SAFETY OF MELOXICAM: A GLOBAL ANALYSIS OF CLINICAL TRIALS

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SUMMARY

Meloxicam is a new preferential cyclooxygenase-2 (COX-2) inhibitor for the treatment of rheumatic disease. This paper presents a global safety analysis of data from meloxicam clinical studies, focusing on gastrointestinal (GI) adverse events. Meloxicam 7.5 and 15 mg (n = 893 and 3282) were compared with piroxicam 20 mg (n = 906), diclofenac 100 mg slow release (n = 324) and naproxen 750–1000 mg (n = 243). With respect to all GI adverse events, meloxicam 7.5 and 15 mg were significantly better than all comparators in a pooled analysis of double-blind studies in rheumatoid arthritis (RA) and osteoarthritis (OA). When examining non-serious GI events, severe GI events, discontinuations due to GI events, dyspepsia, abdominal pain and upper GI events, both meloxicam doses were significantly better than comparator non-steroidal anti-inflammatory drugs (NSAIDs) in most cases. Where statistical significance was not demonstrated, there was generally a trend in favour of meloxicam. With respect to upper GI perforations, ulcers and bleedings, the most serious of NSAID-associated side-effects, meloxicam was better tolerated than the comparators, reaching statistical significance for piroxicam and naproxen. Meloxicam’s improved GI safety profile is likely to be due to its preferential inhibition of inducible COX-2 relative to constitutive COX-1.

KEY WORDS: Meloxicam, NSAID, Safety, Gastrointestinal, PUB, Cyclooxygenase.
PATIENTS AND METHODS

Clinical studies with meloxicam 7.5 and 15 mg once daily have been conducted in healthy volunteers, and in patients with RA, OA and other rheumatoid diseases. In order to make an overall assessment of the safety of meloxicam, data from individual clinical studies have been pooled. Thus adverse-event data from the clinical trials programme of phase I studies (assessing pharmacokinetics, pharmacodynamics and drug interactions) and phase II/III clinical trials conducted in patients with RA, OA and other indications (including low back pain, sciatica and ankylosing spondylitis) have been analysed. Table I gives the number of subjects who received meloxicam 7.5 or 15 mg or the active comparators, piroxicam 20 mg, diclofenac 100 mg slow release and naproxen 750–1000 mg; the duration of patient exposure to the study drugs and the type of study are also shown. Table II details patient characteristics and disease suffered. For the purposes of the analysis, data from patients receiving naproxen 750–1000 mg were combined. Comparator agents were chosen to reflect current practice in the treatment of arthritic disease with NSAIDs and were considered to be of equivalent therapeutic potency to meloxicam 7.5 and 15 mg.

In phase I studies 168 healthy volunteers received single or multiple oral, rectal, intravenous or intramuscular formulations of meloxicam 7.5 or 15 mg. The clinical trials programme included 34 phase II/III studies in 4007 patients. Early dose-ranging studies conducted in patients with various rheumatoid diseases were open-label, non-controlled pilot studies. The safety and efficacy of meloxicam 7.5 and 15 mg oral formulations (tablets or capsules) were evaluated in seven clinical trials in 1820 patients with OA and in six studies in 1889 patients with RA. The safety data from the double-blind active comparators used in these studies are included in this overall safety analysis.

The majority of oral formulation studies were conducted with meloxicam capsules (n = 3611) and the remainder using bioequivalent meloxicam tablets (n = 188). Other formulations used included bioequivalent suppositories (one study in OA, n = 258) and intramuscular injection (one study in OA and RA and another in sciatica, n = 209). Formulations of active comparators used included capsules and ampoules for piroxicam, tablets for naproxen and slow-release tablets for diclofenac.

In RA and OA studies, male and female patients, aged at least 18 yr, were recruited. For OA studies, patients required a clinical diagnosis of OA of the hip or knee, with appropriate radiographic assessments, a defined degree of pain at baseline and treatment with an anti-inflammatory agent had to be considered...
beneficial. In RA studies, patients with active RA and a
diagnosis of definite or classical RA [13] or with a
diagnosis of RA according to the revised criteria of the
American Rheumatism Association [14] were included.
Second-line therapy was allowed when doses were
stabilized before and during the studies. In most studies,
stable doses of corticosteroids (up to 7.5 mg prednis-
one/equivalent/day) were permitted. Paracetamol (up to
4 g/day) was the only permitted rescue analgesic.

