Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study

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Aims A postmarketing Prescription-Event Monitoring study was undertaken to monitor the safety of rofecoxib, a cyclo-oxygenase (COX)-2 selective inhibitor prescribed in primary care in England.

Methods Questionnaires requesting clinical event data were sent to prescribing physicians between February and November 2000, and the data analysed for all events.

Results There were 15 268 patients identified, mean age 62 years, 67% female. The commonest specified indication was osteoarthritis (24%). Dyspepsia and nausea were the most frequently reported adverse events. A history of dyspeptic or upper gastrointestinal (GI) conditions, recent use of other nonsteroidal anti-inflammatory drugs (NSAIDs), use of selected concomitant gastroirritant drugs (NSAIDs, aspirin, anticoagulants, antiplatelet drugs), or gastroprotective drugs (misoprostol, antacids, proton-pump inhibitors, histamine-2 antagonists), and age (≥ 65 years) modified the risk of having minor GI events. During treatment or within 1 month of stopping, 110 serious GI events were reported (including 76 upper GI bleeds/peptic ulcers, one perforated colon), 101 thromboembolic events, three reports of acute renal failure, one each of Stevens–Johnson syndrome, severe anaphylaxis and angio-oedema.

Conclusions Doctors should continue to prescribe NSAIDs including COX-2 selective inhibitors with caution.

Keywords: adverse events, COX-2 selective inhibitors, drug safety, prescription-event monitoring, rofecoxib

Introduction

In June 1999, rofecoxib (Vioxx), a cyclo-oxygenase (COX)-2 selective inhibitor, was launched in the UK, licensed for the symptomatic relief of osteoarthritis [1]. The benefit of selectivity is seen as maximum anti-inflammatory activity by potent inhibition of the COX-2 isoenzyme, with minimal clinically significant effects on COX-1 isoenzyme activity, thus improving the gastrointestinal (GI) adverse event profile [2, 3]. Published studies have shown that rofecoxib has equivalent efficacy to other nonsteroidal anti-inflammatory drugs (NSAIDs) and is associated with a reduced incidence of peptic ulcers, perforations and GI bleeding compared with placebo and other nonselective NSAIDs [4–8]. However, limitations of these published trials include the exclusion of high-risk subgroups with current or recently active GI disease, and/or restrictions in those receiving concomitant gastroprotective agents such as H_2 antagonists.

The Drug Safety Research Unit (DSRU) provides an additional postmarketing drug surveillance scheme which monitors the safety of newly marketed drugs during their immediate postmarketing period in England, using the noninterventional observational cohort technique of prescription-event monitoring (PEM) [9]. PEM systematically collects data on patients prescribed a drug in primary care clinical practice, including high-risk groups who may previously have been excluded from controlled clinical trials, and are also likely to be exposed to the newly marketed drug because of the nature of their disease. This paper reports the results of an observational cohort study undertaken to examine the safety of rofecoxib as used by primary care physicians (GPs) in England.

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Received 18 April 2002; accepted 18 September 2002.

Methods

Patients were identified by means of dispensed British National Health Service (NHS) prescription data supplied in confidence by the Prescription Pricing Authority (PPA) in England, between July and November 1999. A simple questionnaire ('green form') was sent to the prescribing GP approximately 9 months after notification by the PPA of the date of the first dispensed prescription (for each individual patient). This interim period allows for prescribing patterns to establish for the newly licensed drug, collection of prescription data by the PPA to achieve the anticipated cohort size, and enables longitudinal monitoring of patients prescribed and dispensed the drug.

In PEM, the green form requests information on patient age, indication, dose, effectiveness, duration of treatment (start and stop dates), reasons for stopping and any significant health-related events that may have occurred to the patient since the day the drug was started, including events considered an adverse drug reaction (ADR). Reported events are coded using the DSRU event dictionary, a hierarchical dictionary arranged by system–organ class with selective 'lower' terms grouped together under broader 'higher' terms. Those questionnaires returned with no information (clinical or other) provided are classified as 'void' and excluded from the study cohort and subsequent analysis, as there is no means of determining whether forms not completed indicated no reported events.

For this PEM study, the questionnaires also included three additional questions regarding potential risk factors for GI conditions; past medical history of dyspeptic symptoms or other upper GI conditions; whether any NSAIDs had been prescribed in the 3 months prior to rofecoxib and whether any gastroprotective or irritant drugs were prescribed during treatment with rofecoxib (NSAIDs, aspirin, misoprostol, antacids, proton-pump inhibitors (PPIs)/H_2-antagonists, anticoagulants, antiplatelet agents).

Each individual green form was reviewed by a DSRU research fellow and the circumstances of each event assessed. All pregnancies, any events of interest of particular concern with this drug and not mentioned in the Summary of Product Characteristics (SmPC) [1], or considered medically important and where additional information was required, were followed up by sending additional questionnaires to the prescribing GP. Individual case reports were assessed for causality by a clinical research fellow at the DSRU, using four basic considerations (temporality, pharmacological plausibility, clinical and pathological characteristics of the event, exclusion of other possible causes) and five categories (probable, possible, unlikely, awaiting further information, or not assessable). If no reply was received, one further reminder was sent. In the case of deaths, if the cause was not specified, a copy of the death certificate was requested from the Office of National Statistics.

