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# Upper Gastrointestinal Bleeding Associated with the Use of NSAIDs

## Newer Versus Older Agents

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## Abstract

**Aim:** The relative gastrointestinal toxicity of NSAIDs in normal clinical practice is unknown. The aim of this study was to estimate the risk of upper gastrointestinal bleeding associated with NSAIDs and analgesics, with special emphasis on those agents that have been introduced in recent years.

**Design:** Multicentre case-control study.

**Patients:** All incident community cases of upper gastrointestinal bleeding from a gastric or duodenal lesion in patients aged >18 years of age (4309 cases). After secondary exclusions, 2813 cases and 7193 matched controls were included in the analysis.

**Setting:** Eighteen hospitals in Spain and Italy with a total study experience of 10 734 897 person-years.

**Main Outcome Measure:** Odds ratios of upper gastrointestinal bleeding for each drug, with adjustment for potential confounders. For each individual drug the reference category was defined as those not exposed to the drug.

**Results:** The incidence of upper gastrointestinal bleeding was 401.4 per million inhabitants aged >18 years. Thirty-eight percent of cases were attributable to NSAIDs. Individual risks for each NSAID were dose dependent. Ketorolac was associated with the highest risk estimate (24.7; 95% CI 8.0, 77.0). For newer NSAIDs, the risks were as follows: aceclofenac 1.4 (95% CI 0.6, 3.3), celecoxib 0.3 (95% CI 0.03, 4.1), dexketoprofen 4.9 (95% CI 1.7, 13.9), meloxicam 5.7 (95% CI 2.2, 15.0), nimesulide 3.2 (95% CI 1.9, 5.6) and rofecoxib 7.2 (95% CI 2.3, 23.0). The risk was significantly increased in patients with a history of peptic ulcer and/or upper gastrointestinal bleeding, and in those taking antiplatelet drugs.

**Conclusions:** NSAID-induced upper gastrointestinal bleeding is a common cause of hospital admission. Apart from the patient's history of peptic ulcer, its risk depends on the particular drug and its dose, and on concomitant treatments. Our results do not confirm that greater selectivity for COX-2 confers less risk of upper gastrointestinal bleeding.

Studies on upper gastrointestinal bleeding associated with NSAIDs have shown wide differences in the risk associated with each particular drug.[1-8] In recent years, new NSAIDs such as aceclofenac, dexketoprofen, nimesulide, meloxicam and, more recently celecoxib and rofecoxib, have been introduced in therapeutics. Data on the risk of upper gastrointestinal bleeding associated with their use are scarce or lacking.

We performed a multicentre case-control study with the aim of estimating the risk associated with the use of analgesics and NSAIDs, with particular interest in the newer compounds.

## Patients and Methods

Ten hospitals in Spain participated in the study from September 1998 until December 2001, and eight hospitals in Italy participated from November 1999 until December 2001. The population covered by these hospitals was $5.55 \times 10^6$ inhabitants and the total study experience was 10 734 897 person-years. Details on the ascertainment of cases and controls and on primary exclusions can be found at http://www.icf.uab.es/protocols/ugib. Secondary exclusion criteria were the same for cases and controls. Details on the reasons for excluding cases and controls can be found at http://www.icf.uab.es/protocols/ugib.

Sample size calculations were made to detect, with a power of 80%, an odds ratio of five for drugs with a prevalence of use of 0.1%, and an odds ratio of three for drugs with a prevalence of use of 0.3%, with $\alpha = 0.05$ and two controls per case.

### Cases

Records of all endoscopic procedures and lists of admission diagnoses in the participating hospitals were examined daily. All patients aged >18 years admitted with a primary diagnosis of acute upper gastrointestinal bleeding from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis, or mixed lesions were considered for inclusion. Patients with endoscopic diagnoses other than bleeding from the above specified lesions, those on anticoagulant drugs, those with blood dyscrasias and those non-resident in the study area were excluded.