Exclusion criteria for RA and/or OA studies inclu-
ded: pregnant or breastfeeding women and women with
no adequate contraception; any evidence of severe
hepatic, renal, cardiac, metabolic or haematological
disease; patients with untreated hypertension; any
evidence of concomitant disease which may lead to
early termination of the study; patients on prophylactic
therapy for bronchial asthma; any evidence of peptic
ulceration either current or during the previous 6
months; known hypersensitivity to analgesics, anti-
pyretics and NSAIDs; clinically abnormal laboratory
investigations; treatment with any of the following
during or within 3 months of the study: oral
corticosteroids (only in OA studies); treatment with
intra-articular corticosteroids (a limited number of
injections was allowable in RA studies); treatment with
other NSAIDs or topical anti-inflammatory prepara-
tions, more than 4 g paracetamol/day; prophylactic
treatment with any anti-ulcer drugs (however, patients
with a history of peptic ulceration could be treated with
anti-ulcer drugs) except if necessary for gastroduodenal
adverse events occurring during the study; any patient
undergoing orthopaedic surgery; removal of fluid from
an effusion of the affected joint up to 1 month prior to
or during the study; any other rheumatological diseases
or during the study; any other non-rheumatological diseases which may interfere
with evaluation of safety or efficacy; treatment with any
investigational drug within the previous 4 weeks or
participation in more than one meloxicam study.

An adverse event was defined as any reaction,
side-effect, intercurrent disease or untoward event that
occurred during the course of the clinical trial, whether
or not the event was considered drug related. Any
adverse event that was immediately life threatening,
severely or permanently disabling or required, or
prolonged, hospitalization was considered to be a
serious adverse event. In addition, an adverse event with
one of the following outcomes was always considered
serious: death, congenital anomaly, cancer or overdose.
A severe adverse event was defined as incapacitating,
with the inability to do work or usual activity or causing
the patient to discontinue from the trial. Coding of
adverse events was conducted according to the Adverse
Reaction Terminology List (ARTL) of the World
Health Organization [15]. In addition to grouping
according to the 30-system organ classes, adverse events
were also grouped by preferred terms. Preferred terms
were counted only once per patient independent of the
frequency of their occurrence in this patient and of the
number of different terms which were coded under the
same preferred term. An adverse event was defined as a
PUB (upper GI perforation, ulceration or bleeding) if it

was coded as one of the following preferred terms:
duodenal ulcer, duodenal ulcer hemorrhagic, duodenal
ulcer perforated, duodenal ulcer reactive, gastric ulcer,
gastric ulcer hemorrhagic, gastric ulcer perforated,
peptic ulcer aggravated, haematemesis or melena. The
classification of PUB included both serious and
non-serious adverse events. Adverse events which were
recorded during follow-up visits, during prestudy visits
and during wash-out periods are not included in the
safety analysis.

Statistical analysis

Adverse-event data have been stratified by trial
indication (OA or RA), age (<65 yr, £65 yr) and
meloxicam dose. The Kaplan–Meier estimator [16] was
used to calculate the likelihood of a patient remaining
free of an adverse event when treated with meloxicam
relative to active comparators. This analysis was used to
correct for variations in treatment duration occurring
between treatment groups. From this analysis the
survival curves were drawn for GI adverse events,
allowing a visual assessment of the proportion of
patients remaining free of an adverse event with
meloxicam or comparator drugs over time.

Log-rank tests were conducted between treatment
groups on the incidence of adverse events [16]. P-values
of <0.05 were considered statistically significant.

RESULTS

In total, adverse events from 6129 subjects were
included in the pooled safety database, 4175 received
meloxicam 7.5 or 15 mg once daily and 1473 received
comparator drugs. Table I shows the distribution of
patients receiving each treatment and dose of
meloxicam. The total exposure to meloxicam was 1475
patient yr, with 428 patients having been treated for a
year or more. Exposure by dose is given in Table I.

