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Gastroprotective Therapy and Risk of Gastrointestinal Ulcers: Risk Reduction by COX-2 Therapy

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ABSTRACT. ***Objective.*** Proton pump inhibitors (PPI) and misoprostol decrease the risk of development of nonsteroidal antiinflammatory drug induced gastric ulcers and aid healing of upper gastrointestinal (GI) ulcers. H2 receptor antagonists (H2RA) are less effective for this task, but are widely used by patients and physicians for the treatment of GI symptoms and duodenal ulcers. Sucralfate is a weaker agent that is sometimes used for prophylaxis or treatment of upper GI ulcers. We investigated the effect of GI drugs and selective and nonselective NSAID on the incidence of GI ulcer development in a cohort of patients immediately after the release of celecoxib and rofecoxib to investigate the effect of confounding by indication when effective GI agents and cyclooxygenase 2 (COX-2)-specific inhibitors are prescribed to a high risk population.

Methods. During a 6 month period of observation 8547 NSAID users were evaluated by mailed questionnaire concerning NSAID drug use and ulcer development. In the first half of 1999, patients took 12,177 separate NSAID courses. GI therapy that followed the development of upper GI ulcers was excluded from analysis. Ulcer reports were confirmed by followup validation.

Results. GI drugs were used concomitantly in this population by 42% of patients using an NSAID. GI drugs were associated with an increased risk of ulcer. But this risk was confined to PPI (OR 4.1, 95% CI 2.95, 5.69), and not to other GI drugs. Overall, patients using nonselective NSAID compared to those taking COX-2-specific inhibitors had an increased risk of upper GI ulcers (OR 2.12, 95% CI 1.43, 3.34). Patients taking nonselective NSAID plus PPI were also at increased risk for upper GI ulcers compared to those taking nonselective NSAID alone (OR 5.09, 95% CI 3.88, 6.67). Similarly, the risk of upper GI ulcers was increased in the nonselective NSAID plus PPI group (OR 3.83, 95% CI 2.32, 6.31) compared to the COX-2 plus PPI group.

Conclusion. PPI use, but not other GI drug use, is a marker for increased susceptibility to ulcers among NSAID users. This risk of upper GI ulcers is increased in PPI users regardless of which NSAID is used (nonselective or COX-2-specific inhibitor). Although COX-2 use is associated with greater risk factors for upper GI ulcers due to channeling bias, COX-2 users have significantly fewer ulcers than equivalent nonselective NSAID users regardless of concomitant PPI utilization. (J Rheumatol 2002;29:467–73)

Key Indexing Terms:
CYCLOOXYGENASE-2 UPPER GASTROINTESTINAL ULCERS
PROTON PUMP INHIBITORS H2 BLOCKERS RISK

Nonsteroidal antiinflammatory drugs (NSAID) are associated with the development of gastrointestinal (GI) ulcers[1-9]. Various GI therapies have been employed by physicians and patients for the prophylaxis and treatment of upper GI ulcers and symptoms in patients using NSAID, including histamine receptor antagonists (H2RA), proton pump inhibitors (PPI), barrier agents, and prostaglandin analogs. Overall, the prevalence of GI therapy among patients taking prescription NSAID has been reported to range from 26% in Canada to 24–34% in the US[10,11]. H2RA and PPI are the most commonly used gastroprotective agents. In addition to NSAID, additional risk factors for gastroduodenal ulcers have been identified. These factors include age, history of previous upper GI ulcers, GI symptoms, decreased functional ability, corticosteroid and oral anticoagulant use, and heart disease, among others[8,12-21]. At least 2 types of risk factors have been identified and should be considered. The first is biologically based and is related to toxic effects of drugs or to host susceptibility. The use of NSAID and corticosteroids and a history of previous ulcers are examples of this first type of risk factor.

The second type of risk factors are confounder effects, as opposed to causal risk factors. One such confounder is the use of drugs to treat or prevent upper GI ulcers. This is para-

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doxical, of course, for treatments with misoprostol, PPI, and high dose H2RA have been shown to reduce the risk of upper GI ulcers in NSAID users[22-26]. Martin, *et al* studied 19,087 patients in England who were prescribed meloxicam between December 1996 and March 1997, and inquired about adverse events experienced within 6 months of the first meloxicam prescription[27]. Patients receiving gastroprotective agents had an increased rate ratio for peptic ulcers (2.9, 95% CI 1.0, 8.4) compared to those who were not. The definition of gastroprotective agents in this study included PPI, H2RA, and misoprostol. Singh and Ramey reported on 1921 patients with rheumatoid arthritis (RA), among whom H2RA, sucralfate, or antacids were used by 34%[28]. They found no reduction in the risk of GI events by the use of these drugs, but suggested that "symptomatic patients started on antacid or H2 antagonist therapy have a higher risk of serious GI complications compared with those who did not take these medications." They did not provide rates or confidence intervals, and they did not study PPI. Considering short and longterm use, PPI are the most effective drugs in the prevention and treatment of NSAID induced ulcers, and along with misoprostol are the most effective cotherapy for the prevention of NSAID induced ulcer[22,23,29].

