The Effect of Low-Dose Aspirin on the Decreased Risk of Development of Dyspepsia and Gastrointestinal Ulcers Associated to Cyclooxygenase-2 Selective Inhibitors

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ABSTRACT. ***Objective.*** To evaluate the risk of gastrointestinal (GI) symptoms and ulcers associated to the use of low-dose aspirin (ASA) among patients with rheumatoid arthritis (RA) and osteoarthritis (OA) treated with cyclooxygenase-2 (COX-2) drugs, to clarify the controversy in the literature.

Methods. Using a longitudinal databank, a prospective study using Cox proportional hazards models was performed in patients receiving COX-2 therapy for RA or OA to examine the effect of ASA on GI events. In 4 separate analyses patients reported dyspeptic symptoms and GI ulcers at semiannual intervals for up to 3 years. Ulcers were validated by review of medical records.

Results. Among 4240 patients taking COX-2-specific inhibitors, with no ulcer at study start, the age- and sex-adjusted hazard ratios for the effect of ASA on the development of epigastric pain, heartburn, nausea, and ulcers, without these previous events, were 1.11 (95% CI 0.97–1.29), 1.00 (95% CI 0.88–1.15), 1.32 (95% CI 1.13–1.54), and 1.27 (95% CI 0.78–2.05). The use of a propensity score to account for the risk of ASA prescription showed an even lower effect of ASA among all GI variables. This risk occurs within the setting of no prior GI symptoms or GI events, and independently of the use of proton pump inhibitors, other GI drugs, other nonsteroidal antiinflammatory drugs, prednisone, or methotrexate.

Conclusion. In actual practice, the use of low-dose ASA has a small effect on the risk of developing dyspeptic symptoms in a group of patients with rheumatic disease. (First Release July 1 2007; J Rheumatol 2007;34:1765–9)

Key Indexing Terms:
ASPIRIN GASTROINTESTINAL ULCER ARTHRITIS RHEUMATIC DISEASE

Nonsteroidal antiinflammatory drugs (NSAID) continue as drugs of choice for analgesia and antiinflammatory effects and are often prescribed for patients with painful and inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA)[1-8], but the upper gastrointestinal (GI) toxicity of NSAID has been well documented[3,9-14]. Results of randomized clinical trials (RCT) indicate cyclooxygenase-2 NSAID (COX-2) use is associated with fewer GI ulcers and less dyspepsia compared with nonspecific NSAID[15-21].

Patients with RA and OA commonly use low-dose aspirin (ASA) for cardiovascular prophylaxis. While the risk of ASA use to the upper GI tract is recognized, controversy still exists as to the increased risk incurred by those taking low-dose ASA and a coxib[22-24].

Our purpose was to evaluate the risk of GI adverse events associated to the use of low-dose ASA among patients with RA and OA treated with COX-2 drugs in a real practice setting where results might differ from those obtained in RCT.

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 enrolled by 433 practices of US rheumatologists and are followed with semiannual questionnaires that document events in the preceding 6 months[25,26]. This report concerns the status of 15,952 patients, 13,732 with RA and 2220 with OA, who completed questionnaires beginning in January 2002 and were followed prospectively during 3 years. Diagnoses were made by the referring rheumatologists. By definition, a prospective cohort study is defined on the basis of the risk factor or exposure at study initiation, and all subjects must be free from the outcome under investigation. Therefore, at study initiation our cohort was exposed to low-dose ASA and free of GI symptoms and ulcers in order to validly compare the influence of low-dose ASA versus no ASA on

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the development of these outcomes. Our cohort of patients was evaluated every 6 months at 6-month intervals; therefore, we considered baseline the period between time 0 and 6 months, the first followup evaluation between 6 and 12 months, the second between 12 and 24 months, etc. Further, all questions referred to the previous 6-month period.

Demographic and clinical data. NDB participants complete semiannual, detailed 28-page questionnaires about all aspects of their illness. At each assessment, demographic variables are collected including sex, age, ethnic origin, education level, current marital status, and medical history. Study variables also included a visual analog scale (VAS) for each of the following: global disease severity, fatigue, sleep disturbance, and anxiety. Patients also reported all medications, including dose and frequency. We defined low-dose ASA as the use of ASA of < 650 mg per day. Of these, 52% of patients used 81 mg per day and 93% used ≤ 325 per day.

Questionnaires are systematically validated by confirming self-reported medications. In general for major medications the validation rate is about 98%, although on occasion patients may fail to refer to over the counter drugs. We also validate all events. For hospitalized events, the level of validation is about 94%.

