Gastrointestinal Prophylactic Therapy Among Patients with Arthritis Treated by Rheumatology Specialists

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ABSTRACT. ***Objective.*** To determine rates of gastroprotective agent (GPA) use among patients with arthritis treated by rheumatologists, and to determine factors associated with GPA prescription.

Methods. In a longitudinal outcome study, 11,451 patients with rheumatoid arthritis (RA) and osteoarthritis (OA) reported all medication use, ulcer history, functional status, and sociodemographic characteristics.

Results. GPA were used in 21–24% of all patients with RA and OA and in about 35–40% of all high risk patients. In unadjusted analyses, GPA use was similar among NSAID users and non-users. In multivariable logistic regression analyses GPA use was associated with non-specific (NS) NSAID and COX-2 NSAID, prednisone, low dose aspirin, comorbidity, Health Assessment Questionnaire functional score, age < 65 years, increased income, not smoking, and being male. Despite numerous associations, the explanatory power for GPA use was poor (area under ROC curve = 0.680).

Conclusion. GPA are used in 35% to 40% of patients with 4 risk factors for gastrointestinal ulceration. GPA use is not increased in NS NSAID users compared to COX-2 NSAID users, and was inversely associated with socioeconomic status. GPA use does not follow the model predicted by clinical trial results with respect to NS NSAID and age, reflecting a change in the pattern of NSAID use in patients with rheumatic disease. The major determinant of GPA use appears to be physician prescribing behavior. (First Release Mar 1, 2006; J Rheumatol 2006;33:779–84)

Key Indexing Terms:
GASTROPROTECTIVE AGENTS PROTON PUMP INHIBITORS ULCER ARTHRITIS

Risk factors for the development of gastrointestinal (GI) perforations, ulcers, and bleeds (PUB) have been described in numerous studies[1-7]. They include increasing age, a history of peptic ulcer or GI bleeding, nonsteroidal antiinflammatory drug (NSAID) use, and concurrent use of aspirin, corticosteroids, or anticoagulants. Less established associations include smoking, use of alcohol, *Helicobacter pylori*, and female sex, among others. GI therapies that can reduce the risk of GI ulcers include proton pump inhibitors (PPI) and misoprostol[3,8-10].

The potential importance of risk factor reduction by gastroprotective agents (GPA) was emphasized by Howard, *et al* who studied preventable causes of hospital admissions in Nottingham, UK in 2001[11]. They noted that 6.5% of admissions were drug related, and of these 67% were preventable. The most common cause of such hospitalizations was NSAID and/or anti-platelet therapy "in patients with 2 or more risk factors without gastrointestinal prophylaxis."

Despite the recognition of the usefulness of GPA for prophylaxis, use of such therapy appears to be uncommon. Gastroprotective drugs were co-prescribed in only 1,522 (23%) of 6,557 NSAID users in the Netherlands[12] and were noted to be underutilized in other reports, with rates as low as 8% in one general practice database[13] and 22% in another database[14]. Smalley, *et al* noted that only 30% of patients with 2 or more risk factors used a GPA or a COX-2 NSAID in the Tennessee Medicaid program[15]. The development of COX-2 NSAID complicated the issue of prophylaxis, as such agents reduced the risk of PUB compared to non-specific NSAID users (NS NSAID)[16-18], leaving the definition of prophylaxis unclear.

However, even when such therapy was recommended by regulatory groups, compliance was rare[15]. Data from Price-Forbes, *et al*[19] using the UK National Institute for Clinical Excellence (NICE) guidelines for the prescription of COX-2 inhibitors offered some insight into the extent to which risk factors are prevalent in patients with rheumatic disease as well as the rate of appropriate management according to the NICE guidelines. NICE indicated that COX-2 NSAID were appropriate therapy in patients with risk factors that included age > 65 years, previous clinical history of gastroduodenal ulcer, GI

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bleeding or gastroduodenal perforation, concomitant use of medications that are known to increase upper GI adverse events, e.g., corticosteroids and anticoagulants, presence of serious comorbidity, such as cardiovascular disease, renal or hepatic impairment, diabetes, and hypertension, or the requirement for prolonged use of maximum recommended doses of standard NSAID[19]. However, the authors noted that of "791 patients taking NS NSAID, only 65 (8%) patients were receiving appropriate treatment, the remaining prescriptions (92%) being inappropriate. Of the latter, only 191 (26%) were co-prescribed GPA (56% of GPA were PPI)."

