A SIX-MONTH DOUBLE-BLIND TRIAL TO COMPARE THE EFFICACY AND SAFETY OF MELOXICAM 7.5 mg DAILY AND NAPROXEN 750 mg DAILY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

Meloxicam is a new non-steroidal anti-inflammatory drug (NSAID) which preferentially inhibits cyclooxygenase-2 over cyclooxygenase-1. A double-blind, parallel-group trial compared meloxicam 7.5 mg once daily (n = 199) with naproxen 750 mg (n = 180) in rheumatoid arthritis. There was no significant difference between the groups regarding the primary efficacy variables (global efficacy assessment by patient and investigator, number of painful/tender and swollen joints) and eight of the ten secondary efficacy endpoints. Only the swollen joint severity index and the number of discontinuations due to lack of efficacy favoured naproxen 750 mg significantly over meloxicam 7.5 mg. Meloxicam was better tolerated in the gastrointestinal (GI) tract, with fewer GI adverse events in the meloxicam-treated group (30.3%) than in the naproxen-treated group (44.7%), where two patients developed ulcers. No ulcers were seen in meloxicam patients. Significantly more patients discontinued due to GI adverse events in the naproxen group. Additionally, there was a significant decrease in haemoglobin and a significant increase in serum creatinine and urea in the naproxen group compared with the meloxicam group. In conclusion, meloxicam 7.5 mg once daily is a promising treatment in rheumatoid arthritis, with efficacy comparable to naproxen 750 mg. Meloxicam has the advantage of a significantly lower incidence of GI and renal side effects.

KEY WORDS: Meloxicam, Non-steroidal anti-inflammatory drug, Cyclooxygenase-2, Naproxen, Rheumatoid arthritis, Gastrointestinal.

NON-STEROIDAL anti-inflammatory drugs (NSAIDs) are widely used in rheumatoid arthritis (RA) for the relief of pain and inflammation. However, the use of NSAIDs is limited by side-effects, particularly of a gastrointestinal (GI) nature. Vane first recognized that both the anti-inflammatory actions and the common side-effect profile of NSAIDs are mediated through inhibition of prostaglandin biosynthesis via the cyclooxygenase (COX) enzyme [1]. It is now believed that the beneficial effects of NSAIDs are due to the inhibition of one isoform of COX (COX-2, produced by inflammatory mediators), whereas the common side-effects are due to inhibition of COX-1 (which has a ‘housekeeping function’ in cells) [2]. Compounds that have favourable COX-2/COX-1 ratios should have a less irritant action on the stomach and fewer side-effects [3]. Meloxicam, a new enolic acid NSAID, has demonstrated in preclinical studies to have one of the highest selectivity ratios for COX-2 [4] and has also been shown to have minimal damaging effects on the GI tract [4–7]. In this study, the efficacy and safety of meloxicam 7.5 mg was compared with naproxen 750 mg in patients with RA. Naproxen was chosen for comparison because it is a well established NSAID for use in RA [8–10].

METHODS

This controlled, double-blind, double-dummy, parallel-group trial was conducted at trial centres located in the UK (23 centres), Germany (13), France (7), Belgium (3), Mexico (1) and Spain (1). The study was approved by the appropriate Ethics Committees and was conducted in accordance with the provisions of the Declaration of Helsinki. All patients gave informed consent to participate in the study.

Patients

Patients, aged 18–75 yr, with RA were enrolled in the study. RA was defined according to the American College of Rheumatology (formerly the American Rheumatism Association) criteria [11] and patients belonged to functional class I, II or III [12], required anti-inflammatory therapy and demonstrated active disease before and/or during a washout period. Active disease was defined as the presence of three of the following: six or more joints painful or tender on motion; three or more swollen joints; duration of morning stiffness of at least 45 min; Westergren sedimentation rate of ≥28 mm/h.

Patients who had taken part in a previous meloxicam trial were excluded, as well as patients with clinical evidence of peptic ulceration and those with any other rheumatological or non-rheumatological disease which would interfere with the evaluation of efficacy and safety, including collagenosis, dermatomyositis, gout,
infectious arthritis, sarcoidosis, psoriatic arthritis, ankylosing spondylitis, Still’s disease, mixed connective tissue disease, arthritis associated with inflammatory bowel disease, systemic lupus erythematosus, fibromyalgia, Reiter’s syndrome, arteritis (general), polymyalgia rheumatic and scleroderma. Patients were assessed at the start of treatment, at days 14 and 28 and at weeks 8, 12, 19 and 26.

