Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis

Julia Hippisley-Cox, Carol Coupland, Richard Logan

Abstract

Objective To determine the risk of an adverse upper gastrointestinal event in patients taking different cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs.

Design Nested case-control study.

Setting 367 general practices contributing to the UK QRESEARCH database, spread throughout every strategic health authority and each health board in England, Wales, and Scotland.

Participants Patients aged 25 or more with a first ever diagnosis of an adverse upper gastrointestinal event (peptic ulcer or haematemesis) between 1 August 2000 and 31 July 2004 and up to 10 controls per case matched for age, sex, calendar time, and practice.

Main outcome measures Unadjusted and adjusted odds ratios for adverse upper gastrointestinal events associated with celecoxib, rofecoxib, ibuprofen, diclofenac, naproxen, other selective and non-selective non-steroidal anti-inflammatory drugs, and aspirin.

Results The incidence of adverse upper gastrointestinal events was 1.36 per 1000 person years (95% confidence interval 1.34 to 1.39). We identified 9407 incident cases and 88 867 matched controls. Increased risks of adverse gastrointestinal events were associated with current use of cyclo-oxygenase-2 inhibitors and with conventional non-steroidal anti-inflammatory drugs. Risks were reduced after adjustment for confounders but remained significantly increased for naproxen (adjusted odds ratio 2.12, 95% confidence interval 1.73 to 2.58), diclofenac (1.96, 1.78 to 2.15), and rofecoxib (1.56, 1.30 to 1.87) but not for current use of celecoxib (1.11, 0.87 to 1.41). We found clinically important interactions with current use of ulcer healing drugs that removed the increased risks for adverse gastrointestinal events for all groups of non-steroidal anti-inflammatory drugs except diclofenac, which still had an increased odds ratio (1.49, 1.26 to 1.76).

Conclusion No consistent evidence was found of enhanced safety against gastrointestinal events with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs. The use of ulcer healing drugs reduced the increased risk of adverse gastrointestinal outcomes with all groups of non-steroidal anti-inflammatory drugs, but for diclofenac the increased risk remained significant.

Introduction

Non-steroidal anti-inflammatory drugs are among the most commonly prescribed drugs in England and Wales. They are widely used for musculoskeletal pain but can cause serious gastrointestinal side effects, including dyspepsia, peptic ulceration, and haemorrhage, and even result in death. Cyclo-oxygenase-2 inhibitors are a selective type of non-steroidal anti-inflammatory drug licensed in the United Kingdom for symptomatic relief in osteoarthritis and rheumatoid arthritis. They were developed to provide pain relief without the gastrointestinal side effects associated with traditional non-steroidal anti-inflammatory drugs, and their use is already recommended in UK national guidelines.[1] The current treatment options include a traditional non-steroidal anti-inflammatory drug with an ulcer healing drug or a cyclo-oxygenase-2 inhibitor alone. However, trial data to support this, especially for elderly people, are sparse.[2]

Considerable uncertainty surrounds the long term risks associated with cyclo-oxygenase-2 inhibitors outside the trial setting.[3–5] Indeed, rofecoxib has been temporarily withdrawn owing to its adverse cardiovascular profile, and the safety profile of all cyclo-oxygenase-2 inhibitors is under review. The celecoxib long term arthritis safety study, which compared celecoxib with conventional non-steroidal anti-inflammatory drugs, has been criticised on the grounds of study design, analysis, selective presentation of results,[3] increased rates of ulcers after six months of treatment,[3] overall higher rates of extra gastrointestinal adverse events,[4] and lack of data on long term safety.[6] Although other smaller short term trials have shown fewer ulcers under endoscopy in patients taking cyclo-oxygenase-2 inhibitors,[7] it is not known how these ulcers relate to clinical endpoints.

We undertook a population based nested case-control study, using a new general practice research database to determine the comparative risk of adverse upper gastrointestinal events in patients taking different cyclo-oxygenase-2 inhibitors and conventional non-steroidal anti-inflammatory drugs in primary care between 2000 and 2004. A separate paper has examined the risk of myocardial infarction in patients taking non-steroidal anti-inflammatory drugs.[8]

Methods

We carried out our study using UK general practices contributing to the QRESEARCH database (www.qresearch.org).

This is a new clinical database containing the records of over 7 million patients ever registered with 468 practices over the past 16 years throughout every strategic health authority and each health board in England, Wales, and Scotland. QRESEARCH is an aggregated patient level database derived from practices that use the EMIS computer system. EMIS is the major supplier of primary care computer systems in the UK and its systems are in use in two thirds of UK general practices (www.emis-online.com). Information recorded on the database includes patient demographics (year of birth, sex, geographical region), characteristics (height, weight, smoking status), symptoms, clinical diagnoses, consultations, referrals, and prescribed drugs. The computer codes used to record clinical diagnoses in UK general practices are known as Read codes. This hierarchical clinical coding system is analogous to the coding system of the international classification of diseases, 10th revision, which is used in secondary care in the United Kingdom.

