# The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study

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***Aims*** Meloxicam is a novel nonsteroidal anti-inflammatory drug (NSAID) which may be associated with fewer adverse upper gastrointestinal events than other NSAIDs because it preferentially inhibits the inducible enzyme cyclo-oxygenase-2 relative to the constitutive isoform, cyclo-oxygenase-1. The aims of the study were to: determine the rate of adverse events associated with meloxicam in general practice, stratify these rates by selected risk factors, and to identify signals of previously unsuspected adverse events associated with meloxicam.

***Methods*** As part of the national prescription-event monitoring pharmacovigilance system for newly launched drugs in general practice, all patients prescribed meloxicam in England between December 1996 and March 1997 were identified by the central Prescription Pricing Authority. We sent short questionnaires to all prescribers asking about adverse events experienced within 6 months of the first prescription.

***Results*** There were 19 087 patients in the study. The rate of dyspepsia during the first month of exposure was 28.3 per 1000 patient-months. There were 33 reports of upper gastrointestinal haemorrhage during treatment (rate: 0.4 per 1000 months). A history of gastrointestinal disorder in the previous year was associated with an increased rate of dyspepsia (rate ratio: 3.0; 95% confidence interval: 2.6, 3.4), abdominal pain (2.1; 1.6, 2.6), and peptic ulcer (4.0; 1.4, 13.2). Prior NSAID use was associated with a 20–30% decrease in the rate of dyspepsia and abdominal pain in patients starting meloxicam, while patients prescribed concomitant gastroprotective agents had a two to three-fold increased rate of dyspepsia, abdominal pain and peptic ulceration. Other rare events were thrombocytopenia ($n=2$); interstitial nephritis ($n=1$) and idiosyncratic liver abnormalities ($n=1$).

***Conclusions*** In the absence of gastro-intestinal risk factors the incidence of gastro-intestinal disturbance was low. Such risk factors should be carefully reviewed prior to prescribing meloxicam.

*Keywords:* adverse drug reaction, cardiotoxicity, drug monitoring, gastrointestinal toxicity, liver toxicity, meloxicam, nephrotoxicity, nonsteroidal anti-inflammatory agent, pharmacoepidemiology, prescription-event monitoring

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with considerable mortality and morbidity [1], and an excess risk of serious upper gastrointestinal events continues for up to 1 year after discontinuation [2]. There is therefore considerable interest in the development of safer NSAIDs [3]. Meloxicam is a new NSAID which has greater inhibitory action against the inducible isoform of cyclo-oxygenase (COX-2), implicated in the inflammatory response, than against the constitutive form of this enzyme (COX-1), inhibition of which is thought to be associated with gastric and renal adverse effects (Data sheet

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Mobic, meloxicam, Boehringer Ingelheim, 1996). Clinical trials data on meloxicam show that it has a good gastrointestinal side-effect profile, as would be predicted from its more selective inhibition of COX-2 relative to COX-1 [3, 4].

Most drug safety information is obtained during real-life clinical use on large numbers of unselected patients [5]. The UK yellow card spontaneous reporting system is limited by severe under-reporting, which may be partly related to confusion over what to report [6]. An adverse drug reaction (ADR) has been defined as any noxious, unintended, and undesired effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy [7]. In contrast an adverse event has been defined as: 'any untoward medical occurrences that may present during treatment with a pharmaceutical product but which do not necessarily have a causal relationship with this treatment' [8]. The routine recording of all adverse events rather than just suspected ADRs has been proposed on all new drugs intended for widespread long-term use [9, 10]. The recent withdrawals of the calcium antagonist mibefradil and the antidiabetic agent troglitazone, and reports of persistent visual field defects associated with the antiepileptic drug vigabatrin are examples which highlight the continued need for effective postmarketing surveillance [11].

The aims of this study were (i) to determine the incidence rates of adverse events, particularly upper gastrointestinal events, associated with starting meloxicam treatment in clinical general practice in England; (ii) to stratify these rates by selected risk factors; and (iii) to identify signals of previously unsuspected adverse events associated with meloxicam.

## Methods

The methodology of prescription-event monitoring has been described previously [12]. As part of the national prescription-event monitoring pharmacovigilance system for newly launched drugs in general practice, all patients prescribed meloxicam in England between December 1996 and March 1997 were identified by the central Prescription Pricing Authority.

