AN OPEN STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF MELOXICAM 15 mg IN SUBJECTS WITH RHEUMATIC DISEASE AND MILD RENAL IMPAIRMENT

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SUMMARY
Meloxicam is a new non-steroidal anti-inflammatory drug (NSAID) which has shown potent anti-inflammatory properties but good gastrointestinal (GI) and renal tolerability. The safety and tolerability profile of orally administered meloxicam 15 mg given once daily over a 28 day treatment period in renally impaired patients with rheumatic disease is presented here. A total of 25 patients (aged 43–78 yr, mean age 70 yr) with rheumatic disease and mild renal impairment were enrolled in this multicentre, open-label study, with 22 patients completing the 28 day treatment period. The median estimated creatinine clearance and N-acetyl-β-glucosaminidase/creatinine ratios (a marker of renal tubular damage) recorded at day 14, day 28 or 4–7 days after meloxicam treatment was terminated, were not statistically significantly different from baseline values. There was no evidence of accumulation of meloxicam. Overall, meloxicam was well tolerated. The most common adverse events were GI complaints of abdominal pain and dyspepsia. No adverse events related to the urinary system, or increases in serum urea or potassium were recorded. The results suggest that meloxicam, 15 mg once daily, does not further compromise renal function or result in accumulation of meloxicam over this treatment period in patients with pre-existing mild renal impairment.

KEY WORDS: Non-steroidal anti-inflammatory drugs (NSAIDs), Rheumatic disease, Meloxicam, Renal function, Renal impairment, Tolerability.

MELOXICAM is an enolic acid derived non-steroidal anti-inflammatory drug (NSAID) developed for the treatment of rheumatic disease. In animal studies [1] meloxicam has shown potent anti-inflammatory properties in combination with good gastrointestinal (GI) and renal tolerability. Promising results, suggesting these characteristics, have also been observed in early clinical studies conducted in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) [2–6]. In a double-blind comparison over a treatment period of 6 months, patients with RA treated with meloxicam 7.5 mg had no changes in creatinine or urea plasma levels, whereas there was a significant increase in these parameters in patients treated with naproxen 750 mg [7]. Like other NSAIDs, meloxicam is highly plasma protein bound (>99%). Following oral administration, meloxicam is extensively metabolized in the liver and excreted approximately equally via renal and hepatic routes [8]. All metabolites are pharmacologically inactive. Steady-state plasma levels of meloxicam are achieved within 3–5 days after the start of once-daily oral administration [8].

This study represents the first clinical study of meloxicam conducted in patients with rheumatic disease and pre-existing renal impairment. The design of this study is based on a review of similar studies conducted with other NSAIDs over a 2-week period [9–11]. This study was conducted over a 4-week period with a washout period at the end of treatment in order to observe at least a partial recovery in renal function should an initial fall in renal function be observed in association with meloxicam treatment. Improvement in renal function has been observed in previous studies following withdrawal of NSAID therapy [12]. Renal function was assessed by two methods commonly used in studies of this nature: estimated creatinine clearance and N-acetyl-β-glucosaminidase (NAG)/creatinine ratio.

Consequently, the aim of this study was to evaluate the safety and tolerance of meloxicam, 15 mg once daily, in patients with rheumatic disease and mild renal impairment (creatinine clearance 25–60 ml/min).

PATIENTS AND METHODS
This study was an open-label, multicentre study in which patients received a meloxicam 15 mg capsule once daily, with a glass of water after food, for 28 days. Further details of the six centres involved, and the number of patients entered by each centre, are given in the Acknowledgements. All patients had a diagnosis of arthritic disease, defined as RA, either seropositive or seronegative, OA or other rheumatic disease requiring NSAID therapy and had mild renal impairment as defined by an estimated creatinine clearance of 25–60 ml/min.