The database also contains Townsend scores for each patient derived from the UK 2001 census, according to the characteristics of the output area associated with the patients' postcode. Output areas consist of about 125 households and are nested within larger administrative areas, known as electoral wards. The Townsend score is a validated measure of material deprivation[9] and is a composite score based on unemployment, overcrowding, lack of a car, and non-owner occupation. It is strongly related to morbidity,[10 11] use of routine and emergency services,[12 13] and mortality.[14] Higher scores indicate greater levels of deprivation.

QRESEARCH has been validated by comparing the rates of birth, death, consultation, prevalence, and mortality with other data sources, including the general household survey and the general practice research database.[15] The age-sex structure of the population has been compared with that reported in the 2001 census and with the attribution dataset for practices in England and Wales in 2004. We found a good correspondence for all of these measures (data not shown), although in some instances our values for prevalence[16] are marginally higher than less recent data. We have also compared practices taking part in regional research networks on these and other measures and found a good correspondence.[17] Detailed analyses have shown good levels of completeness and consistency.[18] Similar databases have been used for studies investigating risk factors for coronary heart disease[19–22] or effects of conventional non-steroidal anti-inflammatory drugs.[20] In previous studies the diagnosis of acute myocardial infarction has been confirmed by reviewing hospital discharge notes[21 22] or comparing with paper based records[23] and has been found to be correct in over 90% of cases.

We used the fourth version of the QRESEARCH database (downloaded 1 August 2004) for this analysis, which contained 468 practices.

Identification of the cohort

We identified a cohort of patients registered on 1 August 2000. Patients had to have been registered with the practices for the whole of the preceding 12 months to be included. We only included practices that had their current EMIS computer system installed before 1 August 1999 to ensure that there was complete prescribing and population data for each patient in the cohort.

Our study period ran from 1 August 2000 to 31 July 2004. We selected this period as both rofecoxib and celecoxib were available on prescription in the United Kingdom. Patients entered the risk period on 1 August 2000 and left the risk period when they developed an adverse upper gastrointestinal event, died, left the practice, or the study ended.

We identified patients with a first ever adverse upper gastrointestinal outcome as those with a first ever recorded. Read codes for peptic ulcer (including those with a perforation or requiring surgery) or evidence of upper gastrointestinal haemorrhage during the study period. We included similar Read codes for gastrointestinal haemorrhage to those published elsewhere.[24] We categorised these into complicated events (those involving haemorrhage, perforation, or surgery) and uncomplicated events outcomes (codes not shown). Patients were excluded who had already had a diagnosis of an adverse upper gastrointestinal event before the study period. We used this cohort to determine age and sex specific event rates of adverse upper gastrointestinal outcomes.

Case-control analysis

Cases were all patients with an adverse upper gastrointestinal event identified in the cohort analysis and aged 25 years or more at diagnosis. To ensure that the prescribing data were complete, we restricted the cases to patients who had at least three years of continuous medical history recorded on computer before their index date.

We matched up to 10 controls for each case. Controls were patients without any diagnosis of upper gastrointestinal events who had at least three years of recorded medical history on computer. Controls were matched to cases by age (at diagnosis of case), calendar time, sex, and practice using incidence density sampling. Controls were alive and registered with the practice at the time when their matched case developed an adverse upper gastrointestinal event. We derived an index date for each control that corresponded to the date of the adverse upper gastrointestinal event of their matched case.

Assessment of exposure

We used standardised computerised routines to extract and code data on the medical history and use of prescribed drugs before the index date for each set of cases and controls. We identified all prescriptions for selective and non-selective non-steroidal anti-inflammatory drugs and aspirin issued in the three years before the index date in cases and controls. Twenty seven different non-steroidal anti-inflammatory drugs were in use during the study period. We grouped the drugs according to usage and type: celecoxib, rofecoxib, ibuprofen, diclofenac, naproxen, other cyclo-oxygenase-2 inhibitors (meloxicam, etoricoxib, etodolac, valdecoxib, and parecoxib), other non-selective non-steroidal anti-inflammatory drugs (aceclofenac, acemetacin, azapropazone, dexketoprofen, trometamol, diflunisal, fenbufen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, lornoxicam, nabumetone, piroxicam, sulindac, tenoxicam, and tiaprofenic acid), and aspirin.

We used data from the prescribing cost analysis tool PACT to validate prescribing data for each group of non-steroidal anti-inflammatory drugs. This tool comprises a national dataset and analyses drugs prescribed by general practice in terms of cost and number of items (volume). At an organisational level, the tool is used to monitor and control prescribing cost and to set prescribing budgets. We compared the prescribing rates per 1000 population for non-steroidal anti-inflammatory drugs from the QRESEARCH database with the national dataset for 2002 and found similar rates and rank order for the preparations.

Combination preparations such as diclofenac and misoprostol (an ulcer healing drug) were analysed according to their individual constituents—that is, a patient taking this combination would be coded as being prescribed diclofenac and also misopr-

ostol. We included any preparation containing aspirin as a constituent in the aspirin category.