### Controls

For each case, up to three hospital controls were randomly selected and matched according to centre, date of admission (within 2 months), sex and age (± 5 years). Controls were patients admitted with non-alcohol-related trauma, elective surgery for non-painful disorders, (inguinal hernia, prostate adenoma, cataracts, other elective surgery) or acute disorders not related to the use of drugs (acute pneumonia in patients without risk factors, foreign body, acute appendicitis).

### Data Retrieval

After obtaining informed consent, specially trained monitors administered a structured questionnaire within 14 days of admission. Monitors were not blind regarding the case or control status of patients. The interview covered general demographic information, detailed information on the clinical course leading to the present hospital admission, previous history with special emphasis on gastrointestinal, rheumatic and other painful conditions, vascular (heart failure, ischaemic heart disease) and endocrine conditions (diabetes mellitus), smoking, alcohol and coffee intake, and drug history, on a daily basis for the 21 days before admission (and on general basis from 22 days to 3 months), including information about the doses taken and indication for use in each day of exposure. To ensure that drug histories were as complete as possible, after an open question about previous use of drugs, the patients were questioned about a list of common symptoms often prompting use of non-opioid analgesics and NSAIDs, then they were asked to recall the trade names of the most popular non-opioid analgesics, NSAIDs, antiplatelet drugs, calcium channel antagonists and drugs used for dyspepsia and ulcer treatment, by showing patients series of colour pictures reproducing the boxes of the medicines of interest. Two lists (one for each country) were based on marketing data and they included the names of the top selling pharmaceutical specialities of each

group of interest. Relatives were allowed to accompany the patient and aid him or her in the recall exercise, but only information confirmed by the patient was collected. Patients could be phoned or re-interviewed when certain specific details on exposures (e.g. the name of a medicine) were incomplete.

### Exposure Definition

Exposures to drugs and alcohol were defined as any use in the 7 days before the index day. For each case, the index day (i.e. the day on which the upper gastrointestinal bleeding started) was defined blindly to the use of drugs. For the controls it was the day on which the accident occurred, the day of admission, or the day when symptoms appeared.

The average daily dose of each drug was obtained by dividing the cumulated dose in the week before the index day by the number of days of exposure. One to three dose categories were then defined, based on the range of doses taken, those generally recommended and the number of exposed patients in each category.

### Main Outcome Measures and Analysis

Odds ratios and their 95% CIs were calculated by means of a conditional logistic model. Individual drug terms were included in the primary analysis provided there was a minimum of five cases and five controls exposed to the particular drug. The reference category for each drug was made up of non-exposed cases and controls to this individual drug. The following variables were also included: history of peptic ulcer, diabetes, heart failure, smoking, alcohol consumption, and use of antacids, histamine $H_2$ receptor blockers, proton pump inhibitors, misoprostol, sucralfate, nitrates, antiplatelet drugs, topical NSAIDs, calcium channel antagonists and selective serotonin reuptake inhibitors. Aspirin (acetylsalicylic acid) was classified according to its indication because the magnitude of risk may change depending on the duration of use. Thus, it was classified as an antiplatelet drug when it was used for cardiovascular prophylaxis, and as an NSAID in all other indications, independently of the dose taken. When an NSAID was used concomitantly with an antiplatelet drug, these exposures were accounted by the term use of NSAIDs and antiplatelet drugs. The unadjusted odds ratio for systemic corticosteroids was 1.09 (0.69, 1.74), based on 54 cases and 87 controls exposed. An interaction between corticosteroids and NSAIDs was excluded. For these reasons, corticosteroids were removed from the model. Celecoxib had been taken by <5 cases and controls during the aetiological time span, and hence it was not included in the primary analysis as an individual term. However, given the present interest on the risk of gastrointestinal complications associated with the new selective COX-2 inhibitors, an additional analysis was performed with the same terms as in the primary analysis, plus exposure to celecoxib. In order to explore possible confounding by the concomitant use of other analgesics or NSAIDs, a separate analysis restricted to those patients who had only been exposed to one of the drugs of interest was done. Given the difficulty in obtaining information on *Helicobacter pylori* infection status among the controls, this was only recorded, when available, for a proportion of the cases. The effect of duration of therapy was assessed by stratified analysis.

