	9,525	1,632	2,468	1,016	1,318	3,091
Person-years taking NSAIDs	6,741	1,122	1,712	720	903	2,284
GI hospitalizations						
Number of patients	116	13	34	14	16	39
Rate per person-year (%)	1.22	0.80	1.38	1.38	1.21	1.26
Number taking NSAIDs	107	13	30	13	15	36
Rate per year while taking NSAIDs (%)	1.58	1.16	1.75	1.81	1.66	1.58
Number of years of observation after 1st hospitalization	201	24	73	22	27.5	54.5
Number of additional GI hospitalizations while taking NSAIDs	10	2	4	0	2	2
Rate for at least one more GI hospitalization per year while taking NSAIDs (%)	4.98	8.33	5.48	0.00	7.27	3.66
Number of patients with upper GI hospitalizations	95	13	27	11	13	31
Rate of upper GI hospitalizations per year while taking NSAIDs (%)	1.41	1.16	1.58	1.53	1.44	1.36
Number of patients with lower GI hospitalizations	12	0	3	2	2	5
Rate of lower GI hospitalizations per year while taking NSAIDs (%)	0.18	0	0.18	0.30	0.22	0.22

PATIENTS AND METHODS

Two thousand seven hundred and forty-seven patients with RA consecutively enrolled and followed at five ARAMIS centers, for a total of 9,525 years of observation, were available for study (Table I). The Santa Clara County population of 302 patients represents a community population recruited by advertisement. The other populations were formed by consecutive patient accrual at the site. The 679 Saskatoon patients are believed to make up the great majority of patients in Northern Saskatchewan province, the 307 Phoenix patients were drawn from a rheumatology private practice, as were the 1,080 Wichita patients, and the 379 Stanford patients were enrolled from a tertiary care referral center. Data are collected in two modes. First, all routine clinical data including diagnosis, symptoms, signs, demographics, past history, laboratory tests, and treatment are entered for each patient encounter and hospitalization. Second, patients complete the Health Assessment Questionnaire (HAQ) [1,16-18] at 6-month intervals, providing validated self-report of disability, discomfort, drug toxicity, and economic impact. All hospitalizations and deaths are audited by abstraction of discharge summaries and NSAID usage at time of event confirmed. Deaths are reviewed by death certificate discharge summary and recent clinical notes. The system, procedures, and validation techniques have been previously described [2,14-18].

The dependent variable in this study was "GI event," consisting of an event sufficiently serious as

to result in hospitalization or death. Events are counted only when they are the primary basis for hospitalization or death, not if they occurred during a hospitalization or as part of a terminal illness sequence. Patients are considered to be taking NSAIDs if they report on the HAQ immediately prior to the event that they are taking any one of the following drugs: aspirin, naproxen, ibuprofen, piroxicam, indomethacin, sulindac, meclofenamate, tolmetin, fenoprofen, ketoprofen, nonacetylated salicylates, salsalate, diflunisal, or diclofenac.

For risk factor delineation, items considered were those available at the HAQ prior to the event—the predictive visit. Patients had had from one to 13 6-month periods of observation. Obviously, patients analyzed for risk factors for NSAID gastropathy were required to be taking an NSAID at the predictive visit. Among the 130 patients with GI events, 32 patients were not included in the analysis because they were not taking NSAIDs at the predictive visit, or did not have HAQ data within 9 months prior to the event. Therefore, 98 patients with GI events were available for comparison with patients without GI events (controls). Similarly, of the 2,617 (2,747 minus 130) patients eligible as controls, 1,021 were excluded because they did not meet one or more of the above criteria. By definition, the non-event group could not have a GI event; however, control patients' records were randomly truncated to match the number of 6-month periods in which events occurred in patients with GI events. For example, 5% of the GI events occurred at the seventh

TABLE II
Variables Associated with Gastrointestinal (GI) Hospitalization or Death at Predictive Visit