Statistical analysis

Incidence densities (IDs) were calculated for all reported events during treatment within specified time periods and expressed as the number of first reports of an event per 1000 patient months of treatment. IDs for events occurring in the first month of treatment (ID_1), during months 2–6 of treatment (ID_2) and for events occurring during the overall treatment period (ID_A) were calculated either for patients for whom the date of stopping the drug was known, or in those who continued to take the drug until the end of the study period. The difference between the two rates (ID_1–ID_2) was calculated to test the hypothesis that the rate did not change over time. Where the arithmetic difference between ID_1 and ID_2 was above 0 at the level of $P = 0.01$, this was considered to be a signal of a possible ADR, especially for predictable (Type A) reactions.

IDs for all events were stratified according to the responses to the additional questions posed on the green form. Crude IDs were calculated separately for the most frequently reported GI events (dyspepsia, nausea/vomiting, diarrhoea, abdominal pain, unspecified GI events, constipation, abdominal distension, upper GI haemorrhage, GI haemorrhage, rectal haemorrhage, peptic ulcer), and indicators of bleeding (anaemia and iron deficiency anaemia) according to positive and negative response to the additional questions, or age (≥ 65 years *vs* ≤64 years). The ID ratios were then calculated and examined using univariate (Mantel–Haenszel) methods. In order to account for multiple testing, comparisons were modified using the Bonferroni's correction [10]. A Microsoft SQL query was used to retrieve data from the DSRU PEM database, followed by analysis using Excel, Access and STATA 7.0.

All records and computer data are stored at the DSRU to maximize patient confidentiality. PEM is conducted in accordance with international ethical guidelines [11–13].

Sample size

The ability to detect an ADR is dependent upon the expected incidence rate of that ADR for those exposed, the background rate of those unexposed and number of patients available. A sample size of 10 000 patients should allow for the detection of at least three cases of an ADR if it occurred with an incident rate of between 1 in 1000

and 1 in 2000 patients, assuming that it was very rare as a background event. Power, 1-β, given as 0.80 [14].

Results

Of forms posted, 40% (16 861/42 303) were returned. Of these, 1593 (10.4%) were void [reasons: patient or doctor moved ($n = 809$); blank forms ($n = 550$); no record of treatment in notes ($n = 178$); rofecoxib prescribed but not taken ($n = 49$); duplicate green form ($n = 6$); wrong drug dispensed ($n = 1$)]. Thus, useful information was available for 15 268 patients. Overall, the mean age was 62.2 ± 14.6 years; 10 289 (67.4%) patients were females.

The major specified indication was osteoarthritis (23.7%, $n = 3621$). The indication was not specified for 38.1% ($n = 5810$), and the remaining 38.2% ($n = 5837$) were for other (predominantly musculoskeletal) indications. Of 10 977 (71.8%) green forms that included a GP opinion about effectiveness, 7447 (68%) reported rofecoxib as being effective.

An event was coded as an ADR if the GP specified that the event was attributable to the drug; 491 events in 360 (2.4%, $n = 15\,268$) patients were reported as ADRs with 62 (12.6%) of these events documented as reported by the prescriber to the Committee on Safety of Medicines (CSM). Suspected ADRs included dyspepsia (five reports), nausea (five), dizziness (four), melaena (two), cardiac failure (two) and acute renal failure (one).

The clinical events reported most frequently (for which ID_1–ID_2 was significantly greater than 0 at the $P = 0.01$ level) are shown in Table 1, ranked in descending order according to the number of events reported in the first month. Commonly occurring listed events [1] (> 1 in 100 patients) were, in descending order of ID_1 per 1000 patient months: 'dyspepsia', 'nausea/vomiting', 'diarrhoea', 'abdominal pain', 'oedema', 'dizziness' and 'headache/migraine'. Listed events occurring less frequently (< 1 in 100 patients but >1 in 1000 patients) were 'malaise lassitude', 'rash', 'dyspnoea', 'constipation', and 'insomnia'. The event 'drowsiness/sedation' was not listed in the SmPC and 'pruritus' was reported less frequently than listed.

Events of interest which did not occur in sufficient numbers to generate a signal using the ID_1–ID_2 statistic included: haemorrhage of upper GI tract (ID_1 1.4, $n_1 = 16$); cardiac failure (ID_1 1.6, $n_1 = 19$); asthma/wheezing (ID_1 1.4, $n_1 = 16$); inflammatory disease of the colon (ID_1 1.0, $n_1 = 12$); and anaemia (ID_1 1.0, $n_1 = 12$).

Other events of interest included reports affecting the renal system [acute renal failure (all three reports 'possibly' related to rofecoxib) and abnormal renal function tests (9/24 reports 'possibly' related)]; and the hepatic system [pancreatitis (five reports unlikely related), jaun-

Table 1 Incidence densities (ID) for events, ranked in order of number of events in month 1 (where ID_1–$ID_2 > 0$).