Pretreatment phase and exclusion criteria
Patients attended an initial pretreatment screening examination consisting of weight and height measurements, and blood and urine sampling for routine monitoring and determination of creatinine clearance. Patients were excluded from the study, at this stage, for the following reasons: participation in clinical trials.
with an investigational new drug in the month prior to
the screening visit and during the study period itself;
participation in any previous studies with meloxicam;
pregnancy and risk of pregnancy; clinical evidence of
severe cardiac, pulmonary, GI, hepatic or neurological
disease; allergic bronchial asthma; a known hyper-
sensitivity to analgesics, antipyretics and NSAIDs;
clinical evidence of active peptic ulceration during the
previous 6 months; requirement for dialysis; taking
concomitant piroxicam or tenoxicam; treatment with
anticoagulants, lithium, angiotensin-converting enzyme
(ACE) inhibitors or hydantoins; clinically relevant
abnormal baseline laboratory results not associated
with second-line antixheumatic drugs such as metho-
trexate or sulphasalazine which had not been stabilized
for at least 1 month prior to screening; treatment with
cyclosporin, pencillamine or gold which had not been
stabilized for at least 3 months prior to screening.

Patients were allowed to continue with second-line
antirheumatic drugs at a dose stabilized for at least 1
month before the study or not otherwise stipulated in
the exclusion criteria. Paracetamol 500 mg or coprox-
amol (dextropropoxyphene 32.5 mg and paracetamol
325 mg) were supplied as rescue medication (dose
limited to eight tablets per day) for pain relief when
appropriate, during washout and treatment periods.

A second screening visit was conducted no less than 4
days after the first screening visit and patients were not
included in the study if the calculated creatinine
clearance values differed by greater than 10 ml/min on
the two occasions.

**Washout and treatment phase**

Patients who were eligible for the study and taking a
NSAID entered a washout period (4 days for
nabumetone and 3 days for other NSAIDs) after the
second screening visit. After the washout phase,
patients entered the meloxicam treatment phase and
underwent a pretreatment examination including weight,
height, blood pressure and heart rate measurements,
a complete physical examination and laboratory tests.
Patients were then followed up at day 14, 21 and 28 of meloxicam treatment. A further clinic
visit was arranged 4 or 7 days after meloxicam
treatment was finished so that renal function
assessments could be made after treatment washout.
This study was conducted according to the Declaration
of Helsinki (amended 1983) and guidelines for Good
Clinical Practice.

**Assessment of renal function**

Blood and urine samples were collected at the two
screening visits and at each follow-up visit. Creatinine
clearance was estimated from serum creatinine levels
using equations described by Mawer et al. [13]. Renal
function was also assessed using estimation of NAG
derived from a 4 h urine collection and comparison with
creatinine clearance. NAG is an enzyme found in high
concentrations in the epithelial cells of renal tubules
and it has been observed that increased quantities are
excreted in patients with renal dysfunction [14, 15]. The
excretion of NAG is a sensitive indicator of early renal
damage [15], and was therefore measured as one of the
secondary endpoints. Dipstick urine tests were
performed at a screening visit, the first and last treatment
follow-up days, and at either 4 or 7 days after
meloxicam treatment was terminated. Trough plasma
meloxicam concentrations (blood samples taken prior
to dosing) were also determined on the three follow-up
days. Meloxicam plasma levels were determined using a
validated, specific high-performance liquid chroma-
tography (HPLC) method with a lower quantification
limit of 0.05 g/ml [U. Busch, data on file, Boehringer
Ingelheim].

Comparisons of creatinine clearances and NAG/
creatinine clearance ratios before and after treatment
and plasma meloxicam trough levels during treatment
were statistically analysed by paired t-tests and 95%
confidence intervals for within-patient differences.

**Tolerability and efficacy assessments**

Adverse events occurring during the study were
recorded by the investigator and coded using the
WHO-ART system. Adverse events were also
recorded during the study by intensity (mild, moderate
or severe) and frequency. In addition, the mean time to
onset of each event was calculated.

At either 4 or 7 days after meloxicam treatment
discontinuation, patients and investigators completed a
questionnaire where efficacy and tolerability of
meloxicam treatment were rated on a scale of very well,
well, average, poorly or very poorly.

**Sample size estimation**

It was calculated that a sample size of 25 evaluable
patients would be needed to detect a difference in
creatinine clearance of at least 15 ml/min by means of a
paired t-test (α = 5%, β = 10%, two-tailed).