Table II shows the distribution of patients according
to age, sex and indication. The higher mean age of the
diclofenac-treated patients resulted from the fact that
diclofenac was only used in OA patients who are, on
average, older than RA patients.

Gastrointestinal adverse events

The most commonly occurring adverse events
involved the GI tract, and these adverse events have,
therefore, been analysed most extensively. Data for total
GI adverse events are for the whole population and data
from subcategories of GI adverse events are presented
from double-blind studies in RA and OA only. Data
from this subpopulation of patients are presented
because data from double-blind studies are clearly the
best controlled and most reliable.

In both the whole population and double-blind
studies in RA and OA, total (serious and non-serious)
GI adverse events occurred most frequently with
aprofen 750–1000 mg, followed by diclofenac 100 mg,
piroxicam 20 mg, meloxicam 15 mg and meloxicam
7.5 mg (Table III). Both doses of meloxicam were
significantly superior to all comparators in
double-blind studies in RA and OA (P < 0.05, Fig. 1);
in the whole population, the result was similar with the exception that there was no significant advantage for meloxicam 7.5 mg over piroxicam 20 mg.

The most frequently occurring non-serious GI adverse events (≥2%) in patients treated with meloxicam and active comparators were dyspepsia, nausea, abdominal pain and diarrhoea. There was a similar pattern of frequency with non-serious GI adverse events as with total GI adverse events (Table III). Again, both doses of meloxicam were significantly superior to all comparators in double-blind studies in RA and OA (P < 0.05). For GI adverse events defined as severe in intensity, both meloxicam doses were significantly superior to all comparators (P < 0.05, Table III). On examination of the survival curve for this parameter, there is a clear difference between both doses of meloxicam vs the comparator NSAIDs (Fig. 2). Discontinuation due to GI adverse events was least common with meloxicam 7.5 mg, followed by meloxicam 15 mg, piroxicam 20 mg, diclofenac 100 mg and naproxen 750–1000 mg, with a significant difference between both doses of meloxicam compared with diclofenac and naproxen and between piroxicam and meloxicam 7.5 mg (P < 0.05, Table III, Fig. 3).
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### TABLE III

Incidence of GI adverse events
(all data are from double-blind studies in RA and OA, with the exception of total GI adverse events the whole population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Meloxicam 7.5 mg</th>
<th>Meloxicam 15 mg</th>
<th>Piroxikam 20 mg</th>
<th>Diclofenac 100 mg SR</th>
<th>Naproxen 750–1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GI adverse events in the whole population % (n)</td>
<td>16.8 (150)</td>
<td>18.3 (601)</td>
<td>20.2 (183)†</td>
<td>26.5 (86)†</td>
<td>36.6 (89)†</td>
</tr>
<tr>
<td>Total GI adverse events % (n)</td>
<td>17.0 (150)</td>
<td>18.9 (301)</td>
<td>24.5 (169)†</td>
<td>26.2 (86)†</td>
<td>36.6 (89)†</td>
</tr>
<tr>
<td>Non-serious GI adverse events % (n)</td>
<td>16.9 (149)</td>
<td>18.8 (299)</td>
<td>24.1 (166)†</td>
<td>26.2 (85)†</td>
<td>36.2 (88)†</td>
</tr>
<tr>
<td>Severe GI adverse events % (n)</td>
<td>1.7 (15)</td>
<td>1.7 (27)</td>
<td>4.9 (34)†</td>
<td>4.9 (16)†</td>
<td>7.8 (19)†</td>
</tr>
<tr>
<td>Discontinuations due to GI adverse events % (n)</td>
<td>3.5 (31)</td>
<td>4.8 (76)</td>
<td>6.7 (46)†</td>
<td>10.5 (34)†</td>
<td>10.7 (26)†</td>
</tr>
<tr>
<td>Abdominal pain % (n)</td>
<td>2.7 (24)</td>
<td>3.0 (47)</td>
<td>5.7 (39)†</td>
<td>7.1 (33)†</td>
<td>11.9 (29)†</td>
</tr>
<tr>
<td>Dyspepsia % (n)</td>
<td>5.1 (45)</td>
<td>7.4 (117)</td>
<td>9.7 (67)†</td>
<td>9.9 (32)†</td>
<td>14.8 (36)†</td>
</tr>
<tr>
<td>Upper GI adverse events % (n)</td>
<td>4.5 (40)</td>
<td>5.7 (91)</td>
<td>5.5 (38)</td>
<td>7.1 (23)†</td>
<td>11.5 (28)†</td>
</tr>
</tbody>
</table>

n, no. of events; %, incidence in percent of treated patients.