Higher term description	n_1	n_2	ID_1	ID_2	$ID_1 - ID_2$	*CI min*	*CI max*	n_a	ID_a	*Incidence risk (%)*	*No of ADRs*
Dyspepsia	394	332	33.6	10.2	23.4	18.8	28.0	835	13.0	5.47	50
Nausea, vomiting	179	116	15.3	3.6	11.7	8.6	14.8	326	5.1	2.14	51
Diarrhoea	160	109	13.6	3.3	10.3	7.4	13.2	300	4.7	1.96	37
Pain abdomen	160	145	13.6	4.4	9.2	6.3	12.1	358	5.6	2.34	32
Oedema	86	79	7.3	2.4	4.9	2.8	7.1	198	3.1	1.30	7
Dizziness	78	54	6.6	1.7	5.0	3.0	7.0	152	2.4	1.00	25
Intolerance	69	24	5.9	0.7	5.2	3.3	7.0	99	1.5	0.65	4
Headache, migraine	69	66	5.9	2.0	3.9	1.9	5.8	161	2.5	1.05	13
Gastrointestinal unspecified	61	54	5.2	1.7	3.6	1.7	5.4	129	2.0	0.84	35
Malaise, lassitude	59	54	5.0	1.7	3.4	1.6	5.2	136	2.1	0.89	21
Pruritus	50	47	4.3	1.4	2.8	1.2	4.5	114	1.8	0.75	11
Rash	40	59	3.4	1.8	1.6	0.1	3.1	123	1.9	0.81	11
Dyspnoea	35	39	3.0	1.2	1.8	0.4	3.2	89	1.4	0.58	4
Constipation	28	27	2.4	0.8	1.6	0.3	2.8	70	1.1	0.46	2
Unspecified side-effects	27	18	2.3	0.6	1.8	0.6	2.9	51	0.8	0.33	47
Insomnia	24	19	2.0	0.6	1.5	0.3	2.6	50	0.8	0.33	6
Drowsiness, sedation	21	11	1.8	0.3	1.5	0.4	2.5	35	0.5	0.23	11

n_1, Total number of reports of each event during the first month of treatment; n_2, total number of reports of each event during treatment in months 2–6; ID_1, incidence density for each event during the first month of treatment; ID_2, incidence density for each event during treatment months 2–6; ID_1–ID_2, arithmetic difference between ID_1 and ID_2; 99% CI, 99% confidence intervals for ID_1–ID_2; n_a, total number of reports of each event during the total treatment period; ID_a, incidence density for each event for the total treatment period; incidence risk (%) as proportion of events reported by study cohort ($n = 15\,268$); ADR, adverse drug reaction.

dice (one report unlikely), and abnormal liver function tests (4/20 reports 'possibly' related)]. One case each of anaphylaxis requiring urgent hospital treatment, Stevens–Johnson syndrome, and angioneurotic oedema were reported, and all three cases assessed as 'possibly' related. Nine out of 13 reports of oedema of the face were also assessed as possibly related to rofecoxib.

GPs recorded 7430 reasons for stopping rofecoxib for 6653 patients. The commonest reasons given were not effective ($n = 2817$) and condition improved ($n = 1222$). A total of 1499 (20.2%) reports of dyspepsia and other GI symptoms were given as reasons for stopping. Other reasons of interest included: 41 upper GI bleeding, 10 lower GI bleeding, 11 events possibly associated with a thromboembolic event [cerebrovascular accident (CVA), myocardial infarction (MI), aphasia, dysphasia, slurred speech], three reports of acute renal failure, one each of anaphylaxis and angioneurotic oedema.

In total, 2557 (17.9%) out of 14 308 events reported during treatment were associated with the GI system. A summary of events associated with GI bleeding, and anaemia is presented in Table 2. Twenty-one out of 90 events assessed as 'possibly/probably associated' occurred within the first month of exposure, of which eight had been prescribed other NSAIDs in the 3 months prior to rofecoxib, suggesting the possibility of a carry-over effect.

Of the 26 follow-up reports of rectal bleeding reviewed, seven cases who had a history of diverticulitis were assessed as 'possibly' related, six out of seven cases who had a history of rectal bleeding were 'possibly' related, and three out of four cases who had a history of inflammatory bowel disease were considered 'possibly' related. There were 19 reports of inflammatory bowel disease reported during treatment [colitis ($n = 10$), ulcerative colitis ($n = 4$), Crohn's disease ($n = 5$)], diverticulitis ($n = 7$), and 27 reports of irritable bowel syndrome (IBS). On examinations, all ten reports of colitis, two reports of ulcerative colitis and five reports of Crohn's disease were exacerbations of pre-existing disease.