	GI Events (n = 98)		No GI Events (n = 1,596)		p Value
	Number Defined	Mean (SE)	Number Defined	Mean (SE)	
Continuous variables					
Age (years)	98	65.47 (1.05)	1,596	58.65 (0.33)	<0.001
Education level (years)	95	11.94 (0.25)	1,525	12.50 (0.07)	0.06
Disease duration (years)	98	18.75 (1.20)	1,583	16.86 (0.28)	0.11
Disability index (0-3)	98	1.69 (0.08)	1,596	1.38 (0.02)	<0.001
Smoking (packs/day)	75	0.10 (0.04)	1,287	0.17 (0.01)	0.08
Alcohol (drinks/day)	92	0.20 (0.08)	1,529	0.44 (0.12)	0.09
Specialty care	98	0.53 (0.04)	1,558	0.59 (0.01)	0.15
NSAID dose (see text)	95	1.03 (0.06)	1,582	0.91 (0.01)	<0.05
Number of DMARDs	93	0.45 (0.06)	1,583	0.56 (0.01)	0.07
Number of H ₂ -antagonists	74	0.28 (0.05)	1,314	0.09 (0.01)	<0.001
Number of antacids or H ₂ -antagonists	93	0.53 (0.07)	1,583	0.22 (0.01)	<0.001
Categorical variables (% positive)					
Female sex	98	76.5	1,596	76.7	0.97
White race	95	98.9	1,545	94.5	0.06
Smoker	75	10.7	1,287	17.2	0.14
Alcohol	92	13.0	1,529	18.2	0.21
NSAID GI side effect ever	93	32.3	1,583	18.6	<0.001
Prednisone	93	51.6	1,583	31.0	<0.001
Antacids	74	20.3	1,312	10.1	<0.01
H ₂ -antagonists	74	28.4	1,314	9.1	<0.001
Antacids or H ₂ -antagonists	93	40.9	1,583	19.2	<0.001

6-month observation period and, therefore, prediction was made using information at the sixth observation period; similarly, a random 5% of the control subjects were analyzed at the sixth observation period as predictive of an "event" at the seventh observation period. This method was applied to each of the 13 possible 6-month observation periods to adjust for differences that would otherwise have been present in the amount of data available for prediction in cases and controls. The mean time interval between the predictive data at the HAQ prior to the event and the HAQ associated with the event was 6.1 months.

Univariate analyses were performed using a t-test for 11 continuous variables and by using a chi-square test on 2 × 2 tables for nine binary variables. The p values are those computed for each individual comparison and may be adjusted for multiple comparisons by the Bonferroni adjustment. All variables statistically significant as predictors at the 0.05 level (two-tailed) and several additional variables considered as potentially important were further analyzed by multivariate analyses. Stepwise multiple logistic regression and recursive partitioning (classification and regression tree) analyses were employed [19].

RESULTS

Incidence

Of the 2,747 RA patients available for study, 130 had GI events sufficiently serious to result in hospitalization or death. When hospitalizations were tabulated in these 130 patients, 116 patients had

128 hospitalizations (10 patients had two hospitalizations and one patient had three) and 17 had GI-related deaths. Among the 17 GI deaths, three patients had had prior GI hospitalizations. Data presented in Table I describe the 116 hospitalization events (the last event among patients with multiple hospitalizations). Data subsequently presented in Tables II through VI result from analysis of the last GI event (death or hospitalization). Fourteen patients had previous GI events (three pa-

TABLE III
Odds Ratios for Selected Variables with Respect to Gastrointestinal (GI) Hospitalization or Death

Variable	Odds Ratio	95% Confidence Interval
Female sex	1.0	0.61-1.60
White race	5.5	0.75-39.73
Smoker	0.6	0.27-1.22
Alcohol	0.7	0.36-1.25
Prior GI complaint	2.1	1.32-3.27
Prednisone	2.4	1.56-3.62
Antacid	2.3	1.25-4.12
H ₂ -antagonist	3.9	2.30-6.76
Antacid or H ₂ -antagonist	2.9	1.89-4.48
NSAID dose > 1.0 (see text)	1.4	0.87-2.11
Age		
> 45 years	7.0	2.21-22.35
> 50 years	4.4	2.01-9.52
> 60 years	2.7	1.70-4.30
> 65 years	2.4	1.56-3.55
> 70 years	2.0	1.30-3.08
> 75 years	2.2	1.28-3.85
Disability index (0-3)		
> 1	1.8	1.13-2.95
> 2	1.9	1.23-2.91