*P < 0.05 compared with meloxicam 7.5 mg.
†P < 0.05 compared with meloxicam 15 mg.

Non-serious adverse events: events other than immediately life threatening, severely or permanently disabling or requiring prolonged hospitalization.

Severe adverse events: incapacitating, with inability to do work or usual activity or causing the patient to discontinue the trial.

Total no. of patients for double-blind studies in RA and OA is 881 for meloxicam 7.5 mg, 1590 for meloxicam 15 mg, 689 for piroxicam, 324 for diclofenac and 243 for naproxen.

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When various types of GI adverse events are considered, meloxicam also proved to be better tolerated than the standard NSAIDs. Both meloxicam 7.5 and 15 mg were significantly superior to all comparators with respect to abdominal pain (P < 0.05, Table III). For dyspepsia, meloxicam 7.5 mg was the best tolerated, followed by meloxicam 15 mg, piroxicam, diclofenac and naproxen. There were significantly fewer events with meloxicam 7.5 mg compared with piroxicam, diclofenac and naproxen; meloxicam 15 mg...
was significantly superior to naproxen ($P < 0.05$, Table III). With respect to upper GI adverse events (duodenal ulcer, dyspepsia, eructation, nausea, vomiting, gastric ulcer, haematemesis, melena), meloxicam 7.5 mg was significantly better tolerated than both diclofenac and naproxen; meloxicam 15 mg was significantly superior to naproxen ($P < 0.05$, Table III). These events have also been assessed with respect to their relationship to the drug being studied; similar results were seen when the adverse event was assessed as being at least possibly related to the drug under investigation (results not shown). For abdominal pain, the result in this case was the same as above. For dyspepsia, meloxicam 7.5 mg was significantly superior to both the comparator drugs and meloxicam 15 mg; again, the 15 mg dose was better tolerated than naproxen. For upper GI adverse events at least possibly related to the drug being studied, a greater difference was seen between meloxicam 7.5 mg and the other groups than when all relationships to the drug were considered. For at least possibly related events, there were significantly fewer events with meloxicam 7.5 mg compared with meloxicam 15 mg and piroxicam, in addition to diclofenac and naproxen. Meloxicam 15 mg remained significantly superior to naproxen.

### TABLE IV

<table>
<thead>
<tr>
<th>Type of PUB % (n)</th>
<th>Meloxicam 7.5 mg (n = 881)</th>
<th>Meloxicam 15 mg (n = 1590)</th>
<th>Piroxicam 20 mg (n = 689)</th>
<th>Diclofenac 100 mg SR (n = 324)</th>
<th>Naproxen 750-1000 mg (n = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUB % (n)</td>
<td>0.1 (1)</td>
<td>0.2 (3)</td>
<td>1.2 (8)*†</td>
<td>0.6 (2)</td>
<td>2.1 (5)*†</td>
</tr>
<tr>
<td>Serious PUB † % (n)</td>
<td>0.0 (0)</td>
<td>0.1 (2)</td>
<td>0.4 (3)</td>
<td>0.6 (2)</td>
<td>0.4 (1)</td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>0.0 (0)</td>
<td>0.5 (3)</td>
<td>1.7 (4)*</td>
<td>1.1 (2)</td>
<td>4.6 (3)*</td>
</tr>
<tr>
<td>≤ 65 yr</td>
<td>0.2 (1)</td>
<td>0.0 (0)</td>
<td>0.9 (4)†</td>
<td>0.0 (0)</td>
<td>1.1 (2)†</td>
</tr>
<tr>
<td>Type of PUB % (n)</td>
<td>Duodenal ulcer</td>
<td>0.0 (0)</td>
<td>0.1 (1)</td>
<td>0.6 (4)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>0.1 (1)</td>
<td>0.1 (1)</td>
<td>0.4 (3)</td>
<td>0.3 (1)</td>
<td>1.2 (3)</td>
</tr>
<tr>
<td>Melaena or haematemesis</td>
<td>0.0 (0)</td>
<td>0.1 (1)</td>
<td>0.1 (1)</td>
<td>0.3 (1)</td>
<td>0.4 (1)</td>
</tr>
<tr>
<td>Perforated upper GI ulcer</td>
<td>0.0 (0)</td>
<td>0.1 (1)</td>
<td>0.1 (1)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Haemorrhagic upper GI ulcer</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.1 (1)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