Table 3 shows crude rates per 1000 person-years according to response to the additional questions plus age (≥ 65 years, ≤64 years), and rate ratios that achieve statistical significance after adjustment for multiple significance testing. A past history of dyspeptic symptoms or other upper GI conditions, and use of concomitant gastroprotective drugs were each associated with a significantly increased relative risk of dyspepsia and abdominal pain, which is consistent with channelling of patients at high risk of these upper GI events. Conversely, a recent prescription of NSAIDs prior to rofecoxib was associated with a decreased relative risk of dyspepsia. Crosstabulation of use of NSAIDs prior to rofecoxib with use of either H_2 antagonists (χ^2 $P < 0.1$) or misoprostol (χ^2 $P < 0.1$) suggests a link between use of gastroprotective agents and prior use of NSAIDs in this cohort, which may explain the relative reduction in rate of upper GI events (dyspepsia) where NSAIDS were reported to have been used within 3 months prior to rofecoxib. Furthermore, the significant relative reduction in rate of GI haemorrhage for those aged ≥65 years, compared with those aged ≤64 years may be a result of raised suspicion of such symptoms in this age group.

Other events of interest

In view of the concern regarding the possible differential effects of NSAIDs on cardiovascular risk, a summary of

Table 2 Reports of gastrointestinal (GI) events and anaemia followed up and causality assessment.

Event	*Number of all events*	*Number reported*★	*Follow-up response*	*Sex* *Male*	*Female*	*Median age (IQR), years*	*Past history of dyspeptic symptoms or other upper GI conditions*	*NSAID prescribed within 3 months prior to starting rofecoxib*	*Concomitant medication* *Gastro irritant*‡	*Gastro protective*§	*Assessed as 'possibly' or probably' related*
Upper GI bleed/peptic ulceration	105	76	57/76 (75%)	18	27	77 (60, 79)	37	22	15	18	45
Lower GI bleed	48	33	26/33 (79%)	11	11	69 (66, 77)	7	1	7	3	22
Anaemia	98	74	34/48 (71%)†	6	16	74 (61, 80)	18	10	8	9	22
Perforated colon	3	1	1/1 (100%)	1	0	71	1	0	0	1	1

★During treatment or within a month of stopping. †Twenty-six not selected for follow-up: secondary to other disease (19), GI bleed (5), deaths (2) and no further information available. ‡Gastroirritant drugs: aspirin, anticoagulants and antiplatelet drugs. §Gastroprotective drugs: misoprostol, antacids, proton-pump inhibitors/histamine-2 antagonists.

Table 3 Rate per 1000 patient months exposure and relative risks† (95% confidence interval) for selected gastrointestinal (GI) events and anaemia according to response to additional questions‡.

Event	Number of events	Rate	Relative risk (95% CI)	χ^2 P-value*
Past history of dyspeptic symptoms and other upper GI conditions				
Dyspepsia				
Yes	611	18.19	2.69 (2.21, 3.26)	< 0.0001
No	123	6.77	1	
Pain abdomen				
Yes	242	7.20	1.87 (1.43, 2.44)	< 0.0001
No	70	3.85	1	
GI unspecified				
Yes	93	2.77	4.19 (2.30, 7.65)	< 0.0001
No	12	0.66	1	
NSAIDs had been prescribed in the 3 months prior to rofecoxib				
Dyspepsia				
Yes	373	12.48	0.79 (0.68, 0.91)	0.0015
No	360	15.80	1	
Nausea, vomiting				
Yes	137	4.58	0.68 (0.54, 0.86)	0.001
No	153	6.71	1	
Use of concomitant gastroprotective drugs (misoprostol, antacids, proton-pump Inhibitors/H_2 antagonists)				
Dyspepsia				
Yes	329	23.34	2.44 (2.09, 2.85)	< 0.0001
No	317	9.56	1	
Pain abdomen				
Yes	125	8.87	1.84 (1.46, 2.33)	< 0.0001
No	160	4.83	1	
Age: ≥ 65 years, compared with ≤ 64 years				
Diarrhoea				
≥ 65 years	199	5.31	1.42 (1.12, 1.80)	0.003
≤ 64 years	105	3.73	1	
Haemorrhage GI				
≥ 65 years	1	0.03	0.04 (0.01, 0.33)	0.002
≤ 64 years	17	0.60	1	

*Bonferroni's correction for 12 tests comparing event rates of 12 selected events of interest per additional questions: adjusted *P*-value for statistical significance, $P < 0.004$. †Calculated using Poisson regression. ‡Use of concomitant drugs leading to increased risk of bleeding (NSAIDs, aspirin, anticoagulants, antiplatelet drugs); none of selected events achieved statistical significance after introducing Bonferroni's correction.

those lower term events associated with thromboembolism (TE) [including MI, CVA, transient ischaemic attack (TIA), retinal vein thrombosis, deep vein thrombosis (DVT) and pulmonary embolism (PE)] is presented in Table 4. In total, 101 events were reported during treatment or within a month of stopping treatment.