Questionnaires, known as 'green forms', were sent to all prescribers between June and November 1997 asking for details and dates of clinical events recorded in the patient's medical notes within 6 months of starting meloxicam. Other information obtained included date of birth of the patient, indication, the dates of starting and stopping meloxicam, history of gastrointestinal events in the last year, use of other NSAIDs in the previous 3 months, and concomitant prescribing of gastroprotective agents (proton-pump inhibitors, $H_2$-receptor antagonists or misoprostol).

If no clear cause of death could be established from the green form, the death certificate was requested from the Office for National Statistics (ONS). In cases where a serious adverse drug reaction (defined as those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitilization [13]) was suspected, we wrote to the general practitioner to obtain further information. We then systematically assessed the likelihood of a causal association between the event and meloxicam using established algorithms [14].

The number of events per 1000 patient-months of exposure for the first month of meloxicam treatment, months 2–6 of treatment, and for all treatment months were calculated. Person time was computed by subtracting the date meloxicam was stopped from the date it was started. If meloxicam was not stopped then the date the patient stopped being observed (e.g. the date the study was completed or the patient left the general practice) was subtracted from the start date. The arithmetic differences between event rates during months 2–6 of exposure compared with the first month of treatment were calculated, and the 99% confidence intervals of the differences were determined. Where the 99% confidence intervals do not include the null value, this suggests that the event rate in month 1 is significantly greater than in months 2–6. This difference can act as an automated signal for previously unrecognized adverse drug events [15]. Where a signal was generated we examined the Summary of Product Characteristics for meloxicam to determine whether the identified event was a recognized adverse drug reaction.

Rates were stratified by risk factors and rate ratios computed to compare rates in patients with the risk factor *vs* rates in patients without the risk factor. Calculation of rates and rate ratios and their 95% or 99% confidence interval was performed using Stata Statistical Software: Release 5.0 [16].

The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organizations of Medical Science and the Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects issued by the Royal College of Physicians [17, 18].

## Results

Green forms were sent to the general practitioners of the first 39 147 patients who had commenced meloxicam between December 1996 and March 1997. Of these, 1274 (3.3%) were ineligible for evaluation (e.g. patient no longer registered with doctor, or duplicated patient). The final cohort consisted of 19 087 (50.4%) out of 37 873 eligible patients. Response rates in doctors who had only prescribed meloxicam to one or two patients were 65.4%


 

and 60.6%, respectively. However, 2136 (21.5%) general practitioners had prescribed meloxicam to more than five patients, and there was a significant decline in response rate with increasing numbers of patients on meloxicam per general practitioner, such that the response rate in the heaviest prescribers (>10 patients) was only 45% ($\chi^2_1$: 20.6; $P<0.0001$).

Table 1 shows the characteristics of patients prescribed meloxicam. There were 6174 (32.3%) males and 12 588 (66.0%) females. The mean age of males (58.6 years) was significantly lower than that in females (61.4 years) ($P<0.0001$). A significantly higher proportion of females compared with males had a recent history of prior NSAID use (42.9% *vs* 40.1%, respectively; $P=0.0002$) or a history of a gastrointestinal disorder in the previous year (26.0% *vs* 23.6%, respectively; $P=0.0005$). The most common indications for meloxicam were osteoarthritis in 4434 (23.2%) patients and joint pain in 2136 (11.2%) patients. After 6 months, 44% of patients were still being prescribed meloxicam.

An event was coded as an adverse drug reaction (ADR) if the general practitioner specified on the green form that the event was attributable to a drug. Two hundred and fifty-two events in 203 (1.1%) patients were reported as suspected adverse reactions to meloxicam. However, only 22 (8.7%) had also been reported to the Committee on Safety of Medicines (CSM). The majority of these were nonserious or were labelled side-effects of meloxicam. Serious nongastrointestinal events that were suspected adverse drug reactions to meloxicam after follow-up with the reporting general practitioner and formal causality assessment were: (i) two reports of thrombocytopenia; (ii) one report of interstitial nephritis; and (iii) one report of idiosyncratic liver abnormality. There were 7604 recorded reasons for stopping meloxicam in 7021 patients (Table 2). Again, the majority of these were recognized nonserious adverse effects. However, there were 20 reports of gastrointestinal haemorrhage, 7 of melaena, 4 of perforated duodenal ulcer, and 5 of uncomplicated peptic ulcer listed as reasons for stopping meloxicam.