TABLE IV

Risk Factors for Gastrointestinal (GI) Complications Related to Hospitalization or Death: Stepwise Logistic Regression

Step Number	Variable	Coefficient (SE)	Improvement p Value	Odds Ratio	95% Confidence Interval for Odds Ratios
1	Age (years)	0.047 (0.01)	<0.0001	1.05:1 per year	1.03-1.07
2	Prednisone	0.35 (0.11)	<0.0001	1.42:1 yes/no	1.15-1.76
3	Previous NSAID GI side effect	0.39 (0.12)	0.001	1.48:1 yes/no	1.18-1.86
4	NSAID dose	0.29 (0.18)	0.07	1.34:1 per unit	0.95-1.90
5	Disability index (0-3)	0.19 (0.14)	0.18	1.21:1 per unit	0.92-1.59

tients with GI-related deaths who had previous GI hospitalizations, and 11 patients with multiple GI hospitalizations).

Of the 116 last hospitalizations, 107 occurred while patients were taking NSAIDs. Ninety-five of these were noted as upper GI problems on discharge summaries, and 82 of these were gastric in location. Twelve were localized to the lower GI tract. The overall rate of GI hospitalizations per year of observation was 1.2%. During periods when NSAIDs were

being taken, the overall frequency was 1.58% per year. When the analysis was limited to upper GI hospitalizations, the rate during treatment with NSAIDs was 1.4% per year.

Table I breaks down these hospitalizations by data bank center to evaluate the generalizability of the observations. The percentage of GI hospitalizations per year during NSAID treatment ranged from 1.2% in Santa Clara County to 1.8% in Saskatoon and in Phoenix. Upper GI hospitalizations

TABLE V

Characteristics of Classification Tree Subgroups with Respect to Gastrointestinal (GI) Hospitalization or Death

Subgroup Number	Characteristics	Number of Patients GI/No GI Event	Percent of Patients with GI Event	GI Event Rate per Year Taking NSAIDs (%)
1	Age 76 years or older, no prednisone	12/79	13.2	4.2
2	Age 48 years or older, taking prednisone, disease duration > 3.7 years, disability index > 1.7	33/199	14.2	3.9
3	Age 48 to 63 years, previous NSAID side effects, disability index > 1.3	7/36	16.3	3.8
4	GI event group: 10 second events out of 98 (10.2%)			3.1
5	Age 48 years or older, taking prednisone, disease duration > 3.7 years, disability index 0.3 to 1.7	13/148	8.1	2.2
6	Age 63 to 76 years, no prednisone	27/369	6.8	1.9
7	Age < 47 years	3/342	0.9	0.3
8	Age 47 to 63 years, no prednisone, never NSAID side effects	3/340	0.9	0.3
9	Age 47 to 63 years, previous NSAID side effects, disability index ≤ 1.3, no prednisone	0/37	0	0
10	Age 47 years or older, taking prednisone, disease duration ≤ 3.7 years	0/24	0	0
11	Age 47 years or older, taking prednisone, disease duration > 3.7 years, disability index ≤ 0.3	0/22	0	0