**Washout period**

After assessment and randomization to meloxicam or naproxen treatment, patients already taking a NSAID underwent a washout period of 3–11 days (dependent upon the drug).

**Medication**

Following the washout period, the patients were instructed on how to take their trial medication: one capsule (meloxicam 7.5 mg or matching placebo) and two tablets (naproxen 250 mg or matching placebo) each morning and one tablet (naproxen 250 mg or placebo) each evening, all with water after food.

Concomitant medication was allowed but patients whose treatment with second-line antirheumatic therapies was not stable for 3 months before the study were excluded. Those treated with any glucocorticosteroids exceeding a dose of 7.5 mg prednisolone daily (or equivalent) and not stabilized for a month before the study were also excluded. Patients could not receive any intramuscular or intravenous injections of glucocorticosteroids or adrenocorticotropic hormone and no more than two intra-articular injections of corticosteroids in the month before the study or during the study itself. The doses of second-line therapies and oral corticosteroids could be reduced but not increased. However, following a dose reduction, a subsequent increase to the original dose was permitted. If a patient required an increase in dose beyond the original dose, he or she had to be withdrawn from the study.

No analgesics other than paracetamol were allowed during the trial and it was stressed to patients that this should only be taken when absolutely necessary and the daily dose was not to exceed 4 g. Physiotherapy could be continued throughout the study.

**Primary and secondary efficacy endpoints**

There were four primary endpoints for the assessment of efficacy. The patient and the investigator assessed global efficacy using horizontal visual analogue scales (VAS). The question asked was: ‘How effective has the trial drug been?’ Additionally, at the end of the study or at the withdrawal visit, the following question was asked: ‘How effective has the trial drug been throughout the whole trial period?’ The two ends of the 10 cm VAS were defined by vertical lines, with the words ‘excellent’ on the left and ‘extremely bad’ on the right, the time course of global efficacy and the drop-out rate due to lack of efficacy were also considered. Erythrocyte sedimentation rate (ESR) was measured.

**Safety endpoints**

Endpoints used to consider safety included assessment of global tolerance by the patient and investigator using a VAS (the two ends of the 10 cm VAS were defined by vertical lines with the words ‘excellent’ on the left and ‘extremely bad’ on the right), the time course of global tolerability, the number and severity of adverse events and the drop-out rate due to adverse events. The relationship of the trial drug to all adverse events was assessed by the investigator according to the classification of Karch and Lasagna [13]. Haematology, biochemistry and urinalysis laboratory investigations were performed. At the screening visit, the rheumatoid factor was measured.

**Statistical methods**

Results were reported as exploratory significant if $P < 0.05$. Analyses were undertaken on an intent-to-treat basis (all randomized patients). Baseline characteristics were evaluated using the two-sample $t$-test or the $U$-test. Primary endpoints were analysed by the method of two one-sided $t$-tests. The efficacy parameters and meloxicam plasma concentrations were analysed with the analysis of covariance (ANCOVA) model.

Incidence, time, severity and causal relationship of the adverse events were tabulated by body system organ class and crude as well as hazard rates were estimated. The evaluation of laboratory values was performed by score analysis referring to the normal ranges of the parameters [14]. Furthermore, the values were checked for clinically relevant changes by shift tables.

The null hypothesis of interest was that the magnitude of response with regard to the primary endpoints should be the same in both treatment groups. It was calculated that a sample size of at least 140 evaluable patients per treatment group would be sufficient to detect a difference of 20% or more by means of a two-sample $t$-test ($\alpha = 5\%$, $\beta = 10\%$, two-
RESULTS

Three hundred and seventy-nine patients were randomized, 199 to treatment with meloxicam and 180 to treatment with naproxen. The data from these patients were included in the intent-to-treat analysis. Efficacy and safety parameters were assessed after 26 weeks of treatment (i.e. at completion) or at the last trial visit (i.e. at early withdrawal due to lack of efficacy, adverse events or other reasons).