For controls admitted for elective surgery, long-term drug treatments which had been electively withdrawn a few days before the operation (e.g. antiplatelet drugs) were considered as exposures in the week before the index day.

The population attributable risk was estimated for each drug with a significant adjusted odds ratio by using the proportion of cases exposed to it and its adjusted odds ratio; and was calculated according to the method described by Bruzzi et al.[9]

The protocol was approved by the Ethics Committees of the participating hospitals.

## Results

### Population

After a total study experience of 10 734 897 person-years, 4309 incident cases of upper gastrointes-

tinal bleeding were recorded, giving an incidence of 401.4 per million and per year.

After secondary exclusions, 2813 cases and 7193 controls were available for the case-control analysis.

There were no differences between cases and controls in the median time between the index date and interview. Ninety-seven percent of the cases and 99% of the controls were interviewed during the first 14 days from the index date. No differences between cases and controls were found on educational level, interview refusal rate, illiteracy or unreliable interview. Details can be found at http://www.icf.uab.es/protocols/ugib.

### Exposure to Analgesics and NSAIDs

Forty-one per cent of cases (1154) and 11.4% of controls (818) had been exposed to NSAIDs during the week before the index day. No differences in exposure rates were found among the different diagnostic categories of controls. Details can be found at http://www.icf.uab.es/protocols/ugib.

The risk of upper gastrointestinal bleeding associated with the use of any NSAID in the week before

**Table I.** Medications taken in the week before the index day

| Drug | Cases [no (%)] | Controls [no (%)] | Odds ratio (95% CI) | Population attributable risk (%) |
|---|---|---|---|---|
| **NSAIDs**[a] | | | | |
| Aceclofenac | 15 (0.5) | 30 (0.4) | 1.4 (0.6, 3.3) | –[b] |
| Aspirin (acetylsalicylic acid) | 591 (21.1) | 403 (5.7) | 8.0 (6.7, 9.6) | 18.5 |
| Dexketoprofen | 16 (0.6) | 8 (0.1) | 4.9 (1.7, 13.9) | 0.5 |
| Diclofenac | 100 (3.6) | 98 (1.4) | 3.7 (2.6, 5.4) | 2.6 |
| Ibuprofen | 60 (2.1) | 58 (0.8) | 3.1 (2.0, 4.9) | 1.5 |
| Indomethacin | 29 (1.0) | 16 (0.2) | 10.0 (4.4, 22.6) | 0.9 |
| Ketoprofen | 16 (0.6) | 9 (0.1) | 10.0 (3.9, 25.8) | 0.5 |
| Ketorolac | 33 (1.2) | 6 (0.1) | 24.7 (8.0, 77.0) | 1.1 |
| Meloxicam | 14 (0.5) | 11 (0.2) | 5.7 (2.2, 15.0) | 0.4 |
| Naproxen | 52 (1.9) | 27 (0.4) | 10.0 (5.7, 17.6) | 1.7 |
| Nimesulide | 48 (1.7) | 46 (0.6) | 3.2 (1.9, 5.6) | 1.2 |
| Piroxicam | 119 (4.3) | 40 (0.6) | 15.5 (10.0, 24.2) | 4.0 |
| Rofecoxib | 10 (0.4) | 10 (0.1) | 7.2 (2.3, 23.0) | 0.3 |
| Other NSAIDs[c] | 34 (1.2) | 33 (0.5) | 3.6 (2.0, 6.8) | 0.9 |
| NSAIDs + antiplatelet drugs[d] | 140 (5.0) | 54 (0.8) | 16.6 (11.3, 24.2) | 4.7 |
| **Analgesics** | | | | |
| Lysine clonixinate | 26 (0.9) | 47 (0.7) | 1.3 (0.7, 2.6) | –[b] |
| Metamizole | 117 (4.2) | 155 (2.2) | 1.9 (1.4, 2.6) | 2.0 |
| Paracetamol (acetaminophen) | 376 (13.4) | 612 (8.6) | 1.2 (1.0, 1.5) | –[e] |
| Propyphenazone | 17 (0.6) | 38 (0.5) | 1.3 (0.6, 2.8) | –[b] |

a Individual exposures to NSAIDs without concomitant use of antiplatelet drugs.