Seventy-six replies out of 91 acute thromboembolic events followed up were received (84% response). Of these reports, 54 (71%) occurred in patients aged ≥65 years, 58 (76%) reports occurred in patients with one or more risk factors for thromboembolism and coronary heart disease, and 35 (46%) reports occurred in patients taking concomitant aspirin or other anticoagulant or antiplatelet agents. Among those not taking such medication, 20% (8/41) satisfied the Joint British Societies criteria for the use of aspirin for secondary cardiovascular prophylaxis (history of ischaemic heart disease (IHD), MI, CVA, TIA, angioplasty or coronary artery bypass graft) [15]. Causality assessment for cardiovascular events was not carried out because these events are heavily confounded by previous history of cardiovascular disease. Where the prescribing physician gave an opinion of relation of these events to treatment, only one report (for TIA) was thought attributable to rofecoxib use.

Pregnancies

Of 1071 women aged 15–45 years in the cohort, nine pregnancies were reported, two were planned and treatment stopped before the women become pregnant. The seven pregnant women exposed to rofecoxib during the first trimester resulted in five live births, one spontaneous miscarriage and one termination. Other than an undescended testis, there were no abnormalities found.

Deaths

In total, 299 deaths occurred during the study observation period, cause of death was not ascertained for 13 patients. The underlying cause of death was cardiovascular for 103 cases, cancer for 109 cases, and noncardiovascular for 74. For cardiovascular deaths, 11 occurred within the first month of starting treatment; five were recorded as a MI, two from a CVA and one resulting from a PE. Insufficient information was available to undertake a causality assessment in these patients.

Four patients died from serious upper GI adverse events: duodenal ulcer, duodenal ulcer haemorrhage, GI haemorrhage and a perforated peptic ulcer. Additional follow-up information (lifetime medical records) was received only for three patients. All three were elderly (age range 69–83 years) and none were reported to be taking rofecoxib at time of death (treatment had been stopped between 1 and 4 months prior to death). One patient was on another NSAID at the time of death, one was on low-dose aspirin and the third was on both. There were three deaths resulting from large bowel perforation (two from a perforated colon and one from a perforated diverticulum). Additional follow-up information was received for one patient only, which indicated that this patient had discontinued rofecoxib 7 months prior to death.

Table 4 Thromboembolic (TE) lower term events followed up.

Event	Total number of all events	Total number reported★	Follow-up response	Follow-up Sex Female	Follow-up Sex Male	Follow-up Age, median (IQR) years	Risk factors present for TE (≥ 1)†‡	On concomitant anticoagulant‡
Cerebrovascular accident	56	40	25/35 (71%)§	18	7	78 (71, 86)	21	12
Transient ischaemic attack	30	24	22/24 (92%)¶	17	4	75 (66, 79)	17	12
Myocardial infarction	37	24	17/19 (84%)★★	7	9	70 (64, 75)	10	8
Deep vein thrombosis	17	9	9/9 (100%)††	7	2	67 (63, 75)	7	3
Pulmonary embolism	7	3	3/3 (100%)	0	3	55 (54, 57)	3	0
Retinal vein thrombosis	2	1	0/1 (0%)	-	-	-	-	-

★During treatment or within 1 month of stopping. †Risk factors: past medical history ischaemic heart disease, diabetes, hypertension, cigarette smoker, obesity, recent surgery, peripheral vascular disease, polymyalgia rheumatica, atrial fibrillation, previous TE event. ‡Where follow-up received. §Five not selected for follow-up: pre-existing disease (3) and fatalities (2), no further information available, one follow-up was a non-event. ¶One follow-up was a non-event. ★★Five not selected for follow-up: pre-existing disease (2), and fatalities (3), no further information available. IQR, interquartile range.

Discussion

This PEM study provides a descriptive analysis of a population prescribed rofecoxib under primary care conditions in England, a summary of the events reported during use and possible signals of interest. The demographic data of this cohort were consistent with those expected for an NSAID (51% ≥60 years, 67% females). Although only licensed for use in osteoarthritis during the time of the study, rofecoxib was also prescribed for a range of acute and chronic (predominantly musculoskeletal) conditions. The most frequently reported adverse events in this PEM study were those GI events commonly associated with treatment with other traditional nonselective NSAIDS, and which occurred with a similar incidence to that mentioned in the SmPC for rofecoxib [1]. Our study also examined important risk factors for adverse GI events, and the results suggested channelling of patients already at high risk of GI events.

PEM uses a noninterventional observational cohort design that does not interfere in the prescribing decisions of the GPs, or specify strict inclusion criteria that occur within controlled clinical trials. Thus a strength of this study is that it provides information on the general practice use of rofecoxib regardless of age, past medical history or concomitant medication. The large cohort of 15 268 patients enabled a considerable amount of clinical information to be gathered. Furthermore, by asking GPs to supply 'event' data without causality assessments, the study design was capable of identifying signals which none of the participating GPs suspected to have been due to an adverse drug reaction. The methodology of PEM does not lend itself to identifying the background prevalence of events of interest in the population of England, but to identifying possible signals of events of public health interest which then require further evaluation by means of internal comparisons with other suitable PEM drug cohorts, or for example external comparisons using demographic data of the population as a whole. Other sources available in the UK for monitoring the safety of marketed medicines include the General Practice Research database (GPRD), and the Medicines Monitoring Unit (MEMO) record-linked databases [16]. Differences in data collection prevent comparisons with these external databases. For example, because of the size of the population covered by GPRD there is usually paucity of data regarding recently introduced products.

