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Risk of Uncomplicated Peptic Ulcer among Users of Aspirin and Nonaspirin Nonsteroidal Antiinflammatory Drugs

Luis Alberto García Rodríguez[1] and Sonia Hernández-Díaz[2]

[1] Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain.
[2] Slone Epidemiology Center, Boston University, Boston, MA.

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The association between nonsteroidal antiinflammatory drugs (NSAIDs) and upper gastrointestinal complications is well documented. However, epidemiologic data on the risk of clinically symptomatic but uncomplicated peptic ulcer are quite limited. The authors studied the association between prescription NSAIDs and the risk of symptomatic ulcer in a population-based cohort of 458,840 persons and 1,167,469 person-years in the United Kingdom between 1995 and 1999 and conducted a nested case-control analysis of 1,197 cases and 10,000 controls. The relative risk and 95% confidence intervals were estimated and adjusted for several factors known to be associated with gastrointestinal damage. The incidence rate of symptomatic ulcer was 1.03 (95% confidence interval (CI): 0.97, 1.08) cases per 1,000 person-years. Compared with nonusers, the relative risk was 2.9 (95% CI: 2.3, 3.6) for aspirin and 4.0 (95% CI: 3.2, 5.1) for nonaspirin NSAID users. For aspirin users, the relative risk was similar for doses up to 300 mg daily and for both gastric and duodenal ulcers. For nonaspirin NSAIDs, the relative risk was 2.6 (95% CI: 2.0, 3.5) for medium daily doses or lower and 4.9 (95% CI: 3.8, 6.5) for high daily doses; it was 5.6 (95% CI: 3.9, 8.2) for gastric and 3.1 (95% CI: 2.3, 4.2) for duodenal ulcers. The risk of symptomatic ulcer for aspirin and nonaspirin NSAIDs was elevated throughout treatment. These findings suggest that NSAIDs might not only complicate but also originate clinically relevant peptic ulcers.

anti-inflammatory agents, non-steroidal; aspirin; drug toxicity; peptic ulcer

Abbreviations: CI, confidence interval; GPRD, General Practice Research Database; ICD, *International Classification of Diseases*, Eighth Revision; NSAID, nonsteroidal antiinflammatory drug; RR, relative risk.

Gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs) can range from mild dyspepsia to severe complications that lead to hospitalization and even death. The incidence of serious gastrointestinal complications has been estimated to be in the order of one case per 1,000 persons per year, with a fatality rate around 5–10 percent (1–4). This incidence was around two and four times higher for users of aspirin and nonaspirin NSAIDs, respectively (5–7). Less is known about the magnitude of the absolute and relative risk of clinically symptomatic but uncomplicated peptic ulcer among users and nonusers of NSAIDs. Although less serious than complicated events, symptomatic ulcers decrease the quality of life, lead to noncompliance or treatment terminations, increase ambulatory and hospital visits, and increase the concomitant use of medications such as misoprostol and proton pump inhibitors (8, 9). Information on the risk of symptomatic ulcers cannot be extrapolated from data on other gastrointestinal events given the weak correlation among symptoms, endoscopic findings, and serious complications; symptoms can occur without ulcers, most of the endoscopic lesions never give rise to clinically significant complications, and complications can occur without warning symptoms (10, 11).

We used a population-based cohort in the United Kingdom to estimate the incidence of uncomplicated but symptomatic peptic ulcer and performed a nested case-control analysis to study the association between the risk of these ulcers and the use of aspirin and nonaspirin NSAIDs. We examined the role of dose and duration of aspirin and nonaspirin NSAIDs in the risk of peptic ulcer and estimated this risk for gastric and duodenal ulcers.

Correspondence to Dr. Luis Alberto García Rodríguez, CEIFE, Almirante, 28-2, 28004 Madrid, Spain (e-mail: lagarcia@ceife.es).