b The attributable risk was not calculated because the odds ratio was not statistically significant.

c Acemetacin (0 cases, 1 control), benzydamine (2, 0), celecoxib (1, 8), flurbiprofen (5, 3), glafenine (0, 2), lornoxicam (2, 3), morniflumate (0, 1), nabumetone (1, 3), niflumic acid (8, 0), phenylbutazone (1, 1), proglumetacin (0, 2), salicylamide (1, 1), sulindac (1, 1), tenoxicam (4, 2), nonspecified NSAID (9, 5).

d Aceclofenac (10 cases, 3 controls), aspirin (33, 14), celecoxib (1, 1), dexketoprofen (3, 2), diclofenac (24, 16), flurbiprofen (0, 1), glafenine (1, 0), ibuprofen (5, 2), indomethacin (5, 2), ketoprofen (3, 0), ketorolac (6, 1), meloxicam (6, 1), naproxen (10, 2), niflumic acid (2, 1), nimesulide (12, 2), piroxicam (26, 7), rofecoxib (2, 0), tenoxicam (1, 0), nonspecified NSAID (1, 0).

e The attributable risk was not calculated because its odds ratio did not show a dose-related trend.

was 8.2 (95% CI 7.1, 9.5). Table I shows the odds ratio estimates for the most commonly used NSAIDs and non-opioid analgesics. For NSAIDs, these estimates ranged from 1.4 (95% CI 0.6, 3.3) for aceclofenac, to 24.7 (95% CI 8.0, 77.0) for ketorolac. In an additional analysis celecoxib was added to the model as an independent term, yielding an odds ratio of 0.3 (95% CI 0.03, 4.1), based on two cases and ten controls exposed. Analgesics were associated with risks of upper gastrointestinal bleeding substantially lower than those for NSAIDs.

Relatively few patients had been exposed to the newer NSAIDs and the 95% CIs of the risk estimates were therefore wide. Channelling of newer NSAIDs to high-risk patients was investigated in the control patients. The assumption was that the exposure of cases may have been unrepresentative or even exceptional and patients may have developed upper gastrointestinal bleeding because of unusual drug exposure. A complementary assumption was that the pattern of drug exposure among controls would represent the pattern of exposure in the general population. Co-medications taken by patients exposed to these drugs did not materially differ from those taken by patients exposed to older NSAIDs. Controls exposed to selective cyclo-oxygenase (COX)-2 inhibitors (celecoxib, meloxicam, nimesulide or rofecoxib) [n = 80] did not substantially differ from those exposed to other nonselective NSAIDs (n = 746) in potential risk factors for upper gastrointestinal bleeding such as history of peptic ulcer or upper gastrointestinal bleeding (5% vs 9%, respectively), or concomitant use of proton-pump inhibitors (4% vs 5%), antiplatelet drugs (5% vs 7%), or nitrates. No differences were observed in risk factors among the 20 controls exposed to celecoxib or rofecoxib, compared with those exposed to other NSAIDs.

A previous history of peptic ulcer increased the risk of upper gastrointestinal bleeding. The odds ratio was 2.0 (95% CI 1.7, 2.3) in patients with antecedents of dyspepsia, 3.5 (95% CI 2.9, 4.2) in those with a history of confirmed peptic ulcer and 12.9 (95% CI 10.6, 15.8) in those with a history of upper gastrointestinal bleeding. Exposure to antiplatelet drugs was associated with a risk of 3.4 (95% CI 2.9, 4.1). There were 140 cases and 54 controls simultaneously exposed to an NSAID and an antiplatelet drug and the relative risk for this simultaneous exposure was 16.6 (95% CI 11.3, 24.2). For all NSAIDs as a group, short-term users (use of the drug for ≥3 days in the week before, but not in the 2–4 weeks before that) showed an odds ratio of 8.9 (95% CI, 7.0, 11.2), while continuing users (those who took the drug in the week before the bleed and in the 2–4 weeks before that) showed a lower risk, of 4.4 (95% CI 3.4, 5.5).