Table 3 gives the numbers and rates of common adverse events occurring during exposure to meloxicam by time-period from start of treatment. The arithmetic difference between rates during month 1 and rates during months 2–6 is given with the 99% confidence interval for this difference. There were a total of 74 948 months of exposure during the study, 15 382 during the first treatment month, 44 581 during months 2–6 and 14 985 after month 6. The most frequently occurring adverse event was dyspepsia which had a rate during the first month of exposure of 28.3 per 1000 patient-months. However, in those patients who continued treatment, dyspepsia was reported less frequently in months 2–6 of exposure (8.5 per 1000 patient-months; arithmetic difference between rates: 19.8, 99% CI: 16.1, 23.5).

An association between meloxicam exposure in month 1 compared with exposure in subsequent months was also found for the following clinical adverse events: respiratory

**Table 1** Characteristics of 19 087 patients prescribed meloxicam in general practice in England. Figures in parenthesis are percentages unless otherwise stated.

| *Characteristic* | *Male* (n = *6174*) | *Female* (n = *12 588*) | *Sex unknown* (n = *325*) | *Total* (n = *19 087*) | P *value*† |
|---|---|---|---|---|---|
| Mean age (s.d.) | 58.6 (15.5) | 61.4 (15.7) | – | 60.4 (15.7) | <0.0001 |
| Prior nonsteroidal anti-inflammatory drugs | 2475 (40.1) | 5403 (42.9) | 100 (30.8) | 7978 (41.8) | 0.0002 |
| History of gastrointestinal disorder in last year | 1459 (23.6) | 3270 (26.0) | 58 (17.8) | 4787 (25.1) | 0.0005 |
| Concomitant use of gastro-protective agents | 1054 (17.1) | 2139 (17.0) | 39 (12.0) | 3232 (16.9) | 0.14 |
| *Main indications* | | | | | |
| Osteoarthritis | 1253 (20.3) | 3110 (24.7) | 71 (21.8) | 4434 (23.2) | – |
| Pain joint | 689 (11.2) | 1400 (11.1) | 47 (14.5) | 2136 (11.2) | – |
| Pain back | 553 (9.0) | 894 (7.1) | 31 (9.5) | 1478 (7.7) | – |
| Arthritis | 427 (6.9) | 988 (7.8) | 20 (6.2) | 1435 (7.5) | – |
| Rheumatoid arthritis | 284 (4.6) | 960 (7.6) | 9 (2.8) | 1253 (6.6) | – |
| Neck pain | 106 (1.7) | 199 (1.6) | 3 (1.0) | 308 (1.6) | – |
| Cervical spondylosis | 119 (1.9) | 172 (1.4) | 5 (1.5) | 296 (1.6) | – |
| Injury | 105 (1.7) | 116 (0.9) | 6 (1.8) | 227 (1.2) | – |
| Sciatica | 69 (1.1) | 110 (0.9) | 3 (1.0) | 182 (1.0) | – |
| Myalgia | 47 (0.8) | 106 (0.8) | 5 (1.5) | 158 (0.8) | – |

†*Z*-test or comparison of proportions as appropriate in male *vs* female groups.

**Table 2** Main reasons for stopping meloxicam in 7021 patients.

| *Reason*⋆ | *Number (%)* |
|---|---|
| Not effective | 2989 (39.3) |
| Condition improved | 1834 (24.1) |
| Dyspepsia | 432 (5.7) |
| Pain abdomen | 171 (2.3) |
| Nausea | 160 (2.1) |
| Non compliance | 117 (1.5) |
| Gastro-intestinal unspecified | 104 (1.4) |
| Diarrhoea | 103 (1.4) |
| Effective | 81 (1.1) |
| Headache | 68 (0.9) |
| Rash | 64 (0.8) |
| Dizziness | 60 (0.8) |
| Intolerance | 59 (0.8) |
| Orthopaedic surgery | 59 (0.8) |
| Patient request | 50 (0.7) |
| Vomiting | 49 (0.6) |
| Malaise | 48 (0.6) |
| Minor surgery | 45 (0.6) |
| Hospital referral paramedical | 38 (0.5) |
| Gastritis | 37 (0.5) |
| Hospital admission | 36 (0.5) |
| Heartburn | 34 (0.5) |
| Other† | 966 (12.7) |
| Total‡ | 7604 (100) |