Studies cited above addressed risk factors only among patients receiving NS NSAID, generally in a general practice setting. The risk of PUB appears to differ among acute and chronic users[20], and there are data to suggest that GI ulcer risk factors are changing, as high risk patients are switched to COX-2 NSAID or have NSAID discontinued[17,21,22]. In addition, COX-2 NSAID use has become widespread in the US. We studied the use of GPA prophylaxis across all types of NSAID users and non-users, and in the setting of rheumatoid arthritis (RA) and osteoarthritis (OA) managed by rheumatology specialists. In addition, we determined the extent risk factors influenced GPA prescription.

MATERIALS AND METHODS

Patient sample. Patients in our study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes. Patients are recruited from the practices of US rheumatologists, and are followed with semi-annual questionnaires that document events in the preceding 6 months. We investigated the status of 11,451 patients with RA and OA who completed at least one questionnaire in 2003 or 2004. In the event multiple questionnaires were completed, the most recent questionnaire was used.

Demographic and disease status variables. NDB participants complete semi-annual, detailed 28-page questionnaires about all aspects of their illness. At each assessment, demographic variables are recorded including sex, age, ethnic origin, education level, current marital status, and medical history. Patients report all GI symptoms such as nausea, heartburn, epigastric distress, and others. In addition, they indicate a physician diagnosis of GI ulcer within the previous 6 months. These reports are validated by medical records and physician contact. Patients also report all medications, including dose and frequency of use. We specifically identified all GI drugs by name, including antacids, H2-antagonists, PPI, and cytoprotective agents (e.g., misoprostol). A patient was considered to be receiving a GPA if he used either a PPI or a cytoprotective agent. We categorized low dose aspirin as the use of aspirin of less than 650 mg per day. Of these, 52% of patients used 81 mg per day and 93% used 325 mg or less per day.

Definition of a GI risk. Two categories of GI risk were defined. The first GI risk category was defined by a history of a PUB, as reported by the patient. The second category included either current PUB or symptoms of epigastric pain ["pain or discomfort in upper abdomen (stomach)"].

Statistical analyses. Analyses used Stata, version 9.0[23]. The associations of GPA and their risk factors were studied using multivariable logistic regression. Statistical significance was set at the 0.05 level, and all tests were 2-tailed.

RESULTS

Of the 11,451 patients with rheumatic disease in this study, 85.9% had RA (Table 1). GI drugs were used by 39.9%. GPA were used by 22.4%, which included 19.2% using PPI, 2.2% using the diclofenac and misoprostol combination, and 0.8% using misoprostol alone. With respect to previously identified risk factors for GI ulceration, 46.2% of patients were 65 years of age or older, 21.7% had a history of a PUB, and 32.2% had either a PUB or current epigastric symptoms. Low dose aspirin was used by 28.7%. NSAID use was common (56.5%), with NSAID divided about equally between COX-2 specific NSAID (27.6%) and NS NSAID (27.2%). A substantial proportion of study patients had cardiovascular comorbidity as shown in Table 1.

Table 1. Characteristics of 11,451 study participants with RA and OA. Results are expressed as percentages unless otherwise defined.

Variable	%
Mean (SD) age, yrs	62.7 (12.8)
Male	22.0
RA	85.9
Comorbidity	
Cardiovascular disease ever	39.3
Hypertension ever	53.2
CVA ever	7.0
NSAID use	
No NSAID	43.5
COX-2	27.6
NS-NSAID	27.2
NS+COX-2 NSAID	1.7
Low dose aspirin	28.7
Ulcer risk	
Ulcer (PUB) history	21.7
Ulcer (PUB) history + current symptoms	32.2
GI therapy	
Any GI drug	39.9
Gastroprotective agents	22.4
Proton pump inhibitors	19.2
Diclofenac + misoprostol	2.2
Misoprostol	0.8

PUB: perforations, ulcers, and bleeds.

The use of GPA was generally similar among treatment groups, with the prevalence being greatest among COX-2 users (24.1%) and least among the non-NSAID users (20.8%). NS NSAID user prevalence was 23.1% (Figure 1). When all GI therapy was considered, not just GPA, use of GI agents was similar in those using no NSAID (37.0%) and those using NS NSAID (37.1%). Prevalence was highest among COX-2 NSAID users (45.2%).