The mean duration (± S.D.) of RA at baseline was comparable, with 9.3 ± 10.1 years in the meloxicam group and 9.2 ± 9.9 years in the naproxen group. The patients in the two groups had comparable disease characteristics at baseline (Table I). One hundred and seventy-two (86.4%) of the patients in the meloxicam group and 168 (93.3%) in the naproxen group had been treated previously with NSAIDs. Second-line therapies were used by 127 (63.8%) patients in the meloxicam group and 124 (68.8%) patients in the naproxen group. The second-line drugs used most frequently were sulphasalazine, methotrexate, penicillamine, sodium aurothiomalate and auranofin. Only a small number of patients (<10% in each group) received treatment with steroids.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Disease characteristics at baseline</th>
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<tbody>
<tr>
<td></td>
<td>No (%) of patients</td>
</tr>
<tr>
<td></td>
<td>Meloxicam (n = 199)</td>
</tr>
<tr>
<td>Morning stiffness of at least 45 min</td>
<td>186 (93.4)</td>
</tr>
<tr>
<td>Soft tissue swelling in ≥3 joints</td>
<td>199 (100)</td>
</tr>
<tr>
<td>Symmetric swelling ≥6 weeks</td>
<td>192 (96.4)</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>51 (25.6)</td>
</tr>
<tr>
<td>Rheumatoid factor positive*</td>
<td>134 (67.3)</td>
</tr>
<tr>
<td>ESR at least 28 mm/h</td>
<td>124 (62.3)</td>
</tr>
<tr>
<td>Radiographic erosions/osteopenia in hand/wrist joints</td>
<td>163 (81.9)</td>
</tr>
<tr>
<td>Extra-articular organ involvement of R.A.</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Acute onset of disease</td>
<td>82 (41.2)</td>
</tr>
<tr>
<td>Chronic progressive course of disease</td>
<td>143 (71.8)</td>
</tr>
</tbody>
</table>

*Presence of rheumatoid factor measured at the pre-study visit.

Primary efficacy variables

On average, the investigators rated global efficacy somewhat better for naproxen than for meloxicam. For patients who completed 6 months of treatment (106 naproxen-treated patients and 117 meloxicam-treated patients), the mean VAS values were 2.8 ± 2.5 and 3.2 ± 2.6 cm for naproxen and meloxicam respectively. At the last trial visit, including patients who withdrew early, the corresponding values were 4.2 ± 3.2 and 4.8 ± 3.3 cm. These differences were not statistically significant.

The patients' assessment of global efficacy was similar to that of the investigators. Global efficacy assessed by the patient at each study visit is shown in Fig. 1. Global efficacy assessment was not influenced by the patients' age, sex, or weight or by the study centre or country. However, patients with a duration of RA of 8 years or less rated final global efficacy better than those with a duration of >8 years. Investigator assessments of global efficacy rated both trial drugs considerably better in patients not receiving concomitant corticosteroids than in those who were receiving concomitant corticosteroids. A similar pattern was observed with concomitant intra-articular therapy.

The mean number of painful/tender joints was reduced in the meloxicam-treated group by 8.01 and 5.51 at 26 weeks and at the last trial visit respectively. The corresponding figures in the naproxen-treated group were 10.95 and 7.45. For swollen joints, the mean number was reduced by 6.13 and 3.56 in the meloxicam group and 7.20 and 5.76 in the naproxen group. For both variables there was a significant improvement versus baseline but the difference between the two treatment groups was not statistically significant.

![Fig. 1](image-url) — Mean global efficacy assessed by patient over the study period. This was measured using a 10 cm VAS scale, where 0 = excellent and 10 = useless. A higher value on the VAS indicates less efficacy. Numbers above the bars indicate the number of patients.
Secondary efficacy variables

Forty-seven patients (23.6%) treated with meloxicam and 26 (14.4%) patients treated with naproxen discontinued the trial prematurely due to lack of efficacy. This difference was statistically significant (P = 0.036). There appeared to be no correlation between the rate of discontinuation and any other factor, such as patient characteristics or second-line therapy.

In the meloxicam group all secondary endpoints displayed a statistically significant improvement from baseline to 26 weeks and from baseline to last observation. For the naproxen-treated patients the last value ESR did not display a statistically significant improvement from baseline. Changes from baseline to last observation are shown in Table II. Most variables showed no significant difference between patient groups, either at last observation or at completion of treatment. Naproxen patients showed a mean reduction of 9.43 for swollen joint index; this was superior to the change observed with meloxicam patients, who demonstrated a reduction of 4.19 (at last observation). The difference between the groups was highly significant (P = 0.01). The mean paracetamol consumption per month did not differ significantly between the meloxicam-treated group and the naproxen-treated group (50.4 ± 58.1 tablets versus 46.2 ± 58.6 tablets). There was no statistically significant difference between the treatment groups with regard to concomitant corticosteroid therapy.