⋆Reasons for stopping which had a frequency of 0.5% or more. †Other clinically important reasons for stopping included constipation ($n=31$); oesophageal reflux ($n=25$); mouth ulcer ($n=23$); oedema ($n=22$); gastro-intestinal haemorrhage ($n=20$); pruritus ($n=20$); asthma ($n=19$); dyspnoea ($n=16$); tinnitus ($n=16$); cardiac failure ($n=9$); melaena ($n=7$); hypertension ($n=6$); perforated duodenal ulcer ($n=4$); uncomplicated peptic ulcer ($n=5$). ‡There are more reasons for stopping than patients as there could be more than one reason for stopping.

tract infection, nausea/vomiting, abdominal pain, diarrhoea, headache/migraine, oedema, dizziness, gastrointestinal unspecified, malaise, lassitude, intolerance, hypertension, dyspnoea, cardiac failure, and palpitations (Table 3). Of these events, hypertension and cardiac failure were not listed as side-effects in the original Summary of Product Characteristics (Data sheet Mobic, meloxicam, Boehringer Ingelheim, 1996). Despite this, both hypertension ($n=6$) and cardiac failure ($n=9$) were reported as reasons for stopping meloxicam by general practitioners (Table 2, footnote).

### *Gastrointestinal events*

There were a total of 54 reports of upper gastrointestinal haemorrhage, 33 of which occurred during exposure to meloxicam (rate: 0.4 per 1000 months of exposure). There were 35 reports of peptic ulcer, 19 of which occurred during meloxicam exposure (rate: 0.3 per 1000 months of exposure). Table 4 shows age and sex specific rates of dyspepsia and abdominal pain during meloxicam treatment. Dyspepsia was more common in older age groups compared with the youngest age group, and in females compared with males. The rates of abdominal pain were highest in patients aged 10–29 years.

Table 5 shows the rates of gastrointestinal events during treatment with meloxicam stratified by past history of gastrointestinal disorder, prior NSAID use or concurrent use of a gastroprotective agent. Overall, the rate of dyspepsia in patients with a past history of upper gastrointestinal disorder was 22.5 per 1000 patient-months of exposure compared with 7.6 per 1000 patient-months of exposure in patients with no past history of upper gastrointestinal disorder (rate ratio: 3.0; 95% CI: 2.6, 3.4). The rate of dyspepsia in patients with a past history of upper gastrointestinal disorder was highest within the first month of starting meloxicam (57.9 per 1000 patient-months of exposure). The rate ratios for abdominal pain (2.1; 1.6, 2.6) and peptic ulceration (4.0; 1.4, 13.2) were also significantly increased in patients with a past history of gastrointestinal disorder compared with previously asymptomatic individuals. A history of recent prior NSAID use was associated with a reduced rate of dyspepsia (rate ratio: 0.7; 0.6, 0.8) and abdominal pain (rate ratio: 0.8; 0.7, 1.0). A past history of NSAID use had no effect on the rates of upper gastrointestinal haemorrhage or peptic ulceration. There was some evidence of an increased risk of iron deficiency anaemia amongst prior users of NSAIDs, although this was not significant at the 5% level (rate ratio: 2.2; 0.7, 7.7; $P=0.07$). Patients who were currently taking concomitant gastro-protective agents had an increased rate ratio for dyspepsia (3.0; 2.6, 3.4), abdominal pain (2.4; 1.9, 3.0), and peptic ulceration (2.9; 1.0, 8.4) compared with patients not taking concomitant gastro-protective agents.