For each drug group we identified the first and last date for prescriptions and the total number of prescriptions issued during the three years before the index date. We coded exposure according to the time since last prescription into three mutually exclusive groups: drug not prescribed in past three years, drug prescribed within 90 days (defined as current use), and drug prescribed more than 90 days ago (past use). We categorised the number of prescriptions as 0, 1 to 3, and more than 3 and tested for evidence of a trend using the number of prescriptions issued.

Statistical analysis

We used conditional logistic regression for individually matched case-control studies to derive unadjusted and adjusted odds ratios and 95% confidence intervals for adverse upper gastrointestinal outcomes associated with each of the drug groups. The multivariate models contained variables related to the timing of the last prescription or the number of prescriptions for all of the individual non-steroidal anti-inflammatory drug groups and also adjusted for possible confounding effects of smoking (smoker, non-smoker, not recorded), obesity, deprivation (Townsend score in fifths), ulcer healing drugs, antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants),[19] and statins.[25] We also adjusted for comorbidity by creating binary variables to indicate which patients had a computer recorded diagnosis for each of the following diseases: diabetes, hypertension, ischaemic heart disease, osteoarthritis, or rheumatoid arthritis. We repeated this analysis excluding cases and controls who did not have recorded values for body mass index and smoking status.

We included interaction terms in the multivariate model to examine interactions between current use of each of the individual non-steroidal anti-inflammatory drug groups and current use of ulcer healing drugs. We examined interactions with current use of aspirin in the same way.

We repeated the analyses, first including only complicated cases and their matched controls and then uncomplicated cases and their matched controls, and we compared the results. All the analyses were carried out using STATA (version 8.2). We selected a P value of <0.01 (two tailed) as statistically significant.

Results

Over the four year study period 10 892 patients had a first ever diagnosis of an adverse upper gastrointestinal event from a total of 7 993 371 person years of observation. The overall incidence rate of upper gastrointestinal events for all ages was 1.36 per 1000 person years (95% confidence interval 1.34 to 1.39). The incidence rates were higher in men than in women and increased steeply with age (figure), with the highest rates in patients aged 90 to 94 (6.96 per 1000 person years, 6.30 to 7.69). The incidence rate for patients aged 65 or more was 4.03 per 1000 person years.

Baseline characteristics

We identified 9407 cases aged 25 or more with at least three years of recorded medical data, and we matched 88 867 controls by age, sex, practice, and calendar time. Table 1 shows the baseline characteristics of cases and controls. Of the 9407 cases, 4176 (44.4%) had an uncomplicated event and 5231 (55.6%) had a complicated event (haemorrhage, perforation, or surgery). Cases and controls were well matched for age and sex. A higher percentage of cases were obese, smoked, had pre-existing comorbidities (ischaemic heart disease, diabetes, hypertension, osteoarthritis, rheumatoid arthritis), and had used antidepressants, statins, and ulcer healing drugs.

Table 1 Characteristics of cases with adverse upper gastrointestinal event and matched controls (up to 10 per case matched on age, calendar year, sex, and practice). Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=9407)	Controls (n=88 867)
Women	4436 (47.2)	42 166 (47.4)
Men	4971 (52.8)	46 701 (52.6)
Median age at index date (interquartile range)	68 (53-79)	67 (52-78)
Median No of months of data before index date (interquartile range)	87 (63 to 117)	87 (63 to 117)
Median Townsend score associated with output area (interquartile range)*	−0.64 (−2.82-2.58)	−1.04 (−3.03-2.17)
Body mass index (kg/m^2):		
<30	5662 (60.2)	51 554 (58.0)
30	1456 (15.5)	12 241 (13.8)
Not recorded	2289 (24.3)	25 072 (28.2)
Smoking status:		
Non-smoker	5585 (59.4)	54 432 (61.3)
Smoker	2497 (26.5)	17 015 (19.1)
Not recorded	1325 (14.1)	17 420 (19.6)
Morbidity before index date:		
Ischaemic heart disease	1691 (18.0)	10 054 (11.3)
Diabetes	885 (9.4)	5708 (6.4)
Hypertension	2959 (31.5)	23 904 (26.9)
Osteoarthritis	1636 (17.4)	11 385 (12.8)
Rheumatoid arthritis	242 (2.6)	1144 (1.3)
Drugs in three years before index date:		
Statins	1297 (13.8)	8697 (9.8)
Triyclic antidepressants	1649 (17.5)	9017 (10.1)
Selective serotonin reuptake inhibitors	1419 (15.1)	6959 (7.8)
Ulcer healing drugs	4310 (45.8)	15 091 (17.0)

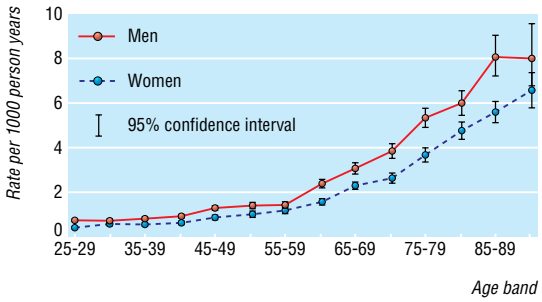
*Odds ratio compares risk in most deprived fifth compared with most affluent fifth.