Confounders, such as GI drugs, are of particular interest because they help us understand factors that might make effective treatments appear ineffective. In addition, confounders can be used to stratify patients by their risk profile before examining the effect of biologically based risk factors. We recently studied channeling bias and confounding by indication following the introduction of celecoxib and rofecoxib. We showed that patients switched to COX-2-specific inhibitors had a history of more severe rheumatic symptoms, lifetime GI adverse events, and GI drug utilization at the time of switch compared to those who were not switched to COX-2-specific inhibitors[30]. Channeling bias is a form of allocation bias, and occurs when drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences[31,32]. For example, in the early days of methotrexate (MTX) usage, MTX was prescribed to RA patients with the worst prognosis. Although MTX improved such patients, the underlying severity of their illnesses outweighed the effectiveness of MTX; MTX appeared not to work well and was a marker for poor outcome. Channeling may lead to another form of bias, confounding by indication[33-36]. This occurs when the indication for the drug prescription results in preferential identification of the patients with the condition and, at the same time, increases the risk of the outcome under study.

We investigated the association of upper GI ulcers with GI drugs and the interaction of GI drugs with COX-2 and nonspecific NSAID in the development of upper GI ulcers in 8547 patients with arthritis during 12,177 courses of therapy. We found that PPI, but not other GI drugs, are a risk marker for upper GI ulcers, and that COX-2-specific inhibitors reduce the risk of upper GI ulcers in those receiving and not receiving GI drugs.

MATERIALS AND METHODS

Study population. Patients in this study are participants in the National Data Bank for Rheumatic Diseases and were enrolled by 581 US rheumatologists[37]. In this project 1342 patients were recruited from the practices of US rheumatologists during a 30 day enrollment period[38]; 3760 were enrolled from community rheumatologists who made their patient populations available to us; 1759 were enrolled at the time they were prescribed leflunomide by community rheumatologists as part of their ordinary medical care; and 1686 were patients followed in the Wichita data bank. The characteristics of the Wichita data bank have been described[39-41]. Patients in this study were 8547 patients with arthritis, including 6375 with RA, and 2172 with fibromyalgia (FM) or osteoarthritis (OA) who were participating in the data bank surveys. Diagnoses were made by the referring rheumatologists. The survey period covered January 1999 through June 1999, after the introduction of celecoxib and in part after the introduction of rofecoxib to the US market.

Demographic and clinical data. In the survey, patients were asked to list all drugs used during the study period. In addition, they listed the start and stop dates of drugs, and the specific side effects attributed to each drug, if any. Doses were recorded for all NSAID, but not for GI drugs. For the purposes of this study, upper GI ulcers were ulcers reported by patients as side effects to a specific medication. Each ulcer was subject to followup validation in which patients were contacted and supporting medical records were obtained. We were able to confirm the patient self-report in ~95% of cases by hospital, endoscopy, and physician report records. We found no instances in which the records refuted the patient self-report.

Although the terminology associated with GI drugs differs among studies, in this report we define gastroprotective agents to include sucralfate and misoprostol and separate these drugs from H2RA and PPI. We combined sucralfate and misoprostol because of their infrequent use, despite evidence of a superior efficacy of misoprostol[42]. The effect of these 2 drugs on ulcer prevention is entirely different.

As part of the survey assessment, demographic and utilization variables were collected. Study variables also included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)[43,44], a visual analog scale (VAS) for pain, a VAS for global disease severity, and the SF-36 mental and physical component scales (MCS and PCS)[45]. The MCS and PCS scores have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the US population. Scores above 50 represent better than average health. Additional details and normative data are available[46]. Except for the SF-36 scores, where higher scores mean better health, higher scores represent worse health/more symptoms.

Statistical methods. GI therapy that followed the development of upper GI ulcers was excluded from analysis. Because Arthrotec (diclofenac plus misoprostol) includes a GI protective agent, this drug was excluded from analysis, excepted as described in the text.

In regression analyses in Table 6, adjustment was made for NSAID dose after transforming reported doses into a proportion of the recommended or usual drug dose.