The population attributable risk for NSAIDs (excluding aspirin used for cardiovascular prophylaxis) was 38% of which 4.0% were contributed by NSAIDs used simultaneously with antiplatelet drugs.

When the analysis was restricted to those cases and controls who had only been exposed to one of the drugs of interest this gave slightly higher estimates. However, the rank order of individual risks did not change, except that the risk associated with ibuprofen was slightly higher than those of diclofenac and nimesulide (details at http://www.icf.uab.es/protocols/ugib).

Twelve cases (six in Spain and six in Italy) and ten controls (five in Spain and five in Italy) had been exposed to rofecoxib. The 95% CI of the risk estimate was therefore wide (2.3–23.0). Four cases and three controls had taken 25 mg/day, and eight cases and seven controls had taken 12.5 mg/day. Dose-related risk could therefore not be estimated. Two cases had also taken other NSAIDs (one aspirin and another nimesulide), and two additional cases were also taking prophylactic aspirin. Information on *H. pylori* status was available for five of the ten patients exposed to rofecoxib, of which three were positive and two were negative.

There was a dose-related trend in the estimates of risk (table II) for all drugs, except ketorolac. The risks associated with the lower-dose bands were particularly high for ketorolac, piroxicam, naproxen, noncardiovascular aspirin, ketoprofen and indomethacin. The doses taken by cases exposed to rofecoxib did not materially differ from those taken

by exposed controls. Dose-related risk for meloxicam could not be estimated, due to few exposed patients. Paracetamol (acetaminophen) did not show a dose-related trend for risk.

**Table II.** Analgesics and NSAIDs taken in the week before admission, by dose[a]

| Drug | Cases [no (%)] | Controls [no (%)] | Odds ratio (95% CI) |
|---|---|---|---|
| **Aceclofenac** | | | |
| ≤100 mg/day | 9 (0.3) | 17 (0.2) | 1.4 (0.5, 4.1) |
| >100 mg/day | 6 (0.2) | 13 (0.2) | 2.3 (0.5, 10.7) |
| **Aspirin (acetylsalicylic acid)** | | | |
| ≤500 mg/day | 394 (14.2) | 314 (4.5) | 7.1 (5.8, 8.7) |
| 501–1499 mg/day | 139 (5.0) | 56 (0.8) | 13.4 (9.2, 19.6) |
| ≥1500 mg/day | 42 (1.5) | 16 (0.2) | 14.6 (7.2, 29.6) |
| **Dexketoprofen** | | | |
| <50 mg/day | 4 (0.1) | 5 (0.1) | 2.3 (0.5, 11.6) |
| ≥50 mg/day | 11 (0.4) | 3 (0.0) | 18.5 (2.4, 139.2) |
| **Diclofenac** | | | |
| <75 mg/day | 35 (1.3) | 54 (0.8) | 1.8 (1.0, 3.1) |
| 75–149 mg/day | 40 (1.4) | 32 (0.5) | 4.2 (2.3, 7.6) |
| ≥150 mg/day | 21 (0.8) | 10 (0.1) | 18.2 (6.8, 48.7) |
| **Ibuprofen** | | | |
| <1200 mg/day | 36 (1.3) | 46 (0.7) | 2.1 (1.2, 3.8) |
| 1200-1799 mg/day | 14 (0.5) | 6 (0.1) | 8.5 (2.7, 27.1) |
| ≥1800 mg/day | 9 (0.3) | 3 (0.0) | 33.0 (4.2, 256.4) |
| **Indomethacin** | | | |
| ≤50 mg/day | 11 (0.4) | 8 (0.1) | 4.6 (1.2, 16.8) |
| >50 mg/day | 17 (0.6) | 8 (0.1) | 13.7 (4.8, 38.8) |
| **Ketoprofen** | | | |
| <200 mg/day | 9 (0.3) | 8 (0.1) | 4.8 (1.6, 14.5) |
| ≥200 mg/day | 7 (0.3) | 1 (0.0) | 119.4 (10.8, 1320.7) |
| **Ketorolac** | | | |
| ≤10 mg/day | 16 (0.6) | 3 (0.0) | 24.9 (4.6, 134.7) |
| >10 mg/day | 16 (0.6) | 2 (0.0) | 23.0 (4.5, 117.5) |
| **Naproxen** | | | |
| ≤750 mg/day | 25 (0.9) | 16 (0.2) | 7.6 (3.5, 16.2) |
| >750 mg/day | 26 (0.9) | 10 (0.1) | 13.4 (5.4, 33.3) |
| **Nimesulide** | | | |
| <200 mg/day | 34 (1.2) | 36 (0.5) | 3.0 (1.6, 5.5) |
| ≥200 mg/day | 14 (0.5) | 7 (0.1) | 7.0 (2.2, 22.7) |
| **Paracetamol (acetaminophen)** | | | |
| ≤650 mg/day | 197 (7.1) | 375 (5.4) | 0.9 (0.7, 1.2) |
| 651–1949 mg/day | 122 (4.4) | 158 (2.3) | 1.8 (1.3, 2.4) |
| ≥1950 mg/day | 41 (1.5) | 55 (0.8) | 1.5 (0.9, 2.6) |
| **Piroxicam** | | | |
| ≤20 mg/day | 79 (2.9) | 33 (0.5) | 12.2 (7.4, 20.2) |
| >20 mg/day | 38 (1.4) | 6 (0.1) | 31.7 (11.8, 85.4) |