Use of cyclo-oxygenase-2 and conventional non-steroidal anti-inflammatory drugs

Of the 9407 cases, 4253 (45.2%) had been prescribed a non-steroidal anti-inflammatory drug in the previous three years compared with 29 615 (33.3% of 88 867) of controls (unadjusted odds ratio 1.69, 1.62 to 1.77, $P<0.001$). Of the 9407 cases, 931 (9.9%) had been prescribed a cyclo-oxygenase-2 inhibitor in the previous three years compared with 4978 (5.6%) of the 88 867 controls (1.89, 1.75 to 2.04, $P<0.001$).

Timing of last prescription

Table 2 shows the odds ratios for adverse upper gastrointestinal events by time since last prescription. The unadjusted analysis showed an increase in risk associated with every type of



Incidence of peptic ulcer or gastrointestinal haemorrhage per 1000 person years in patients registered with 367 practices contributing data to QRESEARCH database, August 2000 to July 2004

Table 2 Odds ratio for adverse gastrointestinal event according to timing of last prescription during three years before index date

Drug and time of last prescription	No (%) of cases (n=9407)	No (%) of controls (n=88 867)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P value
Celecoxib:					
No prescription in past 3 years	9147 (97.2)	87 457 (98.4)	1.00	1.00	
>90 days before index date	156 (1.7)	880 (1.0)	1.70 (1.42 to 2.02)	0.97 (0.80 to 1.18)	0.76
≤90 days before index date	104 (1.1)	530 (0.6)	1.87 (1.50 to 2.31)	1.11 (0.87 to 1.41)	0.39
Rofecoxib:					
No prescription in past 3 years	8939 (95.0)	86 633 (97.5)	1.00	1.00	
>90 days before index date	263 (2.8)	1449 (1.6)	1.79 (1.56 to 2.06)	1.04 (0.89 to 1.21)	0.65
≤90 days before index date	205 (2.2)	785 (0.9)	2.54 (2.17 to 2.98)	1.56 (1.30 to 1.87)	<0.001
Other selective non-steroidal anti-inflammatory drugs:					
No prescription in past 3 years	9054 (96.2)	86 942 (97.8)	1.00	1.00	
>90 days before index date	205 (2.2)	1367 (1.5)	1.46 (1.26 to 1.70)	0.90 (0.76 to 1.06)	0.21
≤90 days before index date	148 (1.6)	558 (0.6)	2.58 (2.14 to 3.11)	1.75 (1.41 to 2.15)	<0.001
Ibuprofen:					
no prescription in past 3 years	7332 (77.9)	73 432 (82.6)	1.00	1.00	
>90 days before index date	1598 (17.0)	12 476 (14.0)	1.29 (1.22 to 1.37)	1.04 (0.97 to 1.11)	0.30
≤90 days before index date	477 (5.1)	2959 (3.3)	1.63 (1.47 to 1.80)	1.42 (1.27 to 1.59)	<0.001
Diclofenac:					
No prescription in past 3 years	7208 (76.6)	74902 (84.3)	1.00	1.00	
>90 days before index date	1429 (15.2)	10 737 (12.1)	1.43 (1.35 to 1.52)	1.10 (1.03 to 1.18)	0.01
≤90 days before index date	770 (8.2)	3228 (3.6)	2.55 (2.34 to 2.77)	1.96 (1.78 to 2.15)	<0.001
Naproxen:					
No prescription in past 3 years	8889 (94.5)	85 796 (96.5)	1.00	1.00	
>90 days before index date	364 (3.9)	2433 (2.7)	1.50 (1.33 to 1.68)	1.12 (0.99 to 1.27)	0.08
≤90 days before index date	154 (1.6)	638 (0.7)	2.45 (2.05 to 2.94)	2.12 (1.73 to 2.58)	<0.001
Other non-selective non-steroidal anti-inflammatory drugs:					
No prescription in past 3 years	8540 (90.8)	83 826 (94.3)	1.00	1.00	
>90 days before index date	585 (6.2)	3835 (4.3)	1.52 (1.39 to 1.67)	1.10 (0.99 to 1.22)	0.07
≤90 days before index date	282 (3.0)	1206 (1.4)	2.29 (2.00 to 2.62)	1.67 (1.43 to 1.94)	<0.001
Aspirin:					
No prescription in past 3 years	6406 (68.1)	71 328 (80.3)	1.00	1.00	
>90 days before index date	771 (8.2)	4314 (4.9)	2.12 (1.95 to 2.31)	1.64 (1.49 to 1.81)	<0.001
≤90 days before index date	2230 (23.7)	13 225 (14.9)	2.03 (1.92 to 2.15)	1.60 (1.49 to 1.72)	<0.001

*Adjusted simultaneously for each other non-steroidal anti-inflammatory drug, ischaemic heart disease, diabetes, hypertension, statins, ulcer healing drugs, tricyclics, selective serotonin reuptake inhibitors, osteoarthritis, rheumatoid arthritis, smoking, obesity, and deprivation.

non-steroidal anti-inflammatory drug for patients currently prescribed the drug (within 90 days) or prescribed it more than 90 days ago compared with those not prescribed it in the previous three years.