MATERIALS AND METHODS

Study design

We conducted both a cohort and a nested case-control study using the General Practice Research Database (GPRD), formerly Value Added Medical Products (VAMP) Research. The GPRD is a population-based database in the United Kingdom where general practitioners store in office computers clinical information on their patients including demographics, diagnoses and comments, referral information, and records of all prescriptions issued by them (12, 13). Data on about 3 million patients are systematically recorded and sent anonymously to the Medicines Control Agency. This agency collects and organizes this information in order to be used for research projects. The computerized information includes demographics, details from visits to general practitioners, diagnoses from referrals to specialists and hospital admissions, results of laboratory tests, and a free text section. Prescriptions issued by the general practitioner are generated directly from the computer. All of these data that are retrieved and stored by the general practitioner are automatically and continuously passed on to the GPRD. A validation study of the GPRD has documented that over 90 percent of all referrals are entered into general practitioners' computers with a code that reflects the specialist's diagnosis (13, 14). An additional requirement for participating practices is recording the indication for new courses of therapy. A modification of the Oxmis classification system is used to code specific diagnoses, and a drug dictionary based on data from the Prescription Pricing Authority is used to code drugs. We have already used this database to carry out two studies on the risk of serious upper gastrointestinal complications (15, 16).

Source population and cohort definition

The study population included persons aged 40–79 years between January 1995 and September 1999 who had been enrolled at least 2 years with the general practitioner, had at least 1 year elapsed since their first computerized prescription, and were free from cancer (*International Classification of Diseases*, Eighth Revision (ICD), codes 1400–2090), uncomplicated and complicated peptic ulcer, esophageal varices (ICD code 4560), Mallory-Weiss disease (Oxmis classification code 5309MW), chronic liver disease (ICD codes 5710–5739), coagulopathies (ICD codes 2860–2879), and alcoholism at the start date. We excluded persons who were aged 65 years or older at the beginning date with a follow-up greater than 1 year and who had no recording of any data during their follow-up time. The latter was to avoid the inclusion of subjects with incomplete data, since we believe it is unlikely that a person older than 65 years had no medical visit over a time period greater than 1 year.

Two cohorts were identified within the population in the GPRD that met inclusion criteria: an exposed cohort (at least one prescription of aspirin and/or nonaspirin NSAIDs during follow-up) of 258,840 subjects and a nonexposed cohort (no prescription of aspirin and/or nonaspirin NSAID during follow-up) of 463,296 subjects. All members in the exposed cohort and an approximate 50 percent random sample (n = 200,000) of the nonexposed cohort (these two cohorts comprised our study's *nested* cohort) were followed until they met a case definition criterion for uncomplicated peptic ulcer, one of the exclusion criteria, their 80th birthday, death, or October 1999, whichever came first. This *nested* cohort included 458,840 subjects who contributed a total of 1,167,469 person-years, calculated by adding the years of follow-up contributed by each subject in the cohort.

Case ascertainment and validation

From our study cohort, nested in the GPRD, we identified 1,967 patients with codes for peptic ulcer and manually reviewed the demographic data and clinical information in their computerized patient profiles. Patient profiles do not have any personal identifiers. Patients had codes for peptic ulcer when the general practitioner or a consultant considered the ulcer clinically relevant; we followed their criteria for defining an ulcer and applied further study-specific inclusion criteria. We considered a patient to be a case of uncomplicated peptic ulcer when no exclusion criterion was found (see cohort definition above), the subject had not been discharged from a hospital in the previous month for reasons other than peptic ulcer, the clinical diagnosis of peptic ulcer was made during a visit to a specialist or during hospitalization (most likely by endoscopic examination, the standard diagnostic technique in the United Kingdom), and the specific site of the ulcer was located in the stomach or duodenum. Patients with complicated peptic ulcer (either bleeding or perforation) or with any of the exclusion criteria in the 2 months after the date of case detection (index date) were excluded. We classified cases according to the site of the ulcer into gastric, duodenal, or multiple site. For all 677 potential cases with no specific site mentioned in the computer profiles, we sent the general practitioners a questionnaire and a request to provide us with all paper-based information related to the episode of peptic ulcer. We received information for 615 patients, with 397 patients confirmed as a case of peptic ulcer. After the review of the computerized files and the manual records received, we ended up with 1,197 cases of symptomatic peptic ulcer, 419 of which had gastric ulcers, 705 had duodenal ulcers, 42 had multiple-site ulcers, and 31 had ulcers at an unknown site. These 31 cases remained with an unknown site because information on the specific site of the lesion was not mentioned in the correspondence of the consultant sent to the general practitioner. For 728 cases, *Helicobacter pylori* status was also mentioned and had been usually determined through urease and breath tests methods.