A possible influence on efficacy caused by changes in concomitant therapy, including the number of intra-articular injections and the dose of oral corticosteroids during the trial, was investigated. Second-line therapy was changed in 5.0 and 8.2% of patients in the meloxicam- and naproxen-treated groups respectively. However, there was no statistical difference with regard to changes in any concomitant therapies between the treatment groups.

Safety

Adverse events. One hundred and twenty-five patients (62.8%) on meloxicam treatment and 106 patients (58.8%) receiving naproxen reported adverse events. Adverse events were considered to be at least probably related to treatment in 8.5 and 13.8% of meloxicam and naproxen patients respectively, and at least possibly related in 34.6 and 39.4% respectively. Twenty-five (12.5%) patients in the meloxicam group and 29 (16.1%) patients in the naproxen group withdrew from the study due to adverse events (Table III).

Gastrointestinal adverse events. The majority of GI adverse events included dyspepsia, diarrhoea, nausea and abdominal pain. A total of 71 GI adverse events occurred in patients treated with meloxicam (0.36 events per patient) compared with 93 events (0.52 events per patient) in naproxen-treated patients. This difference was statistically significant (P = 0.002).

The number of patients who experienced GI adverse events was lower in the meloxicam group (53; 26.6%) than in the naproxen group (64; 35.5%). There was a significant difference (P = 0.046) between the treatment groups with respect to the number of patients discontinuing due to GI adverse events: 12 (6.0%) and 22 (12.2%) patients in the meloxicam and naproxen groups respectively. No patients in the meloxicam group experienced ulcers and/or perforations or bleeding of the GI tract, whereas two patients in the naproxen group suffered a duodenal ulcer (diagnosed by X-ray) and a peptic ulcer (diagnosed by gastroscopy) respectively.

### TABLE II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meloxicam</th>
<th>Naproxen</th>
</tr>
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<tbody>
<tr>
<td>Grip strength right (kPa)</td>
<td>3.99 ± 14.57</td>
<td>3.04 ± 13.44</td>
</tr>
<tr>
<td>Grip strength left (kPa)</td>
<td>4.87 ± 16.40</td>
<td>3.26 ± 15.57</td>
</tr>
<tr>
<td>Swollen joint severity index</td>
<td>-4.19 ± 18.45</td>
<td>-9.43 ± 18.01</td>
</tr>
<tr>
<td>Painful/tender joint severity index</td>
<td>-9.92 ± 25.63</td>
<td>-13.66 ± 23.89</td>
</tr>
<tr>
<td>Morning stiffness (min)</td>
<td>-18.81 ± 89.31</td>
<td>-23.09 ± 103.6</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>-2.33 ± 20.56</td>
<td>-2.31 ± 19.59</td>
</tr>
<tr>
<td>Activities of daily living difficulties (scores)</td>
<td>-0.06 ± 0.47</td>
<td>-0.12 ± 0.55</td>
</tr>
<tr>
<td>Pain in morning (VAS, cm)</td>
<td>-1.07 ± 2.98</td>
<td>-1.50 ± 3.22</td>
</tr>
<tr>
<td>Pain at night (VAS, cm)</td>
<td>-0.57 ± 3.27</td>
<td>-0.93 ± 2.96</td>
</tr>
</tbody>
</table>

Values are given as mean (± S.D.).

*Statistically significant difference (P = 0.01) between treatment groups.

### TABLE III

<table>
<thead>
<tr>
<th>WHO system organ class (SOC)</th>
<th>Meloxicam</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and appendages</td>
<td>6 (3.0)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Central and peripheral nervous systems</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>12 (6.0)</td>
<td>22 (12.2)*</td>
</tr>
<tr>
<td>Liver and biliary system</td>
<td>3 (1.5)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>White cells and RES</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Resistance mechanism disorder</td>
<td>2t (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events in several SOC</td>
<td>5 (2.5)</td>
<td>9 (5.0)</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>25 (12.5)</td>
<td>29 (16.1)</td>
</tr>
</tbody>
</table>

Some patients discontinued due to an adverse event in more than one system organ class. RES denotes reticulo-endothelial system.

*Statistically significant difference (P < 0.05) compared with meloxicam.

†One infection and one abscess.
Both were considered to be possibly causally related to treatment with naproxen.

**Global tolerance.** Both patients and investigators rated meloxicam better than naproxen in global tolerance assessments. Mean global tolerance assessments by patients throughout the whole trial were 1.0 ± 1.3 cm for meloxicam and 1.1 ± 1.4 cm for naproxen, with corresponding values for investigators of 0.8 ± 1.1 and 1.0 ± 1.4 cm, respectively.