The odds ratios were adjusted for each other non-steroidal anti-inflammatory drug group, smoking status, comorbidity, deprivation, use of selective serotonin reuptake inhibitors, tricyclic antidepressants, statins, aspirin, and ulcer healing drugs.

Once adjustments were made for these potential confounding variables, the highest odds ratio was associated with current use of naproxen (2.12, 1.73 to 2.58), followed by current use of diclofenac (1.96, 1.78 to 2.15), other cyclo-oxygenase-2 inhibitors (1.75, 1.41 to 2.15), other non-selective non-steroidal anti-inflammatory drugs (1.67, 1.43 to 1.94), aspirin (1.60, 1.49 to 1.72), rofecoxib (1.56, 1.30 to 1.87), and ibuprofen (1.42, 1.27 to 1.59) each compared with no prescription for the drug in the previous three years. We found no significantly increased risk for current use of celecoxib (1.11, 0.87 to 1.41), but the number of patients taking celecoxib was low.

Previous use of diclofenac and aspirin was associated with significantly increased odds ratios, but we found no associations with previous use of the other drug groups.

Results were similar when restricted to cases and controls with body mass index and smoking status recorded and also when restricted to patients aged 65 or more.

Interactions with ulcer healing drugs

We found significant interactions ($P < 0.001$) between ulcer healing drugs and each type of non-steroidal anti-inflammatory drug except for celecoxib, which was associated with the lowest risk of adverse gastrointestinal events (table 3). All the interaction ratios were less than 1.0, indicating that the risk of adverse gastrointestinal events associated with taking non-steroidal anti-inflammatory drugs is lower in patients also taking ulcer healing drugs than in patients not taking ulcer healing drugs (table 3).

Current use of all non-steroidal anti-inflammatory drugs was associated with significantly increased risks of adverse gastrointestinal outcomes in patients not currently taking ulcer healing drugs. For example, the adjusted odds ratio for current use of naproxen was 2.73 (2.20 to 3.38), for rofecoxib was 2.33 (1.87 to 2.90), and for diclofenac was 2.17 (1.95 to 2.42).

In patients prescribed ulcer healing drugs within the past 90 days, current use of all non-steroidal anti-inflammatory drug groups showed no significantly increased risk of gastrointestinal outcomes, except for diclofenac, which was associated with a significantly increased adjusted odds ratio (1.49, 1.26 to 1.76), although this was significantly lower ($P < 0.001$) than the adjusted odds ratio for patients taking diclofenac but not taking ulcer healing drugs.

The adjusted odds ratio with diclofenac in patients taking proton pump inhibitors was 1.56 (1.28 to 1.90) and in patients

Table 3 Risk of adverse upper gastrointestinal events associated with non-steroidal anti-inflammatory drugs according to use of ulcer healing drugs. Values are adjusted odds ratios* unless stated otherwise

Drug prescribed ≤90 days before index date†	Not prescribed ulcer healing drugs in past 90 days	Prescribed ulcer healing drugs in past 90 days	Interaction ratio‡ (95% CI)	P value for interaction
Celecoxib	1.44	1.06	0.73 (0.46 to 1.16)	0.18
Rofecoxib	2.33	1.06	0.45 (0.32 to 0.65)	<0.001
Other selective non-steroidal anti-inflammatory drugs	2.40	1.29	0.54 (0.36 to 0.81)	<0.001
Ibuprofen	1.65	0.90	0.55 (0.43 to 0.70)	<0.001
Diclofenac	2.17	1.49	0.69 (0.56 to 0.84)	<0.001
Naproxen	2.73	0.83	0.31 (0.19 to 0.49)	<0.001
Other non selective non-steroidal anti-inflammatory drugs	2.03	1.16	0.57 (0.42 to 0.77)	<0.001
Aspirin	1.87	0.81	0.43 (0.38 to 0.49)	<0.001

*Adjusted for each other non-steroidal anti-inflammatory drug, ischaemic heart disease, diabetes, hypertension, statins, trycyclics, selective serotonin reuptake inhibitors, osteoarthritis, rheumatoid arthritis, smoking, obesity, and deprivation.
†Compared with no prescription for drug ≤90 days before index date.
‡Ratio of odds ratios for current use of non-steroidal anti-inflammatory drug in those prescribed ulcer healing drugs compared with those not prescribed ulcer healing drugs in 90 days before index date.

taking misoprostol was 1.34 (0.99 to 1.81), both compared with no current use of diclofenac. These two odds ratios were not significantly different from each other (P = 0.41).

Interactions with aspirin

We found a significant interaction between rofecoxib and aspirin and between other non-selective non-steroidal anti-inflammatory drugs and aspirin. The adjusted odds ratio for current use of rofecoxib in patients currently taking aspirin was 2.98 (2.24 to 3.99) and in those not currently taking aspirin it was 1.22 (0.97 to 1.54).