Controls

A total of 10,000 controls were randomly sampled from the entire *nested* study cohort that gave rise to the cases, so that the likelihood of being selected as a control was proportional to the person-time at risk. Specifically, a date during the study period was generated at random for each of the members of the source population. If the random date of a study member was included in his or her eligible person-time, we used his or her random date as the index date and

marked that person as an eligible control. The same exclusion criteria were applied to controls as to cases. Ten thousand controls, frequency matched to cases by age (within 1 year), gender, and calendar year, were randomly selected from the pool of eligible controls.

Exposure definition

Exposure to aspirin and nonaspirin NSAIDs, assessment based on prescriptions written by the general practitioners and considered independently, was categorized as one of the following: "current," when the supply of the most recent prescription lasted until the index date or ended in the 30 days before the index date based on the length of drug therapy as prescribed by the general practitioner; "recent," when it ended 31–180 days before the index date; "past," when it ended 181–365 days before the index date; and "nonuse," when there was no recorded use during the 365 days prior to the index date.

Among current users, we studied the effect of duration, dose, and formulation. We evaluated duration of use adding the periods of "consecutive" prescriptions, defined as an interval of less than 2 months between two prescriptions. Current nonaspirin NSAID users were divided into "current single users" and "current multiple users." The latter category included patients who received prescriptions for different nonaspirin NSAIDs with their respective supply ending within the month before the index date. We also considered individual nonaspirin NSAIDs among current single users. Finally, we took into account simultaneous use of aspirin and nonaspirin NSAIDs.

Exposure to other drugs, such as acetaminophen, corticosteroids, H_2 receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine), proton pump inhibitors (omeprazole, lanzoprazole, and pantoprazole), and prostaglandin analog (misoprostol), was also evaluated and categorized as current, recent, or past, as defined above.

Analyses

We computed incidence rates of symptomatic peptic ulcer both overall and in age and sex strata. These analyses were based on 1,167,469 person-years and 1,197 incident cases. The case-control analysis included 1,197 cases and 10,000 controls. We computed odds ratio estimates, assumed to provide a valid estimate of the relative risk (17), and the 95 percent confidence interval of symptomatic peptic ulcer associated with current use of aspirin and nonaspirin NSAIDs compared with nonuse with unconditional logistic regression.

All estimates of relative risk were adjusted for age (40–59, 60–69, or 70–79 years), sex (male or female), study calendar year (1995–1999), study cohort (exposed or unexposed), past history of gastrointestinal symptoms (none, dyspepsia, or heartburn), smoking (current, past, or never), and use of corticosteroids, gastroprotective drugs, NSAIDs, and acetaminophen (current, recent, past, or no use, as defined above). Further adjustment for body mass index, alcohol intake, anticoagulants, cardiovascular disease, and indication (i.e., rheumatoid arthritis and osteoarthritis) did not change the results presented above and, therefore, these factors were not included in the final models. Statistical analyses were performed using StatView software (SAS Institute, Inc., Cary, North Carolina).

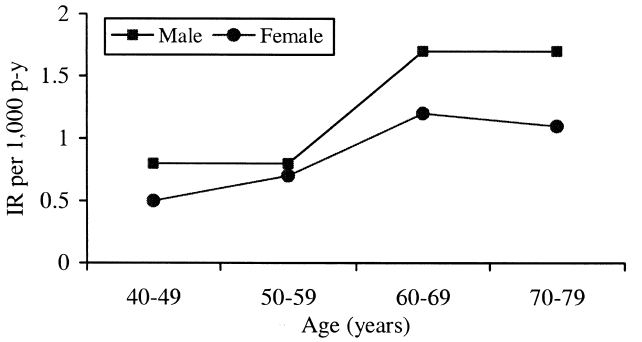

FIGURE 1. Incidence rate of peptic ulcer per 1,000 person-years stratified by age and sex, General Practice Research Database, United Kingdom, 1995–1999. IR, incidence rate; p-y, person-years.

RESULTS

Incidence of symptomatic peptic ulcer

The estimated overall incidence rate of symptomatic peptic ulcer in this population was 1.03 (95 percent confidence interval (CI): 0.97, 1.08) cases per 1,000 person-years. The incidence rate increased with age and was higher for men than for women (age-adjusted relative risk (RR) = 1.4, 95 percent CI: 1.3, 1.6) (figure 1).