$n$, no. of events; %, incidence in percent of treated patients. Some patients are included in more than one category.

* $P < 0.05$ compared with meloxicam 7.5 mg.

† $P < 0.05$ compared with meloxicam 15 mg.

‡ PUBs which were reported as serious adverse events by the investigator (immediately life threatening, severely or permanently disabling or requiring or prolonging hospitalization).

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**Fig. 4.—** Upper GI perforations, ulcerations and bleedings (PUBs) over time in double-blind clinical studies of meloxicam in RA and OA. *$P < 0.05$ compared with meloxicam 7.5 mg.
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Fig. 5.—Upper GI perforations, ulcerations and bleedings (PUBs) according to age in double-blind clinical studies of meloxicam in RA and OA.

TABLE V
Most frequently occurring adverse events* [n (%) of patients treated]

<table>
<thead>
<tr>
<th></th>
<th>Meloxicam 7.5 mg</th>
<th>Meloxicam 15 mg</th>
<th>Piroxicam 20 mg</th>
<th>Diclofenac 100 mg SR</th>
<th>Naproxen 750–1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>150 (16.8)</td>
<td>601 (18.3)</td>
<td>183 (20.2)</td>
<td>86 (26.5)</td>
<td>89 (36.6)</td>
</tr>
<tr>
<td>CNS</td>
<td>69 (7.7)</td>
<td>248 (7.6)</td>
<td>60 (6.6)</td>
<td>22 (6.8)</td>
<td>19 (7.8)</td>
</tr>
<tr>
<td>GOT/GPT increased</td>
<td>53 (5.9)</td>
<td>243 (7.4)</td>
<td>57 (6.3)</td>
<td>52 (16.1)</td>
<td>23 (9.5)</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td>58 (6.5)</td>
<td>203 (6.2)</td>
<td>40 (4.4)</td>
<td>13 (4.0)</td>
<td>20 (8.2)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>55 (6.2)</td>
<td>239 (7.3)</td>
<td>33 (3.6)</td>
<td>20 (6.2)</td>
<td>15 (6.2)</td>
</tr>
<tr>
<td>Urinary system</td>
<td>39 (4.4)</td>
<td>172 (5.3)</td>
<td>44 (4.9)</td>
<td>10 (3.1)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>Creatinine/BUN increased</td>
<td>4 (0.5)</td>
<td>12 (0.4)</td>
<td>8 (0.9)</td>
<td>1 (0.3)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

GOT, glutamate oxalate transaminase; GPT, glutamate pyruvate transaminase; BUN, blood urea nitrogen.
*All adverse events, irrespective of causal relationship to study drug, are shown.

Upper GI perforations, ulcerations and bleedings (PUBs) (which includes events defined as serious and non-serious) occurred most frequently in patients treated with naproxen 750–1000 mg, followed by piroxicam 20 mg, diclofenac 100 mg, and meloxicam 7.5 and 15 mg (Table IV, Fig. 4). Although the incidence of PUB was related to meloxicam dose, both meloxicam 7.5 and 15 mg were significantly superior to piroxicam and naproxen (P < 0.05). The type and incidence of PUB are summarized in Table IV; gastric and duodenal ulcers were the most common PUBs recorded and were responsible for the higher incidence of PUBs observed with comparator drugs compared with meloxicam.

The percentage of patients with PUBs which were considered serious adverse events was highest in the diclofenac 100 mg group and lowest in the meloxicam 7.5 mg group, where no serious PUBs were reported (Table IV). Meloxicam 7.5 mg was significantly superior to diclofenac (P < 0.05) in terms of PUBs considered to be serious. The majority of GI adverse events defined as serious fell into the category of a PUB.