A breakdown of GPA use according to GI risk factors is shown in Figure 2. Among persons with no risk factors the use of GPA was between 17.0% and 20.4%. These values may be thought of as defining the baseline GPA use levels in patients with RA and OA. At the highest risk category [GI risk (+), age > 65, low dose aspirin (+)], the use of GPA was 37.1% for NS NSAID users, 40.3% for no NSAID users, and 41.6% for COX-2 NSAID users. Rates of use were slightly lower among persons older than 65 years. With a more liberal definition of GI risk that included epigastric symptoms within the last 6

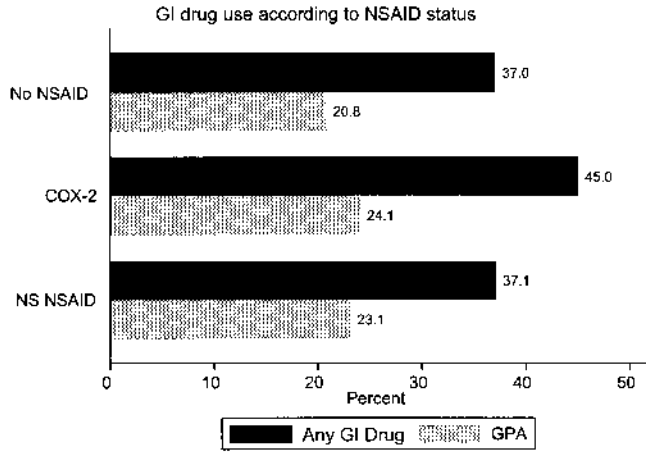

Figure 1. Percentage of patients using any GI therapy or GPA therapy according to NSAID use category.

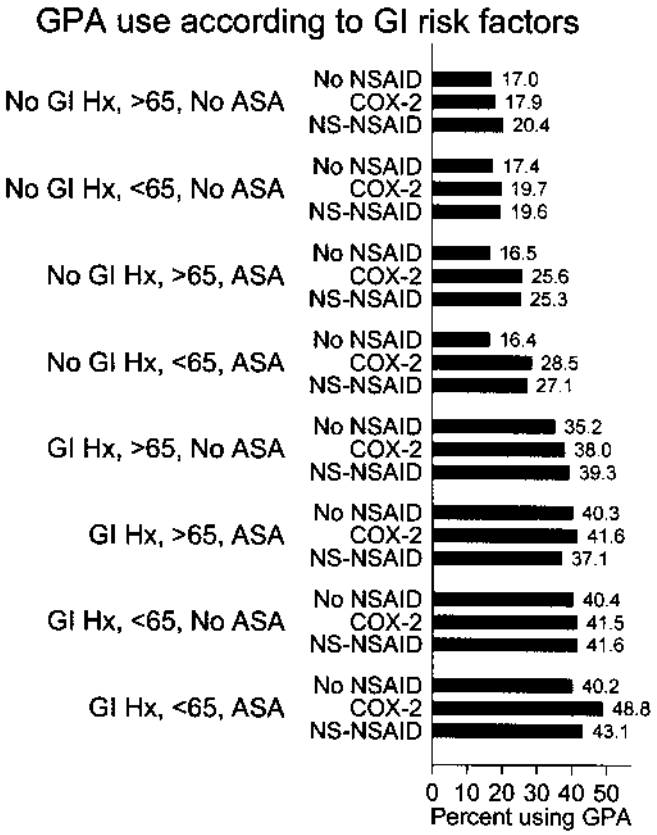

Figure 2. Percentage of patients using GPA in differing risk categories according to NSAID status. GI Hx: history of perforations, ulcers, and bleeds (PUB); < 65 and > 65: age less than 65 years or greater than 65 years; ASA: low dose aspirin.

months (Figure 3), the percentage of patients with GI risk factors who use GPA decreased slightly, and in the highest risk category [GI risk (+), age > 65, low dose aspirin (+)] ranged between 36.1% and 41.4%