TABLE VI
Description of Selected Variables Within Subgroups of Tree (Figure 1)*

	Subgroup Number (GI Event Group)											
	All	1	2	3	4	5	6	7	8	9	10	11
Number of patients	1,694	91	232	43	98	161	396	345	343	37	24	22
Variables												
Age (years)	59 (0.3)	79 (0.3)	65 (0.6)	57 (0.7)	65 (1.1)	63 (0.6)	69 (0.2)	39 (0.3)	56 (0.2)	57 (0.6)	66 (1.8)	64 (1.7)
Disease duration (years)	17 (0.3)	18 (1.2)	21 (0.7)	16 (1.5)	19 (1.2)	19 (0.9)	20 (0.7)	12 (0.4)	17 (0.5)	15 (0.1)	2 (0.2)	15 (0.02)
Disability index (0-3)	1.4 (0.02)	1.7 (0.1)	2.3 (0.02)	1.9 (0.07)	1.7 (0.1)	1.2 (0.03)	1.5 (0.04)	1.1 (0.04)	1.2 (0.04)	0.7 (0.1)	1.5 (0.2)	0.1 (0.02)
Previous NSAID-related GI side effects (%)	20	13	20	100	32	14	20	24	0	100	8	23
NSAID dose (see text)	0.9 (0.01)	0.8 (0.1)	1.0 (0.03)	1.0 (0.1)	1.0 (0.1)	0.9 (0.04)	0.9 (0.03)	0.9 (0.03)	1.0 (0.03)	1.0 (0.1)	1.3 (0.2)	0.8 (0.1)
Use of prednisone	30	0	100	0	52	100	0	29	0	0	100	100
Use of antacids or H ₂ -antagonists (%)	20	20	35	26	41	28	21	15	11	24	21	27
Time taking NSAIDs (months)	41 (0.5)	38 (2.2)	43 (1.3)	51 (3.3)	40 (2.1)	43 (1.6)	43 (1.1)	38 (1.1)	41 (1.2)	45 (3.2)	16 (1.2)	35 (4.0)

*Values are means (SE).

ranged from 1.2% per year with NSAID treatment in Santa Clara County patients to 1.6% in Saskatoon. Results at all centers were similar, without statistically significant differences.

Table I also lists patients taking NSAIDs who were hospitalized more than once. One subject was hospitalized three times. After the first hospitalization, the 10 additional hospitalizations occurred in only 201 years of observation, for a rate of 5% for at least one more GI hospitalization per year during treatment with NSAIDs. This rate varied from 0% in Phoenix to 8.3% in Santa Clara County. This overall rate of rehospitalization is approximately four times the rate of first hospitalization.

There were 17 GI-related deaths occurring during these 9,525 years of observation. Thirteen of these deaths occurred in patients who were reliably known to be taking NSAIDs at the time of death; each of the others might have been. This gives an overall GI death rate of 0.18% per year and a GI death rate during known treatment with NSAIDs of 0.19% per year.

Risk Factor Analyses

Table II lists continuous variables analyzed univariately for their association with serious GI events (hospitalization or death) for patients having taken NSAIDs at the predictive visit. The number of subjects reflects the inclusion criteria previously described. The most significant differences were obtained for age, HAQ disability index, NSAID dose, and use of antacids or H₂-antagonists. The difference in HAQ disability scores of 0.31 is clinically significant, representing the equivalent of 4 years of disease progression in RA. NSAID dose was calcu-

lated by setting a value of 1.00 for the manufacturer's highest recommended dose on the package insert and normalizing the dose of each patient to this standard. Thus, the value 1.03 means that patients with events, on average, were taking 103% of the manufacturer's highest recommended dose. "DMARDs" refers to prior use of "disease-modifying antirheumatic drugs." The variable "specialty care" refers to the proportion of all doctor visits that were made to rheumatologists.

The second part of Table II presents univariate comparisons of potentially predictive categorical variables dichotomized as present or absent (presented as percent positive). The statistically most significant differences were seen for having previously reported GI symptoms attributed to use of an NSAID (nausea, heartburn, loss of appetite, vomiting, or upper abdominal pain), use of prednisone (average dosage 7 mg/day) in the previous 6 months, and use of antacids or H₂-antagonists within 9 months of the event. Female sex was not predictive. Race was not predictive, nor was cigarette smoking or alcohol use, although these analyses were limited in power because of small numbers of nonwhites, smokers, and heavy drinkers. Eight of the 10 statistically significant ($p < 0.05$) differences remain significant after adjustment for the 20 multiple comparisons of Table II.

Odds ratios for selected variables with respect to GI events along with 95% confidence intervals are shown in Table III. For example, the odds ratio for females was obtained as follows: the proportion of females with GI events was 75 of 98 = 76.5%; thus, the odds are $76.5/(100 - 76.5) = 3.26$. Similarly, the proportion of females without GI events was 1,224

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