## Discussion

A high proportion of patients had received an NSAID prior to meloxicam (41.8%) or had a recent history of gastrointestinal disorder (25.1%). Dyspepsia, abdominal pain and peptic ulceration occurred significantly more frequently in patients with a past history of gastrointestinal disorder and in those who were prescribed concomitant gastro-protective agents. Since meloxicam may be perceived as being safe, it is possible that it was prescribed more frequently than certain other NSAIDs to patients at increased risk of gastrointestinal events. Moreover, it has been suggested that the COX-2 enzyme may be cytoprotective in the presence of *H. pylori* gastritis, gastric erosions, gastric injury and at the site of ulcer scars [19–22]. Hawkey has raised the concern that COX-2 inhibitors may not be safe in the presence of gastrointestinal


 

**Table 3** Rates of common adverse events per 1000 patient-months of treatment by time-period from start of treatment with meloxicam.

| *Event*¶ | *Number of events in month 1* | *Number of events in months 2–6* | *Rate† in month 1*[a] | *Rate† in months 2–6*[b] | *Arithmetic difference in rates* | *99% CI⋆ for rate difference* |
|---|---|---|---|---|---|---|
| Dyspepsia | 435 | 379 | 28.3 | 8.5 | 19.8 | 16.1, 23.5 |
| Respiratory tract infection | 214 | 387 | 13.9 | 8.7 | 5.2 | 2.5, 7.9 |
| Nausea, vomiting | 189 | 136 | 12.3 | 3.1 | 9.2 | 6.8, 11.6 |
| Pain abdomen | 146 | 163 | 9.5 | 3.7 | 5.8 | 3.7, 8.0 |
| Diarrhoea | 118 | 110 | 7.7 | 2.5 | 5.2 | 3.3, 7.1 |
| Dose increased | 106 | 206 | 6.9 | 4.6 | 2.3 | 0.4, 4.2 |
| Headache, migraine | 81 | 82 | 5.3 | 1.8 | 3.4 | 1.8, 5.0 |
| Minor surgery | 75 | 100 | 4.9 | 2.2 | 2.6 | 1.1, 4.2 |
| Hospital referrals no admission | 74 | 144 | 4.8 | 3.2 | 1.6 | 0.0, 3.2 |
| Oedema | 74 | 96 | 4.8 | 2.2 | 2.7 | 1.1, 4.2 |
| Dizziness | 68 | 70 | 4.4 | 1.6 | 2.9 | 1.4, 4.3 |
| Gastrointestinal unspecified | 66 | 64 | 4.3 | 1.4 | 2.9 | 1.4, 4.3 |
| Pain joint | 57 | 143 | 3.7 | 3.2 | 0.5 | −0.9, 1.9 |
| Malaise, lassitude | 56 | 81 | 3.6 | 1.8 | 1.8 | 0.5, 3.2 |
| Constipation | 56 | 57 | 3.6 | 1.3 | 2.4 | 1.0, 3.7 |
| Hospital referral paramedical | 51 | 55 | 3.3 | 1.2 | 2.1 | 0.8, 3.4 |
| Cough | 48 | 73 | 3.1 | 1.6 | 1.5 | 0.2, 2.7 |
| Asthma, wheezing | 48 | 46 | 3.1 | 1.0 | 2.1 | 0.9, 3.3 |
| Rash | 46 | 90 | 3.0 | 2.0 | 1.0 | −0.3, 2.2 |
| Hypertension‡ | 42 | 57 | 2.7 | 1.3 | 1.5 | 0.3, 2.6 |
| Cardiac failure‡ | 24 | 29 | 1.6 | 0.7 | 0.9 | 0.0, 1.8 |
| Palpitation‡ | 20 | 22 | 1.3 | 0.5 | 0.8 | 0.0, 1.6 |

¶Ranked by number of events in months 1. †Rate is number of events in time period per 1000 patient-months of exposure in that time period. [a]No. of patient months of exposure in month 1 was 15 382; [b]Number of patient months of exposure in month 2–6 was 44 581. ⋆Confidence interval. ‡There are other events occurring with a frequency in-between rash and these events, which are included in the table as the 99% confidence interval for the difference are greater than or equal to zero.