Table 2 defines the various contributions of treatment and

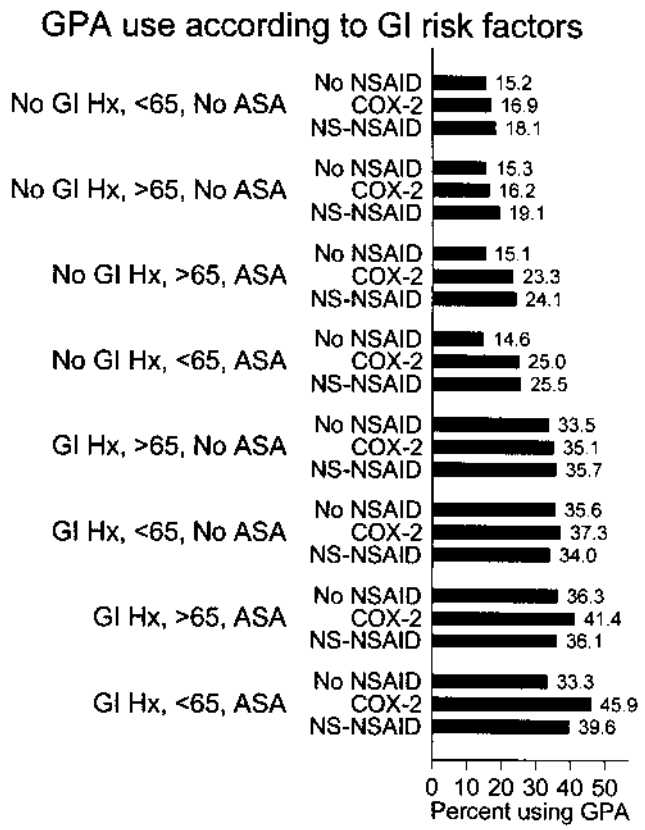

Figure 3. Percentage of patients using GPA or having epigastric distress in differing risk categories according to NSAID status.

age variables to GPA use using a simple model. Age (dichotomized at age 65) was not significant in this model (p = 0.972). In addition, age was not significant when it was dichotomized at age 75 or used as a continuous variable (data not shown). Low dose aspirin, NSAID of both types, and prednisone all were associated with GPA use at an odds ratio (OR) of approximately 1.4. The OR for GI risk (PUB) was 2.89 (95% confidence interval, CI: 2.62-3.19%). Adjusted for these covariates, the predicted prevalences for no NSAID, NS NSAID, and COX-2 NSAID were 17.3% (95% CI: 16.3-18.4%), 23.0% (21.5-24.5%), and 23.8% (22.3-25.4%) for the

Table 2. Multivariable predictors of GPA use (n = 11,451).

Predictors	OR	p	95% CI
Ulcer history	2.89	< 0.001	(2.62, 3.19)
Age > 65 yrs	1.00	0.972	(0.91, 1.10)
Sex (male = 1)	0.98	0.686	(0.87, 1.09)
No NSAID therapy (reference)	1.00		
COX-2 use	1.42	< 0.001	(1.27, 1.59)
NS NSAID use	1.49	< 0.001	(1.33, 1.67)
Aspirin ≤ 650 mg/day	1.39	< 0.001	(1.25, 1.55)
Prednisone	1.38	< 0.001	(1.25, 1.52)

OR: odds ratio; CI: confidence interval.

3 respective groups. This represents an increase in GPA use of approximately 26% for NSAID users compared with non-users. The area under the ROC curve for this model is 0.646.

We also evaluated GPA use with a more comprehensive model that included comorbidity, function, and sociodemographic characteristics (Table 3). There was no statistical difference between NS NSAID and COX-2 NSAID with respect to GPA use in this model, OR 1.1 (95% CI: 0.99-1.30, p = 0.081). In addition to comorbidity, Health Assessment Questionnaire (HAQ) functional score also predicted GPA use. This model also gives insights into sociodemographic predictors. Patients less than age 65 years, those with more income, and non-smokers were more likely to use GPA. Despite the additional predictors, the explanatory power of this model remains low, and the area under the ROC curve for this model is 0.680.

DISCUSSION

Randomized controlled trials (RCT) and epidemiologic studies have identified risk factors for PUB, including GI symptoms, previous GI ulcers, increasing age, NS NSAID use, and the use of low dose aspirin[1-6,24]. PUB estimates vary, but may be as high as 2% annually[25]. In a RCT, PUB were noted to occur at an annualized rate of 3.5% among NS NSAID users compared with 1.4% for RA and OA patients using COX-2 NSAID[24]. GPA offer a degree of protection against the development of PUB. Such data suggest that one might identify patients at risk for ulceration and provide prophylactic therapy.

This idea runs up against several problems. Persons with risk factors are common while the rate of GI ulcers is low. As NS NSAID use appears to be the dominant risk factor in RCT and epidemiologic studies, a seemingly practical method of approach is to apply prophylaxis to NS NSAID users, particularly those with other risk factors. A number of cost analyses have addressed cost-effectiveness in this way based on RCT studies[26-28]. However, patterns of use and risk factors may be different in community practice compared with RCT results[17,21].

Using this approach, we noted that 37.1% of high risk patients were receiving GPA, defining high risk as NS NSAID (+), age > 65 years, GI risk factor (+), and low dose aspirin (+) (Figure 1). This rate was higher than noted in previous studies[12-14]. However, we also noted use of GPA in high risk patients not using any NSAID (40.3%) and in those using COX-2 NSAID (41.6%). In addition to such data, we noted that age was not associated with GPA use.