**RESULTS**

Twenty-five patients, five men and 20 women, mean
age 70 yr (range 43–78 yr), were included in the intent
to-treat population. Twenty-two patients completed the
28 day study-treatment period. Three patients were
withdrawn from the study prematurely: one due to an
adverse event (abdominal pain) thought to be related to
meloxicam, one was lost to follow up and for the
third no reason was specified by the patient. Baseline
characteristics relating to demographics, disease
characteristics and concomitant treatment are listed in
Table I. The majority of patients suffered from either
RA (63%) or OA (29%), with the remaining 8% of
patients suffering from other rheumatic diseases. A
mean duration of 12 yr was recorded for all arthritic
conditions.

**Renal function assessments**

Assessments of renal function conducted throughout
the study period revealed no deterioration in renal
function in this group of patients with mild renal
impairment. Creatinine clearances and NAG/creatinine
STUDIES ON MELOXICAM (MOBIC)

TABLE I
Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70</td>
</tr>
<tr>
<td>S.D.</td>
<td>7</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Duration of rheumatic disease (yr)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.0</td>
</tr>
<tr>
<td>S.D.</td>
<td>8.5</td>
</tr>
<tr>
<td>Median</td>
<td>11.3</td>
</tr>
<tr>
<td>Type of rheumatic disease</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Possible diabetes mellitus</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Investigation of glomerular nephritis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (59)</td>
</tr>
</tbody>
</table>

| Number of patients reporting at least one concomitant therapy | 21 (84) |

| Antihypertensives   | 7 (28) |
| Diuretics           | 5 (20) |
| Antacids/antiulcerant | 6 (24) |
| Psychotropics       | 5 (20) |
| Anti-inflammatories | 4 (16) |
| Analgesics          | 3 (12) |

Aetiology of renal disease unknown in two patients.

TABLE II
Creatinine clearance (ml/min)

<table>
<thead>
<tr>
<th>Visit</th>
<th>No. of patients</th>
<th>Mean</th>
<th>S.D.</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25</td>
<td>50.4</td>
<td>11.0</td>
<td>50.4</td>
</tr>
<tr>
<td>Day 14</td>
<td>24</td>
<td>46.7 (NS)</td>
<td>10.6</td>
<td>49.0</td>
</tr>
<tr>
<td>Day 21</td>
<td>22</td>
<td>50.0 (NS)</td>
<td>10.6</td>
<td>54.9</td>
</tr>
<tr>
<td>Day 28</td>
<td>22</td>
<td>48.9 (NS)</td>
<td>9.7</td>
<td>50.5</td>
</tr>
<tr>
<td>Last visit (days 32/35)</td>
<td>22</td>
<td>50.7 (NS)</td>
<td>10.9</td>
<td>52.1</td>
</tr>
</tbody>
</table>

NS, difference from baseline not statistically significant.

TABLE III
NAG/creatinine ratio (umol/min/g)

<table>
<thead>
<tr>
<th>Visit</th>
<th>No. of patients</th>
<th>Mean</th>
<th>S.D.</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>19*</td>
<td>9.16</td>
<td>6.79</td>
<td>7.28</td>
</tr>
<tr>
<td>Day 14</td>
<td>20</td>
<td>9.68 (NS)</td>
<td>6.99</td>
<td>10.30</td>
</tr>
<tr>
<td>Day 21</td>
<td>18</td>
<td>9.50 (NS)</td>
<td>6.97</td>
<td>9.53</td>
</tr>
<tr>
<td>Day 28</td>
<td>18</td>
<td>10.26 (NS)</td>
<td>6.71</td>
<td>9.05</td>
</tr>
</tbody>
</table>

The shortfall in collected results for evaluation of NAG/creatinine ratios resulted in smaller comparison groups at later study visits. NS, difference from baseline not statistically significant.

TABLE IV
Adverse events assessed by investigator as drug related, intent-to-treat population

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Efficacy and tolerability

The majority of patients tolerated their medication 'very well' or 'well' (96% as assessed by the patient, 88% as assessed by the investigator) and efficacy was assessed as 'very good' or 'good' (52% as assessed by the patient and 75% as assessed by the investigator). Use of rescue analgesia during the study was minimal.

DISCUSSION

This study is the first to investigate the effects of a new NSAID, meloxicam, in older patients with rheumatic disease and mild renal impairment.