There was a higher incidence of PUB in elderly (>65 yr) than in younger patients (Table IV, Fig. 5). There were fewer PUBs in the meloxicam or diclofenac treatment groups than in the naproxen or piroxicam groups for either elderly or younger patients.

Renal function abnormalities

Sixteen (0.4%) of the 4175 subjects who received meloxicam 7.5 or 15 mg showed significantly abnormal renal function during treatment [defined as serum creatinine > 1.8 mg/dl or blood urea nitrogen (BUN) values >40 mg/dl associated with serum creatinine values above the upper limit of normal, with values recorded during treatment higher than those at baseline]. The percentage of patients with abnormal kidney function values after receiving piroxicam 20 mg was 0.9%, diclofenac 100 mg 0.3%, naproxen 750–1000 mg 0.4% and placebo 0.2%. RA patients are generally known to suffer from a higher rate of renal adverse events with NSAIDs than OA patients, but this was not observed with meloxicam. When RA and OA patients were analysed separately, the same incidence (0.4%) of renal adverse effects was found in both groups. In
contrast, piroxicam showed a higher incidence in RA patients (1.6%) compared with OA patients (0.4%).

**General analysis of all adverse events (whole population)**

There was a trend towards a greater number of adverse events occurring in diclofenac- and naproxen-treated patients than in the other treatment groups. In all groups, the most frequently occurring adverse events were GI events (Table V). Adverse events often associated with NSAIDs were reported with a similar incidence across active treatment groups. These included dizziness, headache, rash, pruritus, hypertension and peripheral oedema.

The incidence of non-serious adverse events recorded was similar between the treatment groups (43%, 45%, 44%, 56% and 61% for meloxicam 7.5 and 15 mg, piroxicam, diclofenac and naproxen respectively). The percentage of patients withdrawn due to an adverse event was lowest in the meloxicam 7.5 mg group, followed by meloxicam 15 mg and piroxicam 20 mg, followed by naproxen 750–1000 mg and diclofenac 100 mg (Fig. 6). Both doses of meloxicam were significantly superior to diclofenac ($P < 0.05$).

One patient who received meloxicam 7.5 mg, five patients who received meloxicam 15 mg and five patients who received comparator drugs died during or after clinical trials (Table VI). In all cases the investigator assessed the relationship of this outcome to the study drug as doubtful.

**DISCUSSION**

This first global analysis of safety data from a clinical trial programme for meloxicam, a preferential COX-2 inhibitor, has explored the safety and tolerability of meloxicam in therapeutic doses of 7.5 and 15 mg in 4175 patients, including 1379 patients aged >65 yr, with the majority of patients having OA or RA. This represents a broad database of clinical experience.

The data show that meloxicam 7.5 and 15 mg have a better GI safety profile in comparison with diclofenac 100 mg SR, piroxicam 20 mg and naproxen 750–1000 mg. When considering all GI adverse events, both doses of meloxicam were significantly better than comparators in an analysis of pooled data from double-blind studies in RA and OA. When examining specific categories of GI adverse effects, both doses of meloxicam were significantly better than the comparator NSAIDs in most cases. In the few cases where statistical significance was not demonstrated, there was generally a clear trend in favour of meloxicam.

Dyspepsia, abdominal pain, nausea and diarrhoea were the most commonly occurring adverse events, as is
usual with NSAIDs [1, 17]. Although not life threatening, these symptoms can be extremely unpleasant for the patient and may reduce compliance with therapy. In this analysis, meloxicam showed an advantage with respect to abdominal pain and dyspepsia. As two of the most common NSAID-associated side-effects, abdominal pain and dyspepsia affect large numbers of patients and a good safety profile with respect to these events is essential to patient tolerability, compliance and continued use of therapy. Indeed, discontinuation due to GI adverse events was least common with meloxicam 7.5 mg, followed by meloxicam 15 mg.