**Table 4** Age and sex specific numbers, rates per 1000 years of exposure, and rate ratios for reports of dyspepsia and abdominal pain during treatment with meloxicam.

| *Age (years)* | *10–29* | *30–49* | *50–69* | *70+* | *Male* | *Female* | *Total⋆* |
|---|---|---|---|---|---|---|---|
| *Dyspepsia* | | | | | | | |
| Number | 10 | 144 | 360 | 268 | 227 | 642 | 903 |
| Rate† | 77.7 | 138.3 | 139.7 | 147.1 | 116.5 | 156.1 | 144.0 |
| Rate ratio | 1 | 1.8 | 1.8 | 1.9 | 1 | 1.3 | |
| (95% CI); | (base) | (0.9, 3.8) | (1.0, 3.8) | (1.0, 4.0) | (base) | (1.2, 1.6) | |
| *P* value | | 0.06 | 0.05 | 0.03 | | 0.0001 | |
| *Abdominal pain* | | | | | | | |
| Number | 12 | 66 | 139 | 109 | 107 | 247 | 357 |
| Rate† | 92.9 | 63.1 | 53.5 | 59.1 | 54.6 | 59.5 | 57.6 |
| Rate ratio | 1 | 0.7 | 0.6 | 0.6 | 1 | 1.1 | |
| (95% CI); | (base) | (0.4, 1.4) | (0.3, 1.1) | (0.2, 1.3) | (base) | (0.9, 1.4) | |
| *P* value | | 0.2 | 0.08 | 0.2 | | 0.5 | |

⋆Totals are greater than age and sex specific row totals because of missing age and sex data. †Rate = number of patients with event per 1000 patient-years of exposure.

**Table 5** Risk factors for upper gastrointestinal events and iron deficiency anaemia during the study.

| | | *Number of events* | *Rate (Number of events per 1000 patient-months of exposure)* | *Rate ratio (95% CI)* | P *value* |
|---|---|---|---|---|---|
| *Past history of gastrointestinal disorder*⋆ | | | | | |
| Dyspepsia | No past history | 341 | 7.6 | 1 | |
| | Past history | 464 | 22.5 | 3.0 (2.6, 3.4) | <0.0001 |
| Abdominal pain | No past history | 166 | 3.7 | 1 | |
| | Past history | 156 | 7.6 | 2.1 (1.6, 2.6) | <0.0001 |
| Upper GI haemorrhage | No past history | 21 | 0.5 | 1 | |
| | Past history | 10 | 0.5 | 1.0 (0.4, 2.3) | 0.5 |
| Iron deficiency anaemia | No past history | 11 | 0.2 | 1 | |
| | Past history | 7 | 0.3 | 1.4 (0.5, 3.9) | 0.2 |
| Peptic ulcer | No past history | 6 | 0.1 | 1 | |
| | Past history | 11 | 0.5 | 4.0 (1.4, 13.2) | 0.003 |
| *Past history of NSAID use*† | | | | | |
| Dyspepsia | No past history | 434 | 14.9 | 1 | |
| | Past history | 386 | 10.3 | 0.7 (0.6, 0.8) | <0.0001 |
| Abdominal pain | No past history | 157 | 5.4 | 1 | |
| | Past history | 166 | 4.4 | 0.8 (0.7, 1.0) | 0.04 |
| Upper GI haemorrhage | No past history | 12 | 0.4 | 1 | |
| | Past history | 19 | 0.5 | 1.2 (0.6, 2.8) | 0.3 |
| Iron deficiency anaemia | No past history | 5 | 0.2 | 1 | |
| | Past history | 14 | 0.4 | 2.2 (0.7, 7.7) | 0.07 |
| Peptic ulcer | No past history | 6 | 0.2 | 1 | |
| | Past history | 10 | 0.3 | 1.3 (0.4, 4.3) | 0.3 |
| *Concurrent gastroprotective agent*‡ | | | | | |
| Dyspepsia | No past history | 427 | 8.5 | 1 | |
| | Past history | 393 | 25.5 | 3.0 (2.6, 3.4) | <0.0001 |
| Abdominal pain | No past history | 188 | 3.8 | 1 | |
| | Past history | 137 | 8.9 | 2.4 (1.9, 3.0) | <0.0001 |
| Upper GI haemorrhage | No past history | 21 | 0.4 | 1 | |
| | Past history | 8 | 0.5 | 1.2 (0.5, 2.9) | 0.3 |
| Iron deficiency anaemia | No past history | 13 | 0.3 | 1 | |
| | Past history | 6 | 0.4 | 1.5 (0.5, 4.2) | 0.2 |
| Peptic ulcer | No past history | 9 | 0.2 | 1 | |
| | Past history | 8 | 0.5 | 2.9 (1.0, 8.4) | 0.02 |

⋆Past history of gastrointestinal symptoms in 12 months prior to meloxicam †Use of NSAID's in last 3 months prior to meloxicam ‡ Concurrent use of proton pump inhibitor, or $H_2$-antagonist or misoprostol.

inflammation, that they may retard ulcer healing and that they may cause ulcers in subgroups of patients with erosions and previous ulcers [3]. Our findings suggest that in the absence of gastro-intestinal risk factors the incidence of gastro-intestinal disturbance was low. However, such risk factors should be carefully reviewed prior to prescribing meloxicam.