Of the 1,197 cases, 419 had gastric ulcers, 705 had duodenal ulcers, 42 had multiple-site ulcers, and 31 had ulcers at an unknown site. *H. pylori* status was positive in 621 cases (189 of the gastric, 403 of the duodenal, 21 of the multiple-site, and eight of the unknown-site ulcers), negative in 107 cases, and unknown for 469 cases.

Aspirin

Overall, use of aspirin was associated with an elevated risk of symptomatic peptic ulcer (RR = 2.9, 95 percent CI: 2.3, 3.6) (table 1). The risk was similarly elevated for both regular and enteric coated preparations. The risk of symptomatic peptic ulcer was elevated throughout treatment independently of its duration, was elevated with doses as low as 75 mg per day, and was no different from the one with doses of 150 and 300 mg daily. There was very little use at doses greater than 300 mg daily.

The relative risk was similar for gastric (RR = 2.8, 95 percent CI: 2.0, 3.8) and duodenal (RR = 2.7, 95 percent CI: 2.1, 3.5) ulcers. The relative risk was similar for *H. pylori*-positive (RR = 2.5, 95 percent CI: 1.9, 3.3) and *H. pylori*-negative (RR = 3.0, 95 percent CI: 1.6, 5.5) ulcers.

TABLE 1. Relative risk and 95% confidence interval of peptic ulcer according to recency, dose, and duration of aspirin compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

	Cases (no.)	Controls (no.)	Adjusted RR*,†	95% CI*
Aspirin recency				
Nonuse	935	8,608	Referent	
Current (0–30 days)	194	917	2.9	2.3, 3.6
Regular	147	720	2.9	2.3, 3.6
Enteric coated	47	197	2.8	1.9, 4.0
Recent (31–180 days)	26	147	2.0	1.3, 3.3
Past (>180 days)	42	328	1.0	0.7, 1.5
Aspirin dose‡				
Nonuse	935	8,608	Referent	
75 mg	112	529	2.9	2.2, 3.7
150 mg	44	234	2.6	1.8, 3.9
300 mg	34	144	3.0	1.9, 4.6
>300 mg	4	10	3.8	1.0, 14.4
Aspirin duration‡				
Nonuse	935	8,608	Referent	
1–30 days	11	56	2.4	1.2, 4.8
31–180 days	37	145	3.3	2.2, 5.1
181–365 days	22	123	2.8	1.7, 4.7
>365 days	124	593	2.8	2.2, 3.5

* RR, relative risk; CI, confidence interval.

† Adjusted for age, sex, calendar year, cohort, history of gastrointestinal symptoms, smoking, and steroid, gastroprotective drug, nonaspirin nonsteroidal antiinflammatory drug, and acetaminophen use.

‡ Analyzed only among current users.

Nonaspirin nonsteroidal antiinflammatory drugs

Current intake of nonaspirin NSAIDs increased the risk of symptomatic peptic ulcer four times (95 percent CI: 3.2, 5.1) (table 2). We found a slightly greater relative risk among those already on therapy for more than 6 months (RR = 4.6, 95 percent CI: 3.5, 6.0) than among newer users (RR = 2.8, 95 percent CI: 2.1, 3.7). In users of a medium daily dose or lower, the relative risk was 2.6 (95 percent CI: 2.0, 3.5), while in users of a high daily dose, the relative risk was 4.9 (95 percent CI: 3.8, 6.5). Nonaspirin NSAIDs with and without a slow-release formulation presented relative risks of 4.6 (95 percent CI: 3.1, 6.7) and 3.3 (95 percent CI: 2.6, 4.3), respectively. There was a dose effect within each formulation. Users of both nonaspirin NSAIDs and aspirin in the last month had a relative risk of 6.8 (95 percent CI: 4.5, 10.3) compared with users of neither. This risk is slightly greater than the sum of the independent effects of aspirin and nonaspirin NSAIDs.

Table 3 shows estimates of relative risk for all individual nonaspirin NSAIDs with five or more exposed cases and controls. Relative risks ranged from 2.7 (95 percent CI: 1.9, 3.8) for ibuprofen to 10.1 among users of piroxicam (95 percent CI: 5.2, 19.2). However, these and other risk estimates for individual nonaspirin NSAIDs were based on small numbers. In the stratified analysis by daily dose, all individual nonaspirin NSAIDs presented a relative risk of less than 4 when administrated at low-medium doses; all individual nonaspirin NSAIDs presented a greater relative risk with the high dose (data not shown).