GI adverse events. All GI events were based on patients' self-report of GI symptoms (nausea, heartburn, epigastric discomfort) and ulcer, based on patient symptoms, within the previous 6 months followed by validation of these by medical records and physician contact. GI ulcers were only validated if an endoscopy or upper GI series confirmed the diagnosis. Four separate analyses were undertaken to analyze the effect of ASA on each of these GI events. To assess GI symptom severity we used a VAS with the instructions, "How much trouble have you had with your stomach (i.e., nausea, heartburn, epigastric discomfort)? Place a mark on the line that best describes the severity of your stomach problems on the scale of 0–100." At the start of each of the 4 analyses patients were free of epigastric pain, nausea, heartburn, and ulcers, respectively.

Statistical methods. Incidence rates of GI events were calculated as the number of events divided by person-years of exposure, and expressed in 100 patient-years. Confidence intervals (CI) were calculated based on a Poisson distribution. We tested for the effect of low-dose ASA on each of the GI events, using Cox proportional hazards models. To obtain insight into the causal relationship between ASA and GI outcomes, we computed a propensity score for the risk of ASA prescription and included it into the analyses. For each event, we calculated a separate propensity score for the risk of low-dose ASA prescription. Among the variables included in the various propensity scores were sex, age, pain, prednisone (PDN), proton pump inhibitors (PPI), other GI drugs, ulcer history, COX-2 and non-COX-2 NSAID, anxiety, sleep, fatigue, sleep disturbance, and the presence of cardiovascular disease.

We restricted the analyses of this data set to non-censored cases, in part because of the difficulty of being absolutely sure about the nature of therapy in censored cases. To allow all variables, including missing data, to be used in the multivariable analyses, an approximate Bayesian bootstrap imputation procedure modified from Mander and Clayton was employed[27]. Analyses used Stata, version 9.0[28]. Statistical significance was set at the 0.05 level, and all tests were 2-tailed.

RESULTS

In total, 15,952 patients were identified for inclusion in our study, including 13,732 with RA and 2220 with OA. Of the total number of patients, 8543 patients were enrolled at study start and the rest were enrolled continuously thereafter. The demographic, clinical, and GI status variables for the initial 6 months of followup for these patients are shown in Table 1. To study the effect of COX-2 therapy with ASA on GI symptoms and ulcers versus COX-2 therapy without ASA, we restricted analyses to 4240 patients without an ulcer at study start who were using a COX-2-specific NSAID with or without low-dose ASA. The baseline characteristics of these patients are shown on the second column of Table 1. Interestingly, of the whole population, 18.8% used low-dose ASA, 17.8% a PPI, 38.3% any GI drug, 31.1% a COX-2-specific NSAID, and 35.1% PDN. Ulcers and GI symptoms were common at study start. Validated ulcers were noted in 0.97%, while a lifetime ulcer history was found in 7%. GI symptoms included epigastric discomfort (16%), heartburn (26.7%), and nausea (12%). For the population restricted to those taking COX-2 selective drugs, 16.6% took ASA, 21.5% PPI, 43% GI drugs, and 31.5% PDN.

Table 2 shows that for the 4240 COX-2 (+) patients without epigastric pain at study onset, the age- and sex-adjusted hazard ratio (HR) for the effect of ASA on the development of epigastric pain was 1.11 (95% CI 0.97–1.29), on heartburn 1.00 (95% CI 0.88–1.15), and on nausea 1.32 (95% CI 1.13–1.54). We also analyzed the effect of ASA on the risk of developing ulcers in COX-2-treated patients, restricting analyses only to ulcers that were validated, according to patient medical records. The HR in this analysis was 1.27 (95% CI 0.78–2.05). These results represent the risks of therapy as actually experienced in the study population. Using a propensity score for the risk of ASA prescription made the results for the ASA effect become less significant for all GI variables: epigastric pain (HR 1.05, 95% CI 0.91, 1.21), heartburn (HR 0.95, 95% CI 0.83, 1.09), nausea (HR 1.19, 95% CI 1.01–1.40), and ulcer (HR 1.15, 95% CI 0.70, 1.88). Of note, although we included PDN in the propensity score, we also analyzed models with this variable as an independent covariate and other medications that could confound the relationship between ASA and the outcome. An analysis including other medications, such as any NSAID, methotrexate (MTX), or PDN, did not alter the results (Table 1). We also note the propensity score included the use of any other GI drugs any time during the study period, such as anti-secretory ones, prescribed by a physician or obtained over the counter.

The annual incidence rate (IR) of GI ulcers was 1.08 (95% CI 0.86, 1.35) per 100 patient-years when fully validated cases were considered (Table 3). Heartburn was the most common GI symptom (IR 19.10, 95% CI 17.88, 20.38), followed by epigastric discomfort (IR 12.97, 95% CI 12.07, 13.93) and nausea (IR 10.67, 95% CI 9.87, 11.51).