Clinical studies of meloxicam have been conducted largely in patients with normal renal function and a very favourable safety profile has been observed. Studies with other NSAIDs have indicated that some

Trough plasma meloxicam levels

There were no statistically significant differences in mean trough plasma meloxicam levels recorded at study days 14 (1.72 μg/ml), 21 (1.71 μg/ml) and 28 (1.52 μg/ml).

Adverse events

Overall adverse events assessed by the investigator as probably, possibly or definitely related to meloxicam treatment were recorded in 5% of patients, with GI disorders occurring most frequently (Table IV). No serious adverse events or GI perforations, ulcers or bleeds were reported. One patient was withdrawn from the study experiencing epigastric pain of moderate intensity 3 days after starting meloxicam treatment. There were no clinically significant abnormal trends in haematological or biochemical parameters recorded at any study day.
patients treated with NSAID therapy show an asymptomatic, reversible impairment of renal function [12], characterized by reductions in creatinine clearance and corresponding rises in plasma creatinine, urea and potassium. Meloxicam has shown good renal tolerability in early preclinical studies [1] and in a clinical double-blind trial vs naproxen [7].

The occurrence of adverse renal events induced by NSAIDs in general has been extensively reviewed [16-18]. The majority of renal adverse events observed in association with NSAIDs result from the inhibition of cyclooxygenase (COX) leading to a decreased concentration of the vasodilating prostaglandins, PGE2 and prostacyclin, within the kidney. These mediators are responsible for maintaining renal plasma flow and glomerular filtration rate [19]. Consequently, NSAID intervention may cause acute intrarenal haemodynamic changes in patients whose renal blood flow is dependent on prostaglandins, and this can result in reversible acute renal failure. Certain patients are particularly at risk of NSAID-associated renal adverse events, such as patients with reduced circulating volume, the elderly and those with pre-existing renal dysfunction [20]. Allergic reactions, such as interstitial nephritis, have also been reported [16, 18].

Other studies have considered the effects of various NSAIDs, given over a short term (11 days–3 months), on renal function in patients with rheumatic disease and minor renal dysfunction [9-11]. In an 11 day study comparing ibuprofen 800 mg t.d.s., sulindac 200 mg b.d. and piroxicam 20 mg o.d., only ibuprofen showed changes in renal function necessitating premature withdrawal [11]. In a 4-week study of naproxen, increasing the dose at 2 weeks after initiation resulted in small, transient changes in renal function [10]. In a 3-month study of tenoxicam, creatinine clearances were significantly lower after 12 weeks, with the NAG/creatinine ratio showing a trend toward improvement at week 12 [9]. In this study of meloxicam 15 mg once daily for 28 days, no significant differences between creatinine clearance or NAG/creatinine ratios measured at baseline and during treatment were observed.

Recently, two isomers of COX, known as COX-1 and COX-2, have been identified [21]. COX-1 is a constitutive COX found in the gastric mucosa and intrarenally where it is involved in maintaining the haemodynamic balance [22]. COX-2 is inducible in conditions associated with the acute inflammatory response. It is likely that preferential selectivity for one COX isomer over another is implicated in the differing incidence of renal toxicity observed between various NSAIDs [20]. Interestingly, meloxicam has shown preferential selectivity for the inducible COX-2 over constitutive COX-1 [23, 24].

Over the 28 day treatment period trough meloxicam plasma levels remained similar, indicating a lack of accumulation in patients with mild renal impairment. Meloxicam undergoes extensive hepatic metabolism and the pharmacologically inactive metabolites are excreted approximately equally via the kidney and liver. Only trace amounts, <1%, are eliminated unchanged in the urine and faeces [8]. In addition, like other NSAIDs, >99% meloxicam is plasma protein bound [8].

Reassuringly, no serious adverse events were reported during the study and the most common adverse events—abdominal pain and dyspepsia—were among those previously observed in patients with normal renal function [2-4]. In addition, and importantly, no renal adverse events occurred in any patient, and no laboratory changes (serum creatinine, serum urea or serum potassium) indicative of deteriorating renal impairment were recorded at any time during the study.

ACKNOWLEDGEMENTS

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REFERENCES

3. Reginster JY, Distel M, Bluhmki E. A double-blind study to compare the efficacy and safety of meloxicam 7.5 mg and meloxicam 15 mg in patients with rheumatoid arthritis. Scand J Rheumatol 1994;Suppl 98:abstract no. 112.