The relative risk associated with nonaspirin NSAID use was greater for gastric (RR = 5.6, 95 percent CI: 3.9, 8.2) than for duodenal (RR = 3.1, 95 percent CI: 2.3, 4.2) ulcers. This relative risk estimate was greater for *H. pylori*-negative (RR = 8.5, 95 percent CI: 4.2, 17.1) than for *H. pylori*-positive (RR = 2.5, 95 percent CI: 1.8, 3.4) lesions. The relative risk for ulcers with unknown *H. pylori* status was 5.2 (95 percent CI: 3.7, 7.3). Further, we classified the ulcers according to their site and their *H. pylori* status simultaneously; the relative risk was 3.5 (95 percent CI: 2.1, 6.1) for gastric *H. pylori*-positive ulcers, 16.2 (95 percent CI: 5.4, 48.2) for gastric *H. pylori*-negative ulcers, 2.0 (95 percent CI: 1.3, 3.0) for duodenal *H. pylori*-positive ulcers, and 5.4 (95 percent CI: 1.9, 15.4) for duodenal *H. pylori*-negative ulcers.

Topical nonaspirin NSAIDs were not associated with an increased risk of symptomatic peptic ulcer (RR = 1.0, 95 percent CI: 0.6, 1.7).

TABLE 2. Relative risk and 95% confidence interval of peptic ulcer after nonsteroidal antiinflammatory drug exposure compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

	Cases (no.)	Controls (no.)	Adjusted RR*,†	95% CI*
NSAID* recency				
Nonuse	344	3,706	Referent	
Current (0–30 days)	258	1,192	4.0	3.2, 5.1
Single	250	1,161	3.6	2.9, 4.5
Multiple	8	31	4.4	1.9, 10.3
Recent (31–180 days)	139	1,007	2.6	2.0, 3.3
Past (>180 days)	456	4,095	1.4	1.1, 1.6
NSAID dose‡				
Nonuse	344	3,706	Referent	
Low-medium	112	654	2.6	2.0, 3.5
High	138	507	4.9	3.8, 6.5
NSAID duration§				
Nonuse	344	3,706	Referent	
1–30 days	61	369	3.0	2.1, 4.2
31–180 days	48	301	2.7	1.8, 3.9
181–365 days	26	113	3.9	2.4, 6.4
>365 days	123	409	4.8	3.6, 6.4
NSAID release‡				
Nonuse	344	3,706	Referent	
Normal	198	975	3.3	2.6, 4.3
Slow release	52	186	4.6	3.1, 6.7
NSAIDs and aspirin¶				
None	274	3,191	Referent	
Current aspirin only	48	372	2.7	1.9, 3.9
Current NSAIDs only	194	1,025	3.6	2.8, 4.7
Both	51	117	6.8	4.5, 10.3

* RR, relative risk; CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug.

† Adjusted for age, sex, calendar year, cohort, history of gastrointestinal symptoms, smoking, and corticosteroid, gastroprotective drug, acetaminophen, and aspirin use.

‡ The effect of daily dose and release preparation was analyzed among NSAID current single users. Cutoff values for dose were as follows: aceclofenac, 100 mg; acemetacin, 120 mg; apazone, 600 mg; diclofenac, 75 mg; etodolac, 400 mg; fenbufen, 900 mg; fenoprofen, 1,200 mg; flurbiprofen, 150 mg; ibuprofen, 1,200 mg; indomethacin, 75 mg; ketoprofen, 100 mg; mefenamic, 1,000 mg; meloxicam, 7.5 mg; nabumetone, 1,000 mg; naproxen, 500 mg; piroxicam, 10 mg; sulindac, 200 mg; tenoxicam, 10 mg; and tiaprofenic acid, 450 mg.

§ Analyzed only among NSAID current users.

¶ Current users who had used the other drug group are not counted.

Acetaminophen

Current intake of acetaminophen was associated with a relative risk of 1.9 (95 percent CI: 1.5, 2.3) (table 4). The risk of symptomatic peptic ulcer was elevated months after continuous acetaminophen use but was slightly lower among long-term users. We did not find a dose response; the relative risk was 1.9 (95 percent CI: 1.5, 2.4) for doses up to 2 g and 1.8 (95 percent CI: 1.4, 2.4) for higher doses. The increase in risk did not vary much with either the primary site of the lesion or the *H. pylori* status.