DISCUSSION

This longitudinal study shows that among patients receiving COX-2 therapy for RA and OA, with no previous GI symptoms (epigastric pain, heartburn, and nausea) or ulcers within the previous 6 months, and followed in rheumatologist practices, the use of low-dose ASA has a small effect on the risk of developing dyspeptic symptoms and GI ulcers.

Four important RCT have been performed to assess the risk of upper GI symptoms and events and the interaction of low-dose ASA with a coxib. Two of these showed no increased risk of upper GI events among these patients, as we did. The

Table 1. Demographic, clinical, and GI events in 15,952 RA and OA patients and in the 4240 RA and OA patients taking COX-2 inhibitors without GI ulcers during the initial 6-month period of obervation.

Variable	Mean or % for 15,952 RA and OA Patients Included in the Study	Mean or % for 4240 RA and OA Patients on COX-2 Inhibitors without Previous GI Ulcers
Age, mean (SD) yrs	61.3 (13.0)	61.3 (12.7)
Sex (% male)	22.5	21.5
Pain (0–10), mean (SD)	3.8 (2.7)	4.0 (2.7)
Fatigue (0–10), mean (SD)	4.3 (2.9)	4.5 (2.9)
Sleep disturbance (0–10), mean (SD)	3.6 (3.1)	3.8 (3.0)
Anxiety (0–10), mean (SD)	3.5 (1.9)	3.6 (1.9)
Cardiovascular comorbidity (%)	52.2	52.7
ASA (low dose) (%)	18.8	16.6
Prednisone (%)	35.1	31.5
Proton pump inhibitors (%)	17.8	21.5
COX-2 drugs (%)	31.1	100.0
Any GI drug (%)	38.3	43.0
GI ulcer (validated) %	0.97	0.00
Lifetime ulcer history (%)	7.0	4.4
Heartburn (%)	26.7	28.4
Nausea (%)	12.0	13.6
Epigastric discomfort (%)	16.0	17.2

GI: gastrointestinal; RA: rheumatoid arthritis; OA: osteoarthritis; COX-2: cyclooxygenase 2; ASA: aspirin.

Table 2. Effect of low-dose ASA on GI symptoms and ulcer rates among patients taking COX-2 specific NSAID.

Event	Covariates	p	Hazard Ratio (95% CI) for Low Dose ASA
Epigastric discomfort	Age, sex	0.134	1.11 (0.97, 1.29)
	Age, sex, propensity score	0.520	1.05 (0.91, 1.21)
	Age, sex, PPI	0.379	1.07 (0.92, 1.23)
	Age, sex, PDN, MTX	0.808	0.98 (0.78, 1.21)
	Age, sex, NSAID	0.682	0.96 (0.77, 1.19)
Heartburn	Age, sex	0.933	1.00 (0.88, 1.15)
	Age, sex, propensity score	0.457	0.95 (0.83, 1.09)
	Age, sex, PPI	0.716	0.98 (0.85, 1.11)
	Age, sex, PDN, MTX	0.880	1.01 (0.86, 1.19)
	Age, sex, NSAID	0.833	1.02 (0.86, 1.20)
Nausea	Age, sex	0.001	1.32 (1.13, 1.54)
	Age, sex, propensity score	0.006	1.19 (1.01, 1.40)
	Age, sex, PPI	0.006	1.25 (1.06, 1.46)
	Age, sex, PDN, MTX	0.066	1.27 (0.98, 1.62)
	Age, sex, NSAID	0.091	1.24 (0.97, 1.60)
GI ulcers	Age, sex	0.338	1.27 (0.78, 2.05)
	Age, sex, propensity score	0.590	1.15 (0.70, 1.88)
	Age, sex, PPI	0.489	1.19 (0.73, 1.92)
	Age, sex, PDN, MTX	0.259	0.64 (0.30, 1.39)
	Age, sex, NSAID	0.250	0.64 (0.29, 1.37)

ASA: aspirin; GI: gastrointestinal; COX-2: cyclooxygenase 2; NSAID: nonsteroidal antiinflammatory drugs; PPI: proton pump inhibitors; PDN: prednisone; MTX: methotrexate.

Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE) was a 12-week RCT in 5597 patients with OA in the US and Sweden who were randomized to receive rofecoxib (25 mg daily) or naproxen (500 mg twice daily), and showed that concomitant use of low-dose ASA with rofecoxib does not significantly increase risk of adverse events[29]. The other, the Successive Celecoxib Efficacy and Safety Studies (SUCCESS), showed that — relative to concomitant nonselective NSAID and ASA — the risk of GI adverse events is substantially reduced with concomitant celecoxib and ASA, albeit to a lesser degree than celecoxib without ASA. The

Table 3. Annual incidence rates for GI events and ulcers among patients taking COX-2-specific NSAID.