In PEM studies, a period of at least 6 months is typically used between notification of a prescription being issued and the sending of green forms. This allows the patient time to have the prescription dispensed, take the medication and report events that might occur. As PEM uses record-based data of events deemed of significance to report to the GP, recall bias is likely to be minimal. Regarding the 9-month observation time reported for this study, this is a longer interval than normal, due to a combination of technical difficulties that occurred at the PPA and the DSRU at the time of the study. However, rather than resulting in an underestimate, one could argue that the longer observation period would allow for the detection of possible latent events.

Achieving high response rates is an important issue in any postmarketing surveillance study. This PEM study had a lower than average response rate (normally 59%). Whilst the green form response rate for rofecoxib was 40% (after voids 35%), the response rate was still substantial compared with the proportion of suspected adverse drug reactions which are reported in spontaneous ADR reporting schemes [17, 18]. For data collection systems that are dependent on a third party, such as PEM, response bias is likely [19]. We do not know if the responders were representative of all prescribers. The fall

in GP response rates to postal surveys [19, 20] and PEM has been reported elsewhere as attributable to increased workload [21, 22]. Other methods of improving response to questionnaires such as reminders [23], and providing feedback [24] are being considered for PEM.

Selection bias should be considered as we do not know at present the characteristics of patients of doctors who do not respond and whether these patients experience similar rates of adverse events when compared with patients of doctors who do respond to green form questionnaires. Although one would wish to compare the characteristics (such as age, sex and geographical distribution) of responders to nonresponders, at present this information is not routinely provided by the PPA. Furthermore, as data collection in PEM is systematic, prospective and independent of individual studies, limited information is available on other risk factors, e.g. smoking, alcohol use, and concomitant medication. This study is limited to experience in primary care, excludes information on patients prescribed rofecoxib in secondary care, and it is not possible to estimate the degree of patient compliance.

Reports from clinical trials of rofecoxib in treatment of osteoarthritis indicate that rofecoxib is associated with a lower incidence of treatment discontinuations due to GI adverse events and 'nuisance'-type symptoms than treatment with nonselective NSAIDS [7, 25], and reported to be associated with a significantly lower incidence of upper GI tract bleeding events than treatment with NSAIDS [5]. In our study the most commonly reported adverse events or reasons for stopping were 'nuisance' GI symptoms, such as dyspepsia, nausea and pain in the abdomen.

Upper GI symptoms are not good predictors of the development of upper GI events, and dyspepsia is extremely common in patients not taking NSAIDs. Nevertheless, epidemiological studies show a significant increase in clinical upper GI events with NSAID use (aspirin and nonaspirin NSAIDs) of between two- and six-fold compared with nonusers [26], and this increased risk may persist after discontinuation of NSAID [27]. Dyspepsia has been proposed as a risk factor for NSAID-associated complications [28, 29]. In our study, a past history of dyspeptic symptoms or other GI conditions, and use of an NSAID within 3 months prior to starting treatment, were identified as important risk factors. Stratification of all data by age and response to the additional questions regarding these and other risk factors showed that people aged ≥65 years, a past history of upper GI disorder, a recent prescription of NSAIDs prior to rofecoxib and concomitant use of gastroprotective agents modified the risk of having some minor GI symptoms. Those reported to have a past history of dyspeptic symptoms and other GI conditions, and/or reporting use of concomitant gastroprotective drugs were more likely to get upper GI events during treatment than those who did not. The decreased relative rate of GI symptoms in those using NSAIDS within 3 months prior to starting treatment was unexpected, but in this study use of gastroprotective drugs was associated with use of NSAIDs, which may explain the relative reduction in rate of such events. When the individual case histories of the reports of more serious GI events were examined, at least 60% of those reports assessed as 'possibly/probably related' were in patients with a past history of dyspepsia/upper GI disorder and in patients ≥65 years. The product information states that patients with a past history of perforations, ulcers or bleeds or age ≥65 years are at higher risk of developing a perforation, ulcer or bleed [1]. These results could suggest channelling of patients at high risk of GI events. However, it is expected that GPs would prescribe COX-2 selective drugs to these patients, in the belief that these agents are less likely to cause such complications. Indeed, many GPs would view such patients as prime candidates for a therapeutic trial of a new drug such as this.