Corticosteroids

Current intake of corticosteroids overall was associated with a relative risk of 1.0 (95 percent CI: 0.6, 1.5) (table 5). The risk was slightly elevated only during the first month of therapy (RR = 2.0, 95 percent CI: 1.0, 4.3).

TABLE 3. Relative risk and 95% confidence interval of peptic ulcer according to individual nonsteroidal antiinflammatory drug exposure compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

Individual NSAIDs*,†	Cases (no.)	Controls (no.)	Adjusted RR*,‡	95% CI*
Nonuse	344	3,706	Referent	
Ibuprofen	53	336	2.7	1.9, 3.8
Naproxen	24	138	3.3	2.0, 5.4
Ketoprofen	10	42	3.7	1.7, 8.0
Flurbiprofen	5	16	3.7	1.1, 11.8
Diclofenac	98	377	4.5	3.3, 6.2
Indomethacin	18	67	4.6	2.5, 8.2
Piroxicam	18	33	10.1	5.2, 19.2

* NSAIDs, nonsteroidal antiinflammatory drugs; RR, relative risk; CI, confidence interval.

† For drugs with five or more exposed cases and controls.

‡ Adjusted for age, sex, calendar year, cohort, history of gastrointestinal symptoms, smoking, and corticosteroid, gastroprotective drug, acetaminophen, and aspirin use.

Gastroprotective agents

The crude analysis showed a strong association between use of gastroprotective agents and the risk of symptomatic peptic ulcer. Adjustment for factors such as previous history of gastrointestinal symptoms and antiinflammatory drug use considerably reduced the relative risks to 1.4 (95 percent CI: 1.1, 1.9) for proton pump inhibitors, 4.0 (95 percent CI: 3.2, 5.1) for H_2 receptor antagonists, 0.5 (95 percent CI: 0.3, 0.9) for misoprostol, and 2.1 (95 percent CI: 1.7, 2.7) for antacids. In the stratified analysis by nonaspirin NSAID use, miso-

TABLE 4. Relative risk and 95% confidence interval of peptic ulcer according to recency of acetaminophen exposure, dose, and duration, compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

	Cases (no.)	Controls (no.)	Adjusted RR*,†	95% CI*
Acetaminophen recency				
Nonuse	414	5,205	Referent	
Current (0–30 days)	273	1,097	1.9	1.5, 2.3
Recent (31–180 days)	140	773	1.5	1.2, 1.9
Past (>180 days)	370	2,925	1.2	1.0, 1.4
Acetaminophen dose (mg)‡				
Nonuse	414	5,206	Referent	
≤1,000	71	366	1.5	1.1, 2.1
1,001–2,000	104	337	2.3	1.8, 3.1
2,001–4,000	98	393	1.8	1.4, 2.4
Acetaminophen duration‡				
Nonuse	414	5,205	Referent	
1–30 days	73	267	2.3	1.7, 3.2
31–180 days	66	276	1.9	1.4, 2.6
181–365 days	25	122	1.5	0.9, 2.4
>365 days	109	432	1.7	1.3, 2.2

* RR, relative risk; CI, confidence interval.

† Adjusted for age, sex, calendar year, cohort, history of gastrointestinal symptoms, smoking, and corticosteroid, gastroprotective drug, nonaspirin nonsteroidal antiinflammatory drug, and aspirin use.

‡ The effect of daily dose and duration was analyzed among current users.

TABLE 5. Relative risk and 95% confidence interval of peptic ulcer according to recency, dose, and duration of corticosteroid compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

	Cases (no.)	Controls (no.)	Adjusted RR*,†	95% CI*
Corticosteroid recency				
Nonuse	1,060	9,174	Referent	
Current (0–30 days)	29	157	1.0	0.6, 1.5
Recent (31–180 days)	28	112	1.4	0.9, 2.2
Past (>180 days)	80	557	0.8	0.6, 1.1
Corticosteroid duration‡				
Nonuse	1,060	9,174	Referent	
1–30 days	12	31	2.0	1.0, 4.3
31–180 days	6	29	1.0	0.4, 2.7
181–365 days	3	18	1.0	0.3, 3.8
>365 days	8	79	0.5	0.2, 1.1

* RR, relative risk; CI, confidence interval.