a Dose-related risk could not be calculated for meloxicam or rofecoxib due to the small number of exposed patients.

Information on *H. pylori* infection status was available for 1648 cases (59%). No significant differences in the rate of *H. pylori* infection according to the particular drug were seen, except a slightly higher proportion of *H. pylori* among cases exposed to lysine clonixinate and metamizol.

## Discussion

Thirty-eight percent of all the cases of upper gastrointestinal bleeding (i.e. 152 cases per million inhabitants and per year) were attributable to NSAIDs, assuming that there is no major residual confounding or bias. This emphasises the public health impact of NSAID-induced upper gastrointestinal bleeding. The risk of the latter mainly depends on the dose and choice of drug, and also on concomitant diseases and medications. Here we report risk estimates for newer NSAIDs such as aceclofenac, dexketoprofen, meloxicam, nimesulide and rofecoxib. Although the number of exposed cases was low, we also report on the risk associated to celecoxib. By itself, COX-2 selectivity did not seem to confer much protection. Our results confirm previous reports of higher individual risks associated with ketorolac,[10-12] piroxicam,[1,2,4-8,11,12] ketoprofen,[2,4-6,8] indomethacin,[2,7,11,13] naproxen,[2,5] and aspirin,[1,10,14,15] and they indicate that the lower dose ranges of these drugs are associated with high relative risks of upper gastrointestinal bleeding. The risk was particularly increased in patients with a history of peptic ulcer or upper gastrointestinal bleeding, and in those receiving antiplatelet drugs. The estimates of the relative risks associated with analgesics were much lower than with NSAIDs.

### Effect of New NSAIDs

Rofecoxib was associated with an unexpectedly high risk estimate (OR = 7.2, 95% CI 2.3, 23.0) based on 12 cases and ten controls exposed. The risk did not change when patients exposed to a single NSAID were considered. This estimate is approximately half the risk estimate for high-dose naproxen. This is in agreement with the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) clinical trial,[16] where the risk associated with rofecoxib was half than with high-dose naproxen (0.6 events/100 patient-years with rofecoxib versus 1.4 per 100 patient-years for naproxen). However, as the risk associated with naproxen is relatively high, compared to ibuprofen and diclofenac, we suggest that its use as a reference agent both in practice and in clinical trials should be reconsidered. Although based on low numbers, the odds ratio associated to celecoxib was lower than one. Our results were similar to those of a recent cohort study from an administrative database[17] where celecoxib showed less risk than rofecoxib. Although based on few exposed patients, it is noteworthy that the risk factors associated to upper gastrointestinal bleeding in patients treated with the COX-2 selective inhibitors did not differ from those of patients treated with conventional NSAIDs.