### *Limitations*

An important limitation of this study is that the response rate in general practitioners who prescribed meloxicam was only 50.4%. This bias may artificially inflate event rates if general practitioners were less likely to return 'green-forms' where no events had occurred. On the other hand, general practitioners may also have been less likely to return green-forms if they did not think that the events were of importance to this study, possibly artificially lowering rates for some events. There was a significant decline in response rate with increasing numbers of patients prescribed meloxicam per general practitioner. Those doctors who prescribed the largest quantities of meloxicam were those that were least likely to respond, whereas more limited prescribers had response rates of up to 65%. Heavy prescribers of new drugs may be increasing the public health risk associated with newly launched medicines, by prescribing to several patients soon after launch and by not taking part in safety surveillance of new drugs [23, 24].

The other limitation of the study is lack of a direct


 

control group to calculate estimates of effect such as rate ratios. However, we were still able to compute effect estimates for (i) the temporal relationship between starting meloxicam and all adverse events (rate difference), and (ii) selected risk factors for adverse gastrointestinal events in risk factor positive *vs* risk factor negative patients (rate ratio).

Although the study has important limitations, these should be considered within the context of the overall objective of prescription-event monitoring. Our objective was to systematically collect event data on a national scale amongst new users of meloxicam in order to rapidly assess its safety when used in large numbers of unselected patients in clinical general practice. Since meloxicam was perceived by many in primary care as being an important advance in the use of NSAIDs, postmarketing surveillance studies conducted as soon as possible after its launch are important to determine any unsuspected adverse drug events. The methods of prescription-event monitoring closely resemble those of surveillance routinely carried out to provide early warnings about patterns of communicable diseases. Surveillance has been defined as 'continuous analysis, interpretation, and feedback of systematically collected data, generally using methods distinguished by their practicality, uniformity and rapidity, rather than by accuracy or completeness.' [25] The main limitations of this study are therefore closely related to its strengths as a system of pharmacosurveillance. The technique of prescription-event monitoring may provide rapid signals of adverse events associated with newly marketed drugs which can be examined in hypothesis testing studies, or can confirm signals generated elsewhere, such as via the spontaneous reporting yellow-card scheme [26–28]. In line with previous research, we found that only 8.7% of suspected ADRs had been reported to the CSM [6].

### *Signal generation*

The signals generated in this study were hypertension and cardiac failure. These events are now listed in the updated summary of product characteristics as side-effects. By January 1998 there had been six yellow-card reports of cardiac failure (all forms) and five of hypertensive disease submitted to the CSM (CSM-personal communication) adding support to our signal. COX-2 is expressed consititutively in the kidney and appears important in the control of renin release [29]. Therefore inhibition of COX-2 by meloxicam could theoretically cause fluid retention or exacerbate hypertension [3]. Rare nongastric serious events which were suspected adverse drug reactions on the basis of formal causality assessments were thrombocytopenia ($n=2$); interstitial nephritis ($n=1$) and idiosyncratic liver abnormalities ($n=1$). By January 1998 there had been four yellow-card reports of thrombocytopenia, one of hepatitis and one of interstitial nephritis submitted to the CSM (CSM-personal communication).

## Conclusion

In conclusion we found that serious adverse events associated with the clinical use of meloxicam were relatively rare. However, upper gastrointestinal adverse events occurred more frequently in patients with a past history of gastrointestinal disorder or who were prescribed concomitant gastroprotective agents, suggesting caution should be exercised when prescribing meloxicam to these patients. Comparative studies are needed to assess the risk of upper gastrointestinal events associated with the use of meloxicam *vs* the risks for other nonsteroidal anti-inflammatory drugs.

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