Data were analyzed using logistic regression. The rates of ulcers and GI therapy among the 4 referring sources were similar, and it was judged appropriate to pool the data sources for analysis. In these analyses, we adjusted for within-patient clustering using the Huber/White/sandwich estimator of variance since each patient contributed 6 units of observation for each month of followup. Clustering specifies that the observations are independent across groups (clusters), but not necessarily within groups[47]. All analyses were conducted using Stata software[47]. Because the 8547 patients

had 12,177 individual courses of NSAID therapy, case weights were assigned such that the total weight given to each patient was 1. Statistical significance was set at 0.05 and all tests were 2 tailed.

RESULTS

Demographic and clinical status variables. Table 1 presents patients' basic demographic and clinical status variables.

Use of GI drugs. As shown in Table 2, use of GI drugs among the cohort of NSAID users was common. Excluding antacids that were used by 26% of patients, GI drugs were used by 42% of arthritis patients. The most common class of drug was H2RA (23.8%), followed by PPI (19.9%). Only a few patients were taking gastroprotective agents, including misoprostol 3.6% and sucralfate 1.2%. The distribution of drug usage was similar among the patients with RA and those with OA/FM.

NSAID usage. During the 6 month period of observation the 8547 NSAID users took 12,177 separate NSAID courses. A course is defined as the continued use of a particular NSAID until a switch occurs or the study period ends. Slightly more than 70% used one NSAID; 22.1% used 2 NSAID sequentially, 5.6% used 3 NSAID sequentially, and 2.9% used 4 or more NSAID sequentially.

As shown in Table 3, the 4 most commonly used NSAID were celecoxib, ibuprofen, naproxen, and nabumetone. They accounted for 20.5%, 19.1%, 13.1%, and 9.1% of the 12,177 courses, respectively. Celecoxib and rofecoxib together (COX-2-specific inhibitors) accounted for 3242 courses (26.6%), and nonspecific NSAID accounted for 8935 courses (73.4%). Median doses for each drug are displayed in Table 3.

Upper GI ulcers and association with treatment variables. Upper GI ulcers occurred in 94 or 0.77% of courses, and in 90 of the 8547 patients (1.05%). We evaluated the risk of upper GI ulcers, comparing patients taking GI drugs to those who were not (Table 4). We found no association between prior H2RA or gastroprotective agents and the risk of ulcers. However, there was a very strong risk (OR 4.1, 95% CI 2.95, 5.69) with the use of PPI. This risk was carried over to GI drugs in general (OR 2.86, 95% CI 1.86, 4.42) compared to those no receiving GI drugs.

To understand the relationship between the newer COX-2-specific inhibitors and GI drugs, we analyzed the various combinations of these agents. In doing these analyses we adjusted for NSAID dose (Table 3). First, COX-2 therapy compared to nonselective NSAID therapy was associated with reduced risk of upper GI ulcers (OR 0.45, 95% CI 0.30, 0.70). We next considered the various combination of NSAID and GI drugs (Table 5). Using patients taking nonselective NSAID and no GI drugs as the baseline category,

Table 1. Basic demographic and clinic status data on 8547 patients with arthritis.

Variable	Mean or %	SD
Age, yrs	59.55	12.72
Sex, % male	20.30	
White, (%)	92.26	
Education level, yrs	13.48	2.29
Total income, $US	44,890.14	28,147.31
HAQ disability (0–3)	1.05	0.70
VAS pain (0–10)	4.05	2.75
SF-36 physical component score	30.07	8.65
SF-36 mental component score	43.73	13.57
Lifetime history of upper GI ulcers, %	16.71	
Lifetime history of myocardial infarction,%	5.24	
Any GI symptoms, %	47.94	
Epigastric or abdominal pain	23.55	
Prednisone use, %	39.4	

GI: gastrointestinal, HAQ: Health Assessment Questionnaire, VAS: visual analog scale.

Table 2. GI agents used by 8547 patients with arthritis.

GI Drug	All, N = 8547,%	RA, N = 6375, %	OA, FM N = 2172, %
Sucralfate	1.22	1.22	1.20
Misoprostol	3.63	4.17	2.03
Lansoprazole	6.66	6.57	6.91
Omeprazole	14.23	13.96	15.01
All gastroprotective agents	4.77	5.32	3.18
All proton pump inhibitors	19.89	19.53	20.95
H2RA	23.75	22.89	26.29
Antacids	26.09	24.22	31.58
Any one of PPI, H2RA, sucralfate, or misoprostol	41.99	41.21	44.29
Diclofenac + misoprostol	6.59	5.68	9.25

H2RA: H2 receptor antagonist, PPI: proton pump inhibitor.

Table 3. The use of NSAID in 12,177 courses by 8547 patients with arthritis between January 1999 and June 1999.