However, these data regarding use of GPA in non-NS NSAID patients are different from what one might expect based on RCT results and NICE guidelines. We believe that physicians treating rheumatic disease and their patients have learned about risk factors and have differentially switched the highest risk patients to COX-2 NSAID or to no NSAID. By contrast, patients who have tolerated NS NSAID or have lower risk have been allowed to use these NSAID. Similarly, use of NS NSAID has decreased in the elderly. These prescribing changes have resulted in a different pattern of ulcer risk than found in RCT, a pattern where the rate of GI ulceration is higher in patients receiving the most effective treatments: COX-2 NSAID and GPA[17,21].

If the risk of ulcers no longer depends mostly on the use of a specific type of NSAID, or even on NSAID *per se*, then intrinsic risk factors such as prior GI ulcers, use of corticosteroids, concomitant "high risk" medications, and comorbid illness may be the key determinants for categorizing patients

Table 3. Multivariable predictors of GPA use, comprehensive model (n = 11,451).

Predictor Variables	OR	p	95% CI
Ulcer history	2.39	< 0.001	(2.15, 2.64)
Age ≥ 65 yrs	0.90	0.047	(0.82, 1.00)
Sex (male = 1)	1.11	0.072	(0.99, 1.25)
No NSAID therapy (reference)	1.00		
COX-2	1.29	< 0.001	(1.15, 1.44)
NS NSAID	1.43	< 0.001	(1.28, 1.61)
Low dose aspirin	1.25	< 0.001	(1.12, 1.39)
Prednisone	1.23	< 0.001	(1.11, 1.36)
Comorbidity score 0 (reference)			
1	1.58	< 0.001	(1.25, 2.00)
2	2.00	< 0.001	(1.60, 2.51)
3	2.42	< 0.001	(1.93, 3.03)
≥ 4	3.12	< 0.001	(2.51, 3.88)
HAQ (0–3)	1.28	< 0.001	(1.19, 1.38)
Income > median	1.13	0.024	(1.02, 1.25)
High school graduate	1.15	0.105	(0.97, 1.36)
RA	1.06	0.392	(0.92, 1.22)
Non-Hispanic white	0.98	0.794	(0.82, 1.16)
Current smoker	0.83	0.026	(0.71, 0.98)
Married	0.94	0.284	(0.85, 1.05)

as being at high risk. It would then follow from Figures 1 and 2 that only 35-40% of high risk patients are receiving GPA prophylaxis, and that the use of GI prophylaxis perhaps should be based on actual risk factors rather than merely on the use of NS NSAID.

While we assume in the above discussion that all GPA were being used for prophylaxis, our analyses were unable to distinguish between prophylactic GI ulcer therapy and therapy for symptomatic relief of GI symptoms. Indeed, there was considerable evidence to indicate that the major reason for prescription was symptomatic relief. However, our data can serve to identify the upper limit of "prophylactic" therapy under the assumption that all GPA therapy used in this study was prophylactic. Under such an optimistic assumption, only about 35-40% of patients in the highest risk categories received prophylactic therapy.

There are many reasons that physicians and patients might choose not to follow recommendations regarding ulcer prophylaxis including being unaware of such recommendations, patient preference, patient burden, cost, medical insurance, concomitant therapy, and alternative cost-benefit assessments and assumptions. Our results do not in any way indicate that the rate of observed GPA therapy is appropriate or inappropriate. Instead, our intention has been to provide data on how GI therapy is being used, which may be helpful to physicians and health planners.

We have not addressed the issue of whether the use of COX-2 NSAID is in itself prophylactic. While such may be the case in clinical trials where random allocation occurs, in clinical practice non-random allocation results in higher risk patients receiving COX-2 therapy. It seems possible that such patients might benefit from the use of GPA. It should be understood that our data do not speak to the effectiveness of GPA or COX-2 therapy, but only to practice patterns.

Following identification of COX-2 treatment-associated cardiovascular disease, many patients receiving COX-2 therapy will change to other therapies or discontinue therapy entirely. Data are not yet available to indicate if this higher risk group of patients will switch back to NS NSAID. If that is the case, it is likely that NS NSAID use itself may become a more important risk factor for PUB.

In summary, GPA therapy is used by 21-24% of all patients with RA and OA and in approximately 35-40% of all high risk patients. Use of NS NSAID specifically and NSAID generally is only moderately associated with GPA use (OR of about 1.4). By contrast, the OR for GI risk factors in the simplest model is 2.89 (95% CI: 2.62-3.19).

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