In patients who were not currently taking aspirin the adjusted odds ratio for current use of other non-selective non-steroidal anti-inflammatory drugs was 1.96 (1.66 to 2.33), whereas in patients taking aspirin the adjusted odds ratio for current use of other non-selective non-steroidal anti-inflammatory drugs was 1.07 (0.79 to 1.45).

Number of prescriptions issued

We determined the odds ratios associated with adverse upper gastrointestinal events according to the number of prescriptions issued. Apart from celecoxib, we found significant trends (P < 0.01) for all drugs, with greater number of prescriptions associated with higher risks of adverse outcomes.

Complicated versus uncomplicated outcomes

Table 4 shows the adjusted odds ratios from separate analyses of uncomplicated and complicated adverse upper gastrointestinal events. The odds ratios for current use of different drugs tended to be higher for complicated events, with the exception of naproxen, other cyclo-oxygenase-2 inhibitors, and other non-selective non-steroidal anti-inflammatory drugs, where the odds ratios were slightly lower.

Analysis by time period

We examined the four year study period in two parts. In the first two years of the study (1 August 2000 to 31 July 2002) the adjusted odds ratio for current use of rofecoxib compared with non-use was 1.76 (1.32 to 2.34). For the second period (1 August 2002 to 31 July 2004) the adjusted odds ratio was 1.67 (1.33 to 2.11; test for interaction P = 0.80).

Discussion

Overall we found no strong evidence of enhanced gastrointestinal safety with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs. Ulcer healing drugs were associated with a reduction in risk of adverse events for cyclo-oxygenase-2 inhibitors as a whole, which suggests that there is some risk to protect against and that these drugs may not be as safe as originally thought. Given that enhanced gastrointestinal safety has been one of the main justifications for these drugs, this finding is important.

We found significant interactions between current use of each of the non-steroidal anti-inflammatory drug groups and ulcer healing drugs, with the exception of celecoxib, for which the absolute number of patients taking this drug was low. The risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors and conventional non-steroidal anti-inflammatory drugs was substantially reduced by concurrent use of ulcer healing drugs but for diclofenac the increased risk persisted. Our study design did not allow us to determine why the risk of adverse events for diclofenac persisted in the presence of ulcer healing drugs, and this may represent a chance finding. The risk associated with diclofenac in conjunction with proton pump inhibitors was similar to the risk associated with diclofenac in conjunction with misoprostol.

This is an observational study and may be subject to residual confounding that cannot be fully corrected for. The overall increased risks of gastrointestinal events associated with diclofenac and naproxen were, however, expected, and the overall rank order compares well with previous research.[26] Our odds ratios tended to be lower than those found previously, which is likely to reflect increased simultaneous use of ulcer healing drugs, as shown by our analysis of interactions.

A consistent finding was of no increased risk of adverse gastrointestinal outcomes associated with celecoxib, although celecoxib use was lower than for the other non-steroidal anti-inflammatory drugs so confidence intervals were wider and hence the results more difficult to interpret. In contrast we were concerned to find an increased risk among patients taking rofecoxib since a lower risk of adverse gastrointestinal outcomes was one of the main justifications for its use. We found no evidence that this risk declined with time as it was similar in the first two years and the last two years of the study period. Although rofecoxib has recently been withdrawn, our analysis provides no evidence of enhanced gastrointestinal safety for the other cyclo-oxygenase-2 inhibitors, for which current usage of individual agents is still low.

Methodology

We considered possible causes of bias and confounding in our analysis. We considered whether indication bias (channelling)[24] might be an explanation for our results—that is, patients who were perceived to be at a higher risk of an adverse upper gastrointestinal event were more likely to be prescribed one of the new cyclo-oxygenase-2 inhibitors than patients at lower risk. As our analysis included adjustment for many potential confounders, including comorbidity, concurrent drug use, and deprivation, we would expect this to have minimised the effect of any such bias. We also found no reduction in risk over time despite the increasing use of rofecoxib.

Routinely collected data from aggregated general practice databases has been used successfully to evaluate risks and benefits of treatments in the population.[27 28] This method has the advantages of longitudinal data, large sample size, and access to representative populations. In addition, the exposure data are

Table 4 Risk of uncomplicated and complicated adverse gastrointestinal event according to timing of last prescription during three years before index date