Event	Exposure (patient-years)	Annual Incidence Rate per 100 patients (95% CI)
Epigastric discomfort	5889.0	12.97 (12.07–13.93)
Heartburn	4775.5	19.10 (17.88–20.38)
Nausea	6290.5	10.67 (9.87–11.51)
GI ulcers	7396.5	1.08 (0.86–1.35)

other 2 RCT showed an increased risk. The Celecoxib Long-term Arthritis Safety Study (CLASS) trial was carried out in 7968 patients from 386 centers in the US and Canada and compared celecoxib (400 mg twice daily) with 2 nonselective NSAID: diclofenac (75 mg twice daily) or ibuprofen (800 mg 3 times daily)[20]. Although this reference does not include the full dataset, we can only comment on the published report on the CLASS study, which, in a subanalysis of the coadministration of up to 325 mg of ASA, showed a 4-fold increased risk of complicated ulcers in both Celebrex and diclofenac groups. The other study showed that 12 weeks of low-dose ASA (81 mg) alone did not significantly increase cumulative ulcer incidence (7.3%) when compared to placebo (5.8%), but the addition of a COX-2 NSAID (rofecoxib 25 mg + 81 mg/day) increased ulcer incidence as reported by endoscopy (16.1%) to a rate not significantly less than a nonselective NSAID alone (ibuprofen 800 mg 3 times a day) (17.1%)[22]. We believe that the differences in the results of our study and these last 2 RCT are attributed to a difference between our study population and that of the trials. RCT, considered the gold standard for comparison of the efficacy of drug therapies, select patients based on very restrictive characteristics that are not equivalent to those populations often encountered in clinical practice. While we only excluded patients at study start who had already experienced our outcome at baseline, the CLASS not only excluded ulcers at their study start, but also excluded renal, hepatic and coagulation disorders, malignancy, history of gastric or duodenal surgery, pregnant and lactating women, and history of hypersensibility to COX-2 inhibitors, sulfonamides, ibuprofen or diclofenac. CLASS also prohibited the use of anti-ulcer drugs, antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *Helicobacter pylori*, and anti-neoplasics (except for MTX and azathioprine for RA treatment). Further, our study population had a followup of 3 years compared to 12 weeks for the Laine, *et al* trial and up to a maximum of 1 year for the CLASS. Patients were diagnosed with ulcer in our study only if patients saw their doctor for symptoms. The Laine study performed an endoscopy at 12 weeks for all study patients and reported either ulcers or erosions, while the CLASS definition of ulcer needed to confirm its presence or complications by endoscopic, surgical, or radiological evidence. The differences in the ulcer rate might also result from the fact that only clinically significant ulcers were included in our study and endoscopy was not necessary. The true pathogenesis of COX-2-induced ulcers is not very well known and it might be that although present, the ulcers might heal on their own, not needing any type of medical intervention to avoid complications (GI hemorrhage and perforation). Both trials also excluded the use of a PPI, an exclusion that we did not use, and were not as prone to confounding and channeling bias as ours, since randomization minimized the effects of confounding in the clinical trials. Finally, CLASS analyzed ASA as a secondary analysis, which was not the primary objective of the study. In actual practice, patients with RA and OA are often prescribed a PPI in association with antiinflammatory medication, which reduces the risk of developing ulcers.

The limitations of our study include nonrandomization of the study patients into controlled groups of ASA and COX-2 prescription, and therefore the data are prone to confounding. To decrease the differences between the baseline study populations in the different groups we used a propensity score model. Another limitation is the susceptibility to recall bias. Patients may not accurately recall GI symptoms 6 months prior to answering the questionnaire. The strengths of our study reflect a real-life situation seen in everyday clinical practice, not seen in RCT.

We suggest that further studies be undertaken in other populations in an attempt to generalize our findings. Further RCT and prospective studies using databases such as the NDB are needed to study the effect of PPI use in association with COX-2 and low-dose ASA use. Studies are also needed to study the effect of COX-2 and low-dose ASA on the gastric mucosa and their complications (i.e., hemorrhage and perforation).

In actual practice, the use of low-dose ASA has a small effect on the risk of developing dyspeptic symptoms and nearly no effect in the development of ulcers. This risk occurs within the setting of no prior GI symptoms, prior GI events, and independently of PPI use and represents the "real, practice" risk for ASA in a population with rheumatic disease.

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