Regarding the relationship of the risk of GI events to the duration of exposure to NSAIDs, epidemiological studies have suggested that the risk of GI complications is highest in the first month of NSAID use. The meta-analysis by Gabriel *et al.* [30] reported an odds ratio of 8.0 [95% confidence interval (CI) 6.4, 10.1] for <1 month of NSAID use, 3.3 (95% CI 2.3, 4.8) for 1–3 months use, and 1.9 (95% CI 1.2, 3.1) for >3 months use. Conversely, other prospective trials, such as the VIGOR study, failed to show such a change in risk over time either for clinical upper GI events or complicated upper GI events [7]. Symptoms of acute gastric injury (such as mucosal erythema, superficial erosions or haemorrhages) have been reported with a frequency of 60–100% of patients on NSAID therapy, but complicated events such as gastric or duodenal ulcers occur with a frequency of between 5% and 30% after 1 month of chronic NSAID therapy or more [31]. In PEM, time-dependent treatment effects can be evaluated by comparing the incidence of events reported within the first month of treatment with the subsequent 5 months. While drug-related adverse events often occur within the first few weeks of treatment, and a study examining the immediate postexposure period (weeks) could identify such events, the events in our study are dependent on third-party reporting, and those events deemed less serious by the patient may not be reported immediately. Furthermore, a strength of PEM is that the follow-up period allows for the collection of event data which may signal delayed adverse reactions [32].

Regarding lower GI tract adverse events, there is a link between nonselective NSAIDs and exacerbation of

inflammatory bowel disease (IBD); however, the evidence implicating COX-2-specific inhibitors is weak [33]. Rofecoxib is contraindicated in patients with a known history of IBD [1]. In this PEM study several reports of lower GI tract events were in patients with a known history of such disorders. Inflammatory diseases of the colon were not highlighted as potential signals using the ID_1–ID_2 statistic, but further investigation of this issue is warranted.

Thromboembolic events reported during this study became of interest as a result of the concern that COX-2 selective inhibitors may contribute to an increased risk of platelet-mediated adverse vascular events [7, 34, 35]. Rofecoxib does not appear to inhibit platelet aggregation (mediated by COX-1) or prolong bleeding time [36]. It is plausible that selective inhibition of COX-2 isoenzyme may not protect the cardiovascular system to the same extent as aspirin [37], or some nonselective NSAIDs [38, 39]. PEM is a dynamic process and not all events of interest can be identified in advance of starting any study. This issue regarding possible change in cardiovascular risk was reported subsequent to the completion of this PEM study [34]. The case histories of thromboembolic events in this PEM study showed that 71% of the patients were ≥65 years, 76% had risk factors for IHD or thromboembolism and 46% were on concomitant aspirin. There is no evidence from the PEM data currently available to suggest that any deaths were attributable to rofecoxib. The DSRU is investigating this issue.

The Medicines Control Agency (MCA)/CSM spontaneous reporting system provides one of the major sources of data in the process of pharmacovigilance in the UK. Up to July 2000, most suspected ADRs submitted to the MCA/CSM for rofecoxib were for nonserious GI symptoms (nausea, dyspepsia and abdominal pain) [40]. There were also 68 reports of upper GI bleeding, perforations and ulcerations (five fatal), and 177 cardiovascular system reports, mainly oedema [101] or hypertension [31]. More serious reports included 15 of cardiac failure and nine MIs (three fatal). Most of these patients had risk factors for cardiac disease. The nature of events for which reports of suspected ADRs were submitted to the MCA/CSM and adverse events reported in this PEM study is similar. However, there is a distinct difference in the data collected, in that spontaneous reports assume a causal relationship. Whilst the strength of spontaneous reporting schemes is to identify potential signals of rare adverse reactions, limitations include problems estimating population exposure to calculate incidence rates. Thus this PEM study provides complimentary data regarding incidence rates of commonly reported events.

Assessment of drug safety involves processing all the available information from preclinical studies, pre- and postmarketing clinical trials, spontaneous adverse reaction reporting, epidemiological studies and evaluation of prescription and outcome data collected systematically. Rofecoxib was the first 'coxib' studied using PEM. The vast majority of adverse events reported in this study were minor GI symptoms. However, serious upper and lower GI events, as well as cases of thromboembolic events and renal failure, did occur. Further longer-term comparative studies with nonselective NSAIDs are needed to assess fully the risk–benefit impact of the COX-2 inhibitors in 'real-world' settings. Until such data are available, doctors should continue to prescribe all NSAIDs with caution. In its guidance the National Institute for Clinical Excellence (NICE) restricts the use of COX-2 inhibitors to arthritis patients who are at higher risk of developing serious GI problems [41]. They also advise that they should not generally be prescribed in preference to standard NSAIDs in patients with cardiovascular disease.

Conflict of interest

The Drug Safety Research Unit is an independent charity, which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control of the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of rofecoxib.

We wish to thank all the GPs who have helped during prescription event monitoring studies. We are also extremely grateful for the continued support of the Prescription Pricing Authority and the Office of National Statistics.

References

1 Merck Sharpe Dohme. *Summary of Product Characteristics: Vioxx*. 1999.

2 McKenna F. COX-2: separating myth from reality. *Scand J Rheumatol Suppl* 1999; **109**: 19–29.

3 Kam PC, See AU. Cyclo-oxygenase isoenzymes: physiological and pharmacological role. *Anaesthesia* 2000; **55**: 442–449.

4 Laine L, Harper S, Simon T *et al.* A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterol* 1999; **117**: 776–783.