	Uncomplicated adverse gastrointestinal event		Complicated adverse gastrointestinal event	
Drug and time of last prescription	**Adjusted odds ratio* (95% CI)**	**P value**	**Adjusted odds ratio* (95% CI)**	**P value**
Celecoxib:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	0.93 (0.68 to 1.26)	0.63	1.00 (0.77 to 1.29)	0.97
≤90 days before index date	0.96 (0.67 to 1.37)	0.81	1.25 (0.91 to 1.72)	0.16
Rofecoxib:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	0.94 (0.75 to 1.17)	0.56	1.14 (0.93 to 1.41)	0.22
≤90 days before index date	1.29 (0.97 to 1.73)	0.08	1.79 (1.42 to 2.26)	<0.001
Other selective non-steroidal anti-inflammatory drugs:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	0.93 (0.72 to 1.19)	0.55	0.87 (0.69 to 1.10)	0.24
≤90 days before index date	1.80 (1.31 to 2.46)	<0.001	1.72 (1.29 to 2.29)	<0.001
Ibuprofen:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	1.01 (0.92 to 1.12)	0.80	1.05 (0.96 to 1.15)	0.27
<90 days before index date	1.22 (1.02 to 1.46)	0.03	1.58 (1.37 to 1.83)	<0.001
Diclofenac:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	1.12 (1.01 to 1.24)	0.03	1.09 (0.99 to 1.19)	0.08
≤90 days before index date	1.90 (1.64 to 2.19)	<0.001	2.07 (1.82 to 2.35)	<0.001
Naproxen:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	1.21 (1.01 to 1.46)	0.04	1.06 (0.89 to 1.26)	0.53
≤90 days before index date	2.31 (1.74 to 3.07)	<0.001	1.97 (1.48 to 2.61)	<0.001
Other non-selective non-steroidal anti-inflammatory drugs:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	1.14 (0.98 to 1.32)	0.10	1.08 (0.94 to 1.24)	0.30
≤90 days before index date	1.72 (1.38 to 2.14)	<0.001	1.59 (1.29 to 1.96)	<0.001
Aspirin:				
No prescription in past 3 years	1.00		1.00	
>90 days before index date	1.50 (1.30 to 1.74)	<0.001	1.76 (1.55 to 2.01)	<0.001
≤90 days before index date	1.44 (1.29 to 1.61)	<0.001	1.75 (1.59 to 1.93)	<0.001

*Adjusted for each other non-steroidal anti-inflammatory drug, ischaemic heart disease, diabetes, hypertension, statins, ulcer healing drugs, tricyclics, selective serotonin reuptake inhibitors, osteoarthritis, rheumatoid arthritis, smoking, obesity, and deprivation.

collected before the outcome, so eliminating recall bias; the quality of the electronic record now surpasses the conventional paper based system.[29]

Our cases and controls were well matched on age, sex, and practice, making this an appropriate environment to assess the effects of different non-steroidal anti-inflammatory drugs on risk of adverse upper gastrointestinal events. This approach allowed us to examine timing and duration and also to investigate interactions with aspirin and ulcer healing drugs. Misclassification of exposure status is unlikely as more than 99% of repeat prescriptions from general practice are recorded on computer, and currently most of these drugs are not available without prescription. The exceptions are ibuprofen and aspirin, which are available without a prescription. Hence some patients taking ibuprofen "over the counter" might have been misclassified as not taking ibuprofen; likewise for aspirin. Similarly, some patients may have taken over the counter proton pump inhibitors. This is likely to be a small proportion in patients aged over 65 as they are entitled to free prescriptions in the United Kingdom and so tend to have these prescribed. In an analysis comparing the risks associated with ibuprofen and aspirin in patients aged less than 65 and 65 or more, results were similar in the two age groups. Also such misclassification, if present and if non-differential, would have had the effect of biasing the odds ratio towards one, making the exposure seem less protective or less harmful than it really is.[30] Although we have adjusted for several confounding variables, residual confounding may result from misclassification of those variables and confounding by unmeasured variables.

As part of the data validation for this study we compared incidence rates for upper gastrointestinal events with published data. As in previous studies, incidence rates rose steeply with age and were higher in men than in women.[31 32] Our incidence rates, however, were higher overall, which is likely to reflect our outcome that included all new diagnoses of peptic ulceration or gastrointestinal haemorrhage whether or not they resulted in hospital admission (many patients are managed in primary care or as outpatients).

We thank practices contributing to QRESEARCH, David Stables (EMIS Computing) for his help and expertise in establishing QRESEARCH, and Chris Hawkey for comments.

Contributors: JHC initiated and designed the study, obtained ethical approval, undertook the data extraction and manipulation, undertook the analysis, and drafted the paper. CC contributed to the study design; undertook, supervised, and checked the analysis; advised on interpretation; and contributed to drafting the paper. RL advised on analysis and interpretation and contributed to drafting the paper. JHC is the guarantor.

Funding: None.

Competing interests: RL has been employed on a consultancy basis at various times by Astra Zeneca; Merck, Proctor and Gamble; and Roche.

Ethical approval: Trent multicentre research ethics committee.

1 National Institute for Clinical Excellence. *The clinical effectiveness and cost effectiveness of celecoxib, rofecoxib, meloxicam and etodolac (cox-II inhibitors) for rheumatoid arthritis and osteoarthritis*. London: NICE, 2000.
2 Hooper L, Brown T, Elliott R, Payne K, Roberts C, Symmons D. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ* 2004;329:948-52.
3 Juni P, Rutjes AWS, Dieppe P. Are selective COX 2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.

