MELOXICAM IN OSTEOARTHRITIS: A 6-MONTH, DOUBLE-BLIND COMPARISON WITH DICLOFENAC SODIUM

J. HOSIE,† M. DISTEL† and E. BLUHMKIJ†
†Great Western Medical, Knightswood, Glasgow, and †Department of Clinical Research and †Department of Biometrics, Boehringer Ingelheim GmbH, Birkendorfer Strasse 65, 88397 Biberach/Riss, Germany

SUMMARY
A multicentre, double-blind, randomized study was conducted in patients with osteoarthritis (OA) of the hip or knee in order to compare the efficacy and safety of the new cyclooxygenase-2 (COX-2) inhibitor, meloxicam, with diclofenac sodium, a conventional treatment for this condition. Three hundred and thirty-six patients were treated with oral meloxicam 7.5 mg once daily or diclofenac 100 mg slow release once daily for 6 months. There were no significant differences between the treatment groups with respect to overall pain, pain on movement, global efficacy or quality of life scores at the end of treatment, all of which showed good levels of improvement. Sixty-six patients were withdrawn after the start of the double-blind phase due to adverse events (n = 21, meloxicam; n = 31, diclofenac) or to lack of efficacy (seven in each group). The median dose of paracetamol taken concomitantly was statistically significantly lower in the meloxicam group than in the diclofenac group (185 vs 245 mg/day; \( P = 0.0123 \)) with a comparable proportion of patients taking concomitant paracetamol therapy in both groups. Both drugs were well tolerated, although severe adverse events, treatment withdrawals and clinically significant laboratory abnormalities were more common with diclofenac than with meloxicam. Thus, meloxicam 7.5 mg is a safe and effective treatment for OA of the hip and knee which demonstrates a trend towards an improved safety profile compared with diclofenac.

KEY WORDS: Osteoarthritis, Meloxicam, Diclofenac sodium, Non-steroidal anti-inflammatory drugs.

The non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used therapy for osteoarthritis (OA). However, many are associated with a relatively high incidence of gastrointestinal (GI) side effects which can limit their use [1]. Meloxicam is a new NSAID of the acidic enolic class which has been shown in animal studies to exhibit high anti-inflammatory potency and less gastric irritation than other NSAIDs (e.g. piroxicam, diclofenac, indomethacin) [2]. Moreover, meloxicam has a favourable ratio of high activity (measured in adjuvant arthritis rats) and low ulcerogenic potential, giving the drug a therapeutic index which is considerably higher than that of other NSAIDs, such as diclofenac, indomethacin and piroxicam [2]. Meloxicam is a preferential inhibitor of cyclooxygenase-2 (COX-2), which is induced by inflammatory mediators under pathological conditions, over cyclooxygenase-1 (COX-1), which is responsible for physiological processes [3].

In clinical applications, the short half-life of meloxicam (20 h) [4] allows the maintenance of plasma concentrations in the therapeutic range with a convenient once-daily dosing regimen. This factor is especially important as it helps to maintain compliance in patients receiving chronic treatment.

Results from preliminary studies have indicated that meloxicam at a dose of 7.5 mg once daily is more effective than placebo in patients with OA [5]. The aim of this study was to compare the long-term efficacy and tolerability of meloxicam 7.5 mg with the well-established and widely used NSAID diclofenac, administered once daily using the 100 mg sustained-release formulation, in patients with OA of the knee or hip.

MATERIALS AND METHODS
Patients with OA of the hip or knee were enrolled in a randomized, parallel-group, double-blind study involving 52 general practitioner centres in the UK. The study was approved by local ethics committees and carried out in accordance with the revised Declaration of Helsinki. All patients gave written informed consent. Patients were eligible for inclusion if they were at least 18 yr of age, and had clinically and radiographically confirmed OA of the knee or hip with symptoms present for at least 3 months. For radiographic confirmation of OA, X-rays from different projections must have indicated a narrowing of the femoropatellar and/or femorotibial space in the knee and a narrowing of the acetabulofemoral space in the hip. Additionally, both knee and hip must have shown the presence of osteophytes and/or subchondral sclerosis and/or cysts. Other criteria included at least moderate overall pain in the affected joint [a score of at least 35 mm as assessed by the patient on a 100 mm horizontal visual analogue scale (VAS) with 0 mm equivalent to no pain and 100 mm equivalent to unbearable pain], requiring treatment with an anti-inflammatory drug, and being ambulant. Patients were excluded if they were pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures, or if they had any concomitant clinically unstable disease, clinically relevant laboratory test abnormalities, clinical evidence of active peptic ulceration within the previous 6 months, hypersensitivity to analgesics, antipyretics and NSAIDs, or required, or had recently received, treatment with any...
drug or procedure which might interact with or obscure the action of the study medication. Patients receiving medications not considered to affect the study outcome were allowed to continue with treatment. Paracetamol (up to 4 g daily) was permitted as a rescue analgesic throughout the study, and massage and exercise were continued unchanged.

Following a washout period of at least 3 days for all patients currently receiving treatment with a NSAID, all patients meeting the eligibility criteria were randomly assigned to double-blind treatment with capsules of meloxicam 7.5 mg or slow-release tablets of diclofenac sodium 100 mg once daily for 6 months. Due to the different formulations of the two treatments, it was necessary to employ a double-dummy technique in order to maintain the blindness of the study.