† Adjusted for age, calendar year, sex, cohort, history of gastrointestinal symptoms, smoking, and aspirin, gastroprotective drug, nonaspirin nonsteroidal antiinflammatory drug, and acetaminophen use.

‡ Analyzed only among current users.

prostol was associated with a reduced risk among current NSAID users (there was hardly any use of misoprostol in NSAID nonusers), while proton pump inhibitors, H_2 receptor antagonists, and antacids showed no risk reduction.

Misoprostol was the only gastroprotective agent associated with a reduced risk of symptomatic peptic ulcer regardless of the duration of therapy; the relative risk was 0.4 (95 percent CI: 0.2, 0.9) for patients who started taking misoprostol during the previous month and 0.5 (95 percent CI: 0.2, 1.5) for patients taking misoprostol for more than 1 month. The relative risks for treatments started during the last month were 2.9 (95 percent CI: 2.1, 4.2) for proton pump inhibitors, 8.3 (95 percent CI: 6.2, 11.2) for H_2 receptor antagonists, and 3.7 (95 percent CI: 2.8, 5) for antacids. The relative risks for treatments started more than 1 month ago were 0.6 (95 percent CI: 0.4, 1.0) for proton pump inhibitors, 1.7 (95 percent CI: 1.2, 2.4) for H_2 receptor antagonists, and 1.0 (95 percent CI: 0.6, 1.4) for antiacids. These results were similar for gastric and duodenal ulcers.

Other analyses

The risk of symptomatic peptic ulcer among current users of the antiinflammatory drugs studied above was elevated across all age categories and in both sexes, and it was similar for subjects with and without osteoarthritis. We did not find an association between the use of nitrates and the risk of symptomatic peptic ulcer.

DISCUSSION

In this population-based cohort from the United Kingdom, the incidence rate of symptomatic uncomplicated peptic ulcer was 1 per 1,000 person-years. A nested case-control analysis showed a higher risk of symptomatic uncomplicated peptic ulcer associated with the use of aspirin (RR = 2.9) and nonaspirin (RR = 4.0) NSAIDs.

These findings are consistent with those of previous studies. In clinical trials, from 1 percent to 2 percent of the patients treated during 1 year with NSAIDs developed a symptomatic ulcer (18, 19). However, clinical trials often include a very selective group of patients, and the trials have limited power to study the risk of more relatively uncommon events, such as clinically relevant ulcers. Observational studies have estimated an incidence rate of hospitalizations for noncomplicated gastrointestinal events from 0.5 to 10 per 1,000 person-years (2, 20–25); the incidence was increased from two to six times with NSAID use (2, 23, 24, 26–28). The magnitude of these incidence rates and relative risks is similar to that estimated for complicated ulcers, for which the incidence has been estimated to be in the order of one case per 1,000 person-years among nonusers (1–4) and around two and four times higher for users of aspirin and nonaspirin NSAIDs, respectively (5–7).

In our population, the increased risk of symptomatic peptic ulcer remained elevated, or even intensified, with chronic treatment beyond 6 months of NSAID use. A higher relative risk among long-term users might be due in part to a lag of time between mucosal damage and clinical symptoms/diagnosis in some patients. Persistent gastrotoxic effects throughout therapy translate into an ever-increasing cumulative risk for chronic NSAID users. For aspirin, we did not find a dose effect over the range of cardioprotective doses nor a lower risk among users of enteric coated preparations. For nonaspirin NSAIDs, we found an increased risk associated with higher doses and for slow-release formulations. The relative risk was relatively similar among individual nonaspirin NSAIDs except for piroxicam that presented a

greater risk. Nonaspirin NSAIDs presented a greater association with gastric than with duodenal ulcers.

We also considered *H. pylori* infection among cases and found that the relative risk for nonaspirin NSAID use was higher for noninfected than for infected lesions. This finding would be consistent with a protective effect of *H. pylori* infection against the ulcerogenic effect of nonaspirin NSAIDs (29). These data are intriguing, especially in light of the ongoing debate on the potential interaction between *H. pylori* and NSAIDs. However, because of incomplete data on *H. pylori* status (we did not have data on *H. pylori* for noncases, and the *H. pylori* diagnosis for cases was incomplete and not validated), our study cannot adequately contribute to our understanding of the role of *H. pylori*.