Our results do not confirm that COX-2 selectivity is associated with better gastrointestinal tolerability. For example, although meloxicam has been classed as a relatively COX-2 selective[18,19] or as a highly selective[18,20] agent, depending on the assay system, it was associated with an intermediate risk. This confirms the results of clinical trials where the incidence of gastrointestinal events was not lower than with diclofenac, naproxen or piroxicam.[21] We found a modest risk associated to another selective COX-2 inhibitor, nimesulide, which is compatible with the experience from clinical trials,[18] although observational studies had given conflicting results.[10-12] Although piroxicam has shown similar[18] or higher[18-20] COX-2 selectivity than ibuprofen *in vitro*, it was associated with one of the highest individual risks of upper gastrointestinal bleeding. Rofecoxib shows a >50-fold COX-2 selectivity,[18] but nevertheless it was associated with an intermediate individual risk. As in previous studies, low-dose ibuprofen and low-dose diclofenac were associated with low risk estimates. Aceclofenac at both dose ranges appeared to be associated with a low risk, thus confirming the results of an observational study[22] and of clinical trials.[23]

### Validity

Bias in the selection of cases and controls is unlikely. Cases were ascertained by a method that is independent of previous exposures. The controls were patients with conditions unrelated to the use of the drugs of interest, and previous studies on upper gastrointestinal bleeding did not find any differences in the prevalence of use of the drugs of interest between hospital and community controls.[2,3] The prevalence of use of analgesics and NSAIDs among controls was similar across the various diagnostic categories.

To reduce information bias, patients were excluded if they could not be interviewed within 14 days of admission, and information on exposures was carefully collected, by means of a structured questionnaire.

Potential confounding by various factors was controlled by multivariate analysis including all known risk factors for upper gastrointestinal bleeding, by restriction, and by stratified analyses by matching factors. The odds ratio estimates for patients exposed to only one NSAID were not materially different from those for the whole study population, indicating adequate control of confounding by simultaneous exposures among different NSAIDs.

Our risk estimates for individual NSAIDs were generally slightly higher than those found in previous studies. There are five complementary explanations for this. First, we considered an aetiological window of 1 week, because, based on the current knowledge about the mechanisms of NSAID-induced upper gastrointestinal bleeding, it can be assumed that 1 week after the last drug exposure the risk would be negligible. Other studies have considered exposure in the month before or even in the 3 months before. We believe that inappropriate widening of the aetiological window results in dilution and underestimation of the true risk. Second, we considered actual use referred by the patients, while other studies have considered a surrogate indicator of exposure, i.e. the prescription of the drugs of interest, which tends to dilute the magnitude of the risk and does not allow considering potential confounding such as exposure to over-the-counter drugs. Third, adjusted risk ratios in the multivariate model were higher than crude values (not shown), suggesting that consideration of potential confounders – which is not possible in studies where detailed information is not available – gives higher (but more reliable) estimates of risk. Fourth, we used a conditional model, which gives higher coefficient estimates. Fifth, we included patients aged >18 years, while other studies have generally excluded those aged <65. As the relative risk of upper gastrointestinal bleeding associated with NSAID is higher in younger patients,[1,9] this may have contributed to higher relative risks estimates.

## Conclusion

NSAID-induced upper gastrointestinal bleeding is common. Its risk varies widely depending on the individual drug, its dose, concomitant medications, and individual patients' risk factors such as previous history of peptic ulcer. Among the newer NSAIDs, aceclofenac and nimesulide were associated with low risks, and dexketoprofen, meloxicam and rofecoxib were associated with intermediate risks. Our results do not support the view that COX-2 selectivity confers better gastrointestinal safety. Ketorolac, piroxicam, ketoprofen, indomethacin, naproxen and noncardiovascular aspirin were associated with particularly high individual risks of upper gastrointestinal bleeding, even at low doses. In the majority of patients with non-inflammatory musculoskeletal pain, analgesics and those NSAIDs associated with relatively lower risks of upper gastrointestinal bleeding should be the first choice alternatives, at the lowest effective dose.

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