Both doses of meloxicam showed a statistically significant decrease in the incidence of PUB over piroxicam 20 mg and naproxen 750–1000 mg; in addition, there was a significant difference in favour of meloxicam 7.5 mg over diclofenac 100 mg with respect to PUBs which were reported as serious adverse events. Diclofenac is thought of as one of the safer NSAIDs with respect to bleeding, perforation and other serious GI adverse events [18]. The risk of PUB is generally greater in the elderly compared with younger patients [4, 19]. With all NSAIDs examined in this analysis, with the exception of meloxicam 7.5 mg, there was a higher incidence of PUB in the elderly than in younger patients. However, the increase in incidence for elderly patients was less for meloxicam 15 mg than for the comparator drugs. No elderly patient (>65 yr) experienced a PUB when treated with meloxicam 7.5 mg.

Although both meloxicam 7.5 and 15 mg showed an advantage over the comparator NSAIDs in their GI safety profile, there was some evidence of a dose–effect relationship with respect to GI side-effects. Overall, meloxicam 7.5 mg was rather better tolerated than meloxicam 15 mg, although there was no statistically significant difference between them with respect to any of the parameters examined. Of the comparator drugs, naproxen 750–1000 mg was the least well tolerated with respect to most categories of GI adverse events. When considering PUBs, diclofenac appeared rather better tolerated than piroxicam, as has been previously observed in epidemiological studies [18]. However, there were fewer non-PUB GI events with piroxicam than with diclofenac. Overall, when considering PUBs and other GI adverse events, meloxicam was consistently the best tolerated of all the drugs compared in this analysis.

Renal impairment is an adverse event also commonly associated with NSAID treatment. This is usually manifested as mild and reversible renal impairment but cases of acute renal failure have also been observed [20]. It is clear that some NSAIDs have a greater likelihood of causing renal impairment than others [21]. In this analysis, treatment with piroxicam 20 mg had the highest risk of inducing an increase in serum creatinine and/or BUN. Meloxicam, naproxen and diclofenac SR treatment groups recorded a similar incidence of renal function abnormalities. The incidence of other adverse events was similar across all treatment groups. This analysis confirms the now well-recognized fact that there are clear differences between NSAIDs at equipotent doses in terms of their potential to cause GI side-effects [3, 4]. The differential inhibition of COX-1 relative to COX-2 by NSAIDs may explain the differences between them regarding GI tolerability, and presents an opportunity for the development of new NSAID treatment. The favourable GI profile shown by meloxicam compared with piroxicam, diclofenac SR and naproxen in this safety analysis may be a consequence of meloxicam’s preferential inhibition of COX-2 over COX-1. In several models designed to investigate the COX selectivity of various NSAIDs, meloxicam has shown preferential selectivity for COX-2 [9–11]. In contrast, NSAIDs such as diclofenac, piroxicam, indomethacin and naproxen either inhibited both COX isoforms to a similar degree or preferentially inhibited COX-1 over COX-2 [9–11, 22, 23]. The relative selectivity of a NSAID is reflected in its COX-2/COX-1 inhibition ratio; low ratios indicate more potent inhibition of COX-2 than of COX-1.

The clinical relevance of differences in COX-2 inhibition relative to COX-1 can be illustrated when NSAID-related upper GI bleeding ratings from case-control studies or UK Committee on Safety of Medicines (CSM) spontaneous adverse event reports are considered [3, 4, 18]. For example, odds ratios for the risk of experiencing an upper GI bleeding and/or perforation from two case-control studies were 18.0 and 13.7 for piroxicam, compared with odds ratios of 3.9 and 4.2 for diclofenac, and 3.1 and 9.1 for naproxen [3, 4]. A similar ranking in the relative incidence of PUBs in CSM spontaneous adverse event reports between these agents was recorded [18]. In this respect, there is a clear link between lower GI toxicity and more potent inhibition of COX-2 relative to COX-1 by these NSAIDs [9, 22]. As meloxicam consistently demonstrates a lower COX-2/COX-1 ratio than these standard NSAIDs, it might be expected that this would be reflected in a superior GI safety profile. The results of the present analysis provide good evidence that this is the case.

In conclusion, it has been shown that meloxicam, at therapeutic doses of 7.5 and 15 mg once daily, has an improved GI safety profile in comparison with standard doses of well-established NSAIDs. This may be explained by meloxicam’s preferential inhibition of COX-2 relative to COX-1.

REFERENCES