NSAID	% of Courses	Median Dose, mg
Celecoxib	22.50	200
Ibuprofen	19.09	600
Naproxen	13.06	750
Nabumetone	9.12	1000
Diclofenac	5.54	75
Oxaprozin	5.00	1200
Diclofenac + misoprostol	4.62	75
Rofecoxib	4.12	25
Etodolac	4.04	500
Ketoprofen	2.61	200
Sulindac	2.52	200
Salsalate	2.33	1500
Piroxicam	2.09	20
Indomethacin	1.38	75
Flurbiprofen	0.93	600
Tolmetin	0.53	600
Meclofamate	0.32	100
Fenoprofen	0.19	600

Table 4. The association of GI drugs with risk of GI ulceration among users of selective and nonselective NSAID.

Drug Group	OR	SE	T	p	Lower 95% CI	Upper 95% CI
No GI drugs	1.0	—	—	—	—	—
Any GI drug(s)	2.86	0.63	4.76	0.000	1.86	4.42
Proton Pump inhibitors	4.10	0.69	8.42	0.000	2.95	5.69
H2RA	1.07	0.21	0.36	0.722	0.73	1.57
Gastroprotective agents	0.79	0.29	–0.65	0.517	0.38	1.62

H2RA: H2 receptor antagonists. Gastroprotective agents: misoprostol and sucralfate.

Table 5. Distribution of COX-2 drugs and GI drugs.

Combination	N	%
Nonselective NSAID, no GI drug	5198	42.69
Nonselective NSAID + GI drugs	3737	30.69
COX-2-specific inhibitor, no GI drugs	1530	12.56
COX-2-specific inhibitor + GI drugs	1712	14.06
Non selective NSAID, no PPI	7228	59.36
Non selective NSAID + PPI	1707	14.02
COX-2-specific inhibitor, no PPI	2260	18.56
COX-2-specific inhibitor + PPI	982	8.06

Nonselective NSAID: nonselective COX agents containing varying degrees of nonselective NSAID and COX-2 activity. COX-2-specific inhibitors: celecoxib and rofecoxib. PPI: proton pump inhibitors. GI drugs: proton pump inhibitors, H2RA, sucralfate, misoprostol.

Table 6 (2 regression analyses) shows that the use of PPI together with nonselective NSAID was associated with a strong increase in the risk of upper GI ulcers compared to those not taking PPI, with OR > 5. COX-2 specific inhibitors had a lower risk of ulcers, in the subgroups without GI drugs (OR 0.32, compared to NSAID users without GI drugs) and in the COX-2 subgroup without PPI (OR 0.52, compared to NSAID users without PPI). However, these reductions in ulcers did not reach statistical significance in this analysis. Compared with the COX-2 (+), PPI (+) group, the risk of upper GI ulcers was increased in the nonselective NSAID plus PPI group (OR 3.83, 95% CI 2.32, 6.31). Rates of GI ulceration per 100 patients per 6 month period are also described in Table 6.

Results for all GI drugs combined were similar to the PPI analyses shown in Table 6, but were attenuated owing to the lack of contribution from the H2 and gastroprotective agents. Arthrotec (diclofenac plus misoprostol) was excluded from these analyses, but had a nonsignificant association with upper GI ulcers (OR 1.70, 95% CI 0.81, 3.59).

DISCUSSION

The results of this study confirm reports that use of GI drugs is associated with an increased risk of upper GI ulcers, even though many of these agents are known to be effective in the

Table 6. The association between NSAID, GI drugs, and the risk and rates of GI ulceration. Rates are per hundred patients per 6 month period.

Drug Grouping	OR	p	Lower 95% CI	Upper 95% CI	Rate	Lower 95% CI	Upper 95% CI
Analysis 1							
Nonselective NSAID no GI drug	1.0	—	—	—	0.004	0.003	0.005
Nonselective NSAID + GI drugs	2.93	0.000	1.90	4.50	0.011	0.009	0.014
COX-2 + no GI drugs	0.32	0.204	0.05	1.87	0.001	0.000	0.007
COX-2 + GI drugs	1.27	0.144	0.92	1.74	0.005	0.005	0.006
Standardized dose	1.45	0.133	0.89	2.36			
Analysis 2							
Nonselective NSAID no PPI	1.0	—	—	—	0.004	0.003	0.005
Nonselective NSAID + PPI	5.09	0.000	3.88	6.67	0.021	0.017	0.026
COX-2 + no PPI	0.52	0.216	0.19	1.46	0.002	0.001	0.005
COX-2 + PPI	1.33	0.218	0.85	2.09	0.006	0.003	0.010
Standardized dose	1.48	0.128	0.89	2.44			

Nonselective NSAID: nonselective COX agents containing varying degrees of nonselective NSAID and COX-2 activity. COX-2-specific inhibitors: celecoxib and rofecoxib. PPI: proton pump inhibitors. GI drugs: proton pump inhibitors, H2RA, sucralfate, misoprostol.

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