What is already known on this topic

Traditional non-steroidal anti-inflammatory drugs are associated with serious gastrointestinal side effects

Long term population based safety data on new cyclo-oxygenase-2 inhibitors are lacking

Evidence on the clinical effectiveness of ulcer healing drugs used in combinations with non-selective non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors is lacking

What this study adds

No consistent evidence was found of enhanced safety against gastrointestinal events with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs

The use of ulcer healing drugs reduced the increased risk of adverse gastrointestinal outcomes with all groups of non-steroidal anti-inflammatory drugs except diclofenac, for which the increased risk remained significant

4 Wright JM. The double-edged sword of COX-2 selective NSAIDs. *CMAJ* 2002;167:1131-7.
5 Jones R. Efficacy and safety of Cox 2 inhibitors. *BMJ* 2002;325:607-8.
6 Micklewright R, Lane S, Linley C, Thompson F, Maskrey N. Review article: NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors. *Ailment Pharmacol Ther* 2003;17:321-32.
7 Hawkey C, Laine L, Simon T, Beaulieu A, Maldonado-Cocco J, Acevedo E, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2-specific inhibitor, ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized double-blind placebo controlled trial. *Arthritis Rheum* 2000;43:370-7.
8 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005;330:1366-9.
9 Morris R, Carstairs V. Which deprivation? A comparison of selected deprivation indexes. *J Public Health Med* 1991;13:318-26.
10 Eachus J, Williams M, Chan P, Davey Smith G, Grainge M, Donovan J, et al. Deprivation and cause specific mortality: evidence from the Somerset and Avon survey of health. *BMJ* 312;312:287-92.
11 Hippisley-Cox J, Groom L, Kendrick D, Coupland C, Webber E, Savelyich B. Cross sectional survey of socioeconomic variations in severity and mechanism of childhood injuries in Trent 1992-7. *BMJ* 2002;324:1132.
12 Payne N, Saul C. Variations in the use of cardiology services in a health authority: comparison of coronary artery revascularisation rates with prevalence of angina and coronary mortality. *BMJ* 1997;314:257-61.
13 Pollock A, Vickers N. Deprivation and emergency admissions for cancers of the colorectum, lung, and breast in South East England: ecological study. *BMJ* 1998;317:245-52.
14 Roper N, Bilous R, Kelly W, Unwin N, Connolly V. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. *BMJ* 2001:1389-93.
15 Office of National Statistics. *Key health statistics from general practice*. London: Department of Health, 1998.
16 Hippisley-Cox J, Pringle M. Prevalence, care and outcomes for patients with diet controlled diabetes in general practice: cross sectional survey. *Lancet* 2004;364:423-5.
17 Hammersley V, Hippisley-Cox J, Wilson A, Pringle M. A comparison of research general practices and their patients with other practices—cross sectional survey in Trent. *Brit J Gen Pract* 2002;52:463-8.
18 Hippisley-Cox J, Hammersley V, Pringle M, Coupland C, Crown N, Wright L. How useful are general practice databases for research? Analysis of their accuracy and completeness in one research network. *Health Inform J* 2004;10:91-109.
19 Hippisley-Cox J, Pringle M, Hammersley V, Crown N, Meal A, Wynn A. Antidepressants as a risk factor for ischaemic heart disease: case-control study in general practice. *BMJ* 2001;323:666-9.
20 Schlienger R, Jick H, Meier CR. Use of non steroidal anti-inflammatory drugs and risk of first time acute myocardial infarction. *Br J Clin Pharmacol* 2002;54:327-32.
21 Jick H, Vasilakis C, Derby LE. Antihypertensive drugs and fatal myocardial infarction in persons with uncomplicated hypertension. *Epidemiology* 1997;8:446-8.
22 Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory infections and risk of first time acute myocardial infarction. *Lancet* 1998;351:1467-71.
23 Hippisley-Cox J, Pringle M. Depression and risk of ischaemic heart disease in men: authors' reply. *BMJ* 1998;316.
24 MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003;52:1265-70.
25 Scandinavian Simvastatin Survival Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
26 Henry D, Lim J, Garcia Rodriguez L, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:1563-6.
27 Jick H Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000;356:1627-31.
28 Jick H, Kaye J, Vasilakis-Scaramozza C, Jick S. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000;321:1190-5.
29 Hippisley-Cox J, Pringle M, Cater R, Wynn A, Hammersely V, Coupland C, et al. The electronic record in primary care—regression or progression? A cross sectional study. *BMJ* 2003;326:1439-43.
30 Rothman K, Greenland S. *Modern epidemiology*. Vol 1, 2nd ed. Boston: Lippincott-Raven, 1998.
31 Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *BMJ* 1997;315:510-4.
32 Rockall T, Lofan R, Devlin H, Northfield T. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *BMJ* 1995;311:222-6.

(Accepted 21 October 2005)

BMJ 2005;331:1310

Division of Primary Care, University of Nottingham, Nottingham NG2 7RD
Julia Hippisley-Cox *professor of clinical epidemiology and general practice*
Carol Coupland *senior lecturer in medical statistics*

Division of Epidemiology and Public Health, University of Nottingham
Richard Logan *professor of clinical epidemiology*

Correspondence to: J Hippisley-Cox julia.hippisley-cox@nottingham.ac.uk