5 Langman MJ, Jensen DM, Watson DJ *et al.* Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999; **282**: 1929–1933.

6 Cannon GW, Caldwell JR, Holt P *et al.* Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 2000; **43**: 978–987.

7 Bombardier C, Laine L, Reicin A *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343**: 1520–1528.

8 Hawkey C, Laine L, Simon T *et al*. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. *Arthritis Rheum* 2000; **43**: 370–377.

9 Mann RD. Prescription-event monitoring—recent progress and future horizons. *Br J Clin Pharmacol* 1998; **46**: 195–201.

10 Campbell M, Daly L, Machin D. Special topics. In *Statistics with Confidence*, eds Altman D, Machin D, Bryant T, Gardner MJ. Bristol: BMJ Books, 2000.

11 Legemaate J. The CIOMS guidelines for biomedical research involving human subjects. *Eur J Health Law* 1994; **1**: 161–165.

12 Royal College of Physicians of London. *Guidelines on the Practice of Ethical Committees in Medical Research Involving Human Subjects*. 1996.

13 Multi-Centre Research Ethics Committees Guidance Notes. *Examples of Enquiries and Surveys in the Public Interest Where No Reference to a Research Ethics Committee Is Necessary*. Appendix C, 2000: 19.

14 Machin D, Campbell M, Fayers P *et al*. *Sample Size Tables for Clinical Studies*. Oxford: Blackwell Science, 1997.

15 British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* 1998; **80** (Suppl 2): S1–S29.

16 Strom B. Study designs available for pharmacoepidemiology studies. In *Pharmacoepidemiology*, Strom B, ed. Chichester: John Wiley & Sons Ltd., 2000: 17–29.

17 Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *BMJ* 1998; **317**: 119–120.

18 Heeley E, Riley J, Layton D, Wilton LV, Shakir SA. Prescription-event monitoring and reporting of adverse drug reactions. *Lancet* 2001; **358**: 1872–1873.

19 Templeton L, Deehan A, Taylor C, Drummond C, Strang J. Surveying general practitioners: does a low response rate matter? *Br J General Pract* 1997; **47**: 91–94.

20 McAvoy BR, Kaner EF. General practice postal surveys: a questionnaire too far? *BMJ* 1996; **313**: 732–733.

21 Deehan A, Templeton L, Taylor C, Drummond C, Strang J. The effect of cash and other financial inducements on the response rate of general practitioners in a national postal study. *Br J General Pract* 1997; **47**: 87–90.

22 Key C, Layton D, Shakir SA. Results of a postal survey of the reasons for non-response by doctors in a Prescription Event Monitoring study of drug safety. *Pharmacoepidemiol Drug Saf* 2002; **11**: 143–148.

23 Wensing M, Mainz J, Kramme O, Jung HP, Ribacke M. Effect of mailed reminders on the response rate in surveys among patients in general practice. *J Clin Epidemiol* 1999; **52**: 585–587.

24 Whitfield M. Giving feedback to questionnaire responders—essential task? *Br J General Pract* 1997; **47**: 241–243.

25 Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. *Arch Intern Med* 2000; **160**: 2998–3003.

26 Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001; **120**: 594–606.

27 Talley NJ, Evans JM, Fleming KC, Harmsen WS, Zinsmeister AR, Melton LJ III. Nonsteroidal antiinflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci* 1995; **40**: 1345–1350.

28 Hansen JM, Hallas J, Lauritsen JM, Bytzer P. Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. *Scand J Gastroenterol* 1996; **31**: 126–130.

29 MacDonald TM, Morant SV, Robinson GC *et al*. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315**: 1333–1337.

30 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non steroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991; **115**: 787–796.

31 Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. *Am J Med* 1999; **106**: 3S–12S.

32 Wilton LV, Stephens MD, Mann RD. Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999; **319**: 1165–1166.

33 Lipsky PE, Brooks P, Crofford LJ *et al*. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. *Arch Intern Med* 2000; **160**: 913–920.

34 Food and Drug Administration Advisory Committee. Cardiovascular safety review of rofecoxib. http:/http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf 8–9-2001. 2001.

35 Daniels B, Seidenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials. *Arthritis Rheum* 1999; **42** (Suppl. S143).

36 Van Hecken A, Schwartz JI, Depre M *et al*. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol* 2000; **40**: 1109–1120.

37 The physicians' health study: aspirin for the primary prevention of myocardial infarction. *N Engl J Med* 1988; **318**: 924–926.

38 Brochier ML. Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction. The Flurbiprofen French Trial. *Eur Heart J* 1993; **14**: 951–957.

39 Boers M. NSAIDS and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection. *Lancet* 2001; **357**: 1222–1223.

40 CSM/MCA. In focus . . . Rofecoxib (Vioxx). *Current Problems Pharmacovigilance* 2000; **26**: 13.

41 National Institute of Clinical Excellence. *Guidance on Use of Cyclo-Oxygenase (COXII) Selective Inhibitors Celecoxib, Rofecoxib, Meloxicam and Etodoloac for Osteoarthritis and Rheumatoid Arthritis*. Technology Appraisal No. 27. London: Department of Health, 2001.