The current study has several strengths and limitations. Both cases and controls were identified from a well-defined population, which minimizes the probability of biased selection of controls. Furthermore, the population-based design expands the generalizability of the results. Drug use was ascertained prior to the diagnosis of the outcome, which minimizes the probability of information bias. The computer profiles of patients with possible peptic ulcer were manually reviewed, and cases were included in this study only when the clinical diagnosis of peptic ulcer was made during a visit to a specialist or hospitalization. In addition, we reviewed copies of original medical records of patients with an unclear ulcer site. These procedures minimize the probability of false positive cases. However, even after our effort to confirm and validate cases and our conservative exclusion of potential cases, there might still be a certain level of misclassification, which would tend to bias the results toward the null. On the other hand, due to our conservative approach and to undiagnosed ulcers among patients who do not seek medical advice, the reported incidence might be an underestimate.

Unlike most clinical trials, the current study had no information on compliance and, therefore, our observational data can only resemble an intention to treat analysis. Although the GPRD contains detailed information on prescribed medications, we did not have information on over-the-counter medications. However, nondifferential misclassification of drug use due to noncompliance or over-the-counter use would underestimate the association between NSAIDs and peptic ulcer. A preferential use of over-the-counter NSAIDs among ulcer patients, as suggested by the small amounts of NSAIDs often found in their serum despite denying the use of these drugs, would yield to an underestimation of the NSAID effect. Although differential misclassification of exposure is unlikely, a differential outcome misclassification might be plausible. That is, physicians might preferentially search for ulcers when their patients are on NSAIDs, which would reduce the probability of false negatives among NSAID users more than among nonusers. The latter would tend to overestimate the association between NSAIDs and peptic ulcer.

A plausible alternative explanation to a causal relation between NSAIDs and peptic ulcer is confounding by the indication for which the drug was prescribed. However, when we controlled for the main indications (i.e., rheumatoid arthritis and osteoarthritis) in the analysis, the association remained practically unchanged. Nonetheless, since we did not validate data on concomitant illnesses or other potential confounders such as alcohol consumption or smoking, residual confounding remains of some concern. More worrisome is the role of confounding in the association between gastroprotective drugs and peptic ulcer. Ulcers occurred more often in users of gastroprotective medications, which does not imply that these drugs are ineffective but rather that they are prescribed to high-risk patients. Patients using gastroprotective drugs were older, had a history of gastrointestinal symptoms, and were using antiinflammatory medications more often than were nonusers. Although we controlled for these well-known risk factors, residual channeling bias might explain at least partially the remaining elevated ulcer risk. Nonetheless, there was a clear trend toward protection with long-term use of proton pump inhibitors. In addition, use of misoprostol was associated with a reduced risk of developing symptomatic peptic ulcer among NSAID users. Clinical trials, which are unaffected by channeling bias, have shown the efficacy of acid-suppressing drugs in the general population and of misoprostol in NSAID users for the prevention of peptic ulcers (30).

An additional challenge encountered in the study of outcomes of the nature of uncomplicated peptic ulcers is the uncertainty around the incidence date, that is, the moment when the ulcer began. Unlike studies on severe complications or in series of screening endoscopies, the date of clinical diagnosis might occur months after the appearance of the first symptoms of peptic ulcer. Such misclassification would have several implications. The relevant drug exposure might have happened months before the date of diagnosis, which could explain the increased risk associated with NSAID use that terminated more than 1 month before the diagnosis. For the same reason, the relative risk assigned to "current" NSAID use would be under- or overestimated because of the inclusion of NSAID use that actually occurred after ulcer development. An additional potential implication of mixing incident cases with at least some prevalent cases is that part of the association found between NSAID exposure and peptic ulcer might be due to an effect on the duration of the ulcer (e.g., NSAIDs delay ulcer healing) rather than to a causal effect on the occurrence of the ulcer. Nonetheless, analyses of the data as if the actual incidence date occurred several months before the diagnosis weakened the associations (data not shown).

In summary, findings from a population-based study in the United Kingdom suggest that the incidence rate of symptomatic uncomplicated peptic ulcer is about one case per 1,000 person-years and that aspirin and nonaspirin NSAIDs multiply this risk by a factor of three and four, respectively, which is consistent with the incidences and relative risks reported in other observational studies. These findings, together with prior endoscopic evidence, suggest that NSAIDs might not only complicate preexisting peptic ulcers but also cause clinically relevant ones de novo.

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