'Last value' observations of global tolerance, which included patients withdrawn prematurely from the study, showed a similar trend: 1.9 ± 2.6 and 2.4 ± 3.0 cm in the meloxicam and naproxen groups, respectively. Similar values were again given by investigators: 1.8 ± 2.6 and 2.3 ± 3.0 cm respectively.

The effects of demographic characteristics and concomitant therapy were assessed and it was found that patients who had suffered from RA for >8 years had the worst global tolerance of the trial drugs.

**Laboratory parameters**

In the naproxen-treated group, mean values for haemoglobin, erythrocytes and haematocrit decreased significantly from baseline values. There was no significant decrease in these parameters in the meloxicam-treated group and the difference between the two groups was significant for the decrease in haemoglobin ($P = 0.025$).

Mean serum creatinine showed a significant difference between the treatment groups ($P = 0.03$), with meloxicam-treated patients demonstrating a decrease and naproxen-treated patients an increase in mean values. The same pattern was observed for the mean serum urea values, with a significant difference between the groups ($P = 0.01$).

**DISCUSSION**

Most patients in this study had received previous treatment with NSAIDs, including naproxen, and almost 70% were receiving second-line therapies at the start of the study. The primary endpoints of efficacy show that meloxicam has a potent anti-inflammatory and analgesic action. There was a significant decrease in the number of painful/tender joints and in the number of swollen joints from the start of treatment. Both investigators and patients rated global efficacy of meloxicam and naproxen well on the VAS. There was no significant difference between the two treatments in the primary efficacy endpoints. Although there was a trend in favour of naproxen, the results for meloxicam compared well with those achieved with naproxen.

The secondary efficacy endpoints also displayed a significant improvement with both meloxicam and naproxen compared with baseline (with the exception of ESR in the naproxen-treated group). Most variables showed no significant difference between the two treatment groups. However, there was a significant difference in favour of naproxen with respect to the swollen joint index and the number of patients withdrawing due to lack of efficacy.

The results of this study are comparable with other trials of meloxicam in RA, in which a dose of 15 mg was also investigated. In a comparative study with piroxicam [15], meloxicam 15 mg showed similar efficacy to piroxicam 20 mg but with a lower incidence of adverse effects. In a placebo-controlled study [16], both meloxicam 15 mg and 7.5 mg were more effective than placebo, with a trend in favour of meloxicam 15 mg. Safety was comparable between the two meloxicam doses.

As expected, GI disturbances were the most frequently reported adverse events in both groups. These GI disturbances are thought to be caused by inhibition of prostaglandin biosynthesis, thereby interfering with the role of prostaglandins in gastric mucosal defence systems [17, 18]. This effect has been demonstrated by patients on naproxen in a recent study [19]. The number of adverse events and withdrawals due to GI disturbances were significantly greater in the naproxen-treated group and two cases of upper GI ulcer were reported. Similarly, significant decreases in mean values of haemoglobin, erythrocytes and haematocrit occurred in this group, suggesting higher GI blood loss with naproxen.

NSAIDs also inhibit prostaglandin synthesis in the kidney, which results in an increase in plasma urea and creatinine and, in extreme cases, renal failure [20]. Renal prostaglandins function to increase renal blood flow and the loss of urinary electrolytes and water. They also counteract the adverse events that occur when the renin–angiotensin system is stimulated or when catecholamines are released [21]. Without these compensatory mechanisms adverse reactions are more likely to occur. In this study there was a significant difference between the treatment groups regarding both the plasma creatinine and plasma urea results. The mean values of both parameters increased in the naproxen group but decreased in the meloxicam-treated patients when compared with the baseline results before the washout stage. This suggests that, at the doses used in this study, meloxicam may have less effect on renal prostaglandins than naproxen.

These results are in accord with the current view on selective COX-2 inhibition. Meloxicam as a COX-2 inhibitor shows a favourable safety profile on the GI tract and the renal system, as expected due to its low inhibition of COX-1.

In conclusion, the COX-2 inhibitor meloxicam shows promise as a treatment in RA. Meloxicam's efficacy in a dosage of 7.5 mg seems comparable to that of naproxen 750 mg, although there was a non-significant trend in favour of naproxen. Meloxicam 7.5 mg has the advantage of a lower incidence of side-effects, including a significantly lower incidence of GI and renal disturbances.

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