Patients were assessed after 2 weeks and 1, 2, 3 and 6 months of treatment. The primary efficacy measure was the overall pain in the affected joint during the previous week as assessed by the patient. Secondary efficacy variables included assessment of pain on movement/activity and duration of stiffness after being at rest on the day before the visit. Quality of life was evaluated on the basis of a quality-of-life profile (consisting of 22 variables included assessment by the patient of overall pain in the affected joint during the previous week). The primary efficacy measure was the overall pain in the affected joint during the previous week. Quality of life was evaluated on the basis of a quality-of-life profile (consisting of 22 questions from three of the six sections of statements from part 1 of the Nottingham Health Profile and three of six sections from part 2 covering physical mobility, social isolation, energy levels and influences on various aspects of life) after 2 and 6 months of treatment. Global efficacy was rated at the end of treatment and paracetamol consumption was recorded throughout. All assessments of pain and global efficacy were made by the patient on a horizontal VAS ranging from 0 mm, which corresponded to 'no pain' for pain measurements or 'excellent' for global efficacy, to 100 mm, which corresponded to 'unbearable pain' or 'useless'. Safety variables included assessment by the patient of tolerability of treatment at each visit and global tolerability at the end of treatment. The VAS scales for tolerability were defined as 'excellent' at 0 mm and 'extremely bad' at 100 mm. The occurrence of any adverse events with an indication of severity (mild, moderate or severe) or premature withdrawals due to poor tolerability or inadequate efficacy was also recorded.

Biochemistry, haematology and urinalysis were performed at screening and at each visit during treatment. A physical examination was also performed at screening and at the end of the study. The plasma level of meloxicam was determined after 3 months of treatment for a compliance check. Compliance was also assessed by counting the amount of returned trial medication.

**Statistical methods**

All patients were evaluated using an intent-to-treat analysis. A two-sample t-test was performed on assessments of the pain parameters, global efficacy and global tolerability, and a Wilcoxon test was performed on duration of stiffness and quality-of-life profile tests. Differences with P values ≤0.05 were considered statistically significant. Incidence of adverse events were tabulated by the World Health Organization (WHO) body systems organ class.

The sample size was estimated on the basis of demonstrating therapeutic equivalence between the two treatments, as defined by an interval of equivalence of ±5 mm in the mean difference from baseline for the primary endpoint (overall pain in the target joint during the last week). Assuming a S.D. of 14 mm for this measure, an alpha of 5% and a beta of 20%, a sample of 270 patients (135 in each of the treatment groups) was estimated.

### RESULTS

Three hundred and thirty-six patients were randomized to treatment with meloxicam (n = 169) or diclofenac (n = 167). Data for one patient in the diclofenac group were not included in the intent-to-treat analysis for administrative reasons (results were omitted from the database in error).

The demographic and baseline data from the 335 patients included in the intent-to-treat analysis were similar in the two treatment groups, although the duration of OA was significantly longer in the diclofenac group (P < 0.05) (Table I). The mean duration of treatment with meloxicam and diclofenac was 151 and 143 days respectively.

#### Efficacy assessments

Overall pain, pain on movement, and duration of stiffness following inactivity showed marked reductions with both meloxicam and diclofenac treatment. A maximum reduction in overall pain and pain on movement had occurred after 1 month of treatment in both groups and this reduction was maintained throughout the remainder of the study (Table II). However, the amelioration in the duration of stiffness at the end of the study was greater in the meloxicam group than in patients treated with diclofenac (Table II), although this parameter showed a high variability.

The mean global efficacy assessed by the patient at the end of the study was slightly in favour of meloxicam (Table II) and the quality-of-life profile demonstrated improvements in all four sections (physical mobility, social isolation, energy levels and influences) at the end of the study in both treatment groups. There were no statistically significant differences between the groups. The 'quality-of-life total score', was improved to a

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**TABLE I**

<table>
<thead>
<tr>
<th>Demographic and baseline characteristics</th>
<th>Meloxicam 7.5 mg (n = 169)</th>
<th>Diclofenac 100 mg (n = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>69 male/100 female</td>
<td>68 male/98 female</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.3 ± 9.6</td>
<td>64.2 ± 11.5</td>
</tr>
<tr>
<td>Broca Index* (%)</td>
<td>18.4 ± 21.3</td>
<td>20.9 ± 25.5</td>
</tr>
<tr>
<td>Duration of OA (yr)</td>
<td>5.6 ± 5.4</td>
<td>7.0 ± 7.0†</td>
</tr>
<tr>
<td>Most painful joint</td>
<td>24% hip/76% knee</td>
<td>34% hip/66% knee</td>
</tr>
</tbody>
</table>

*Broca Index = (body weight - [height in cm - 100 cm])/(height in cm - 100 cm) × 100%.
†P < 0.05 vs meloxicam group.
similar extent by both meloxicam and diclofenac (Table II).

The proportion of patients taking concomitant paracetamol was comparable in both groups and remained constant throughout the study. However, the median dose was statistically significantly lower in the meloxicam group than in the diclofenac group (185 vs 245 mg/day; \( P = 0.0123 \)).

There were no statistically significant differences between the treatment groups at baseline or at the end of the study in all efficacy assessments, and seven patients in each group were withdrawn at the start of the double-blind phase due to lack of efficacy.

### Safety and tolerability

Safety was assessed in all 336 patients randomized to treatment. Adverse events were reported by 101/169 patients (59.8%) in the meloxicam group and 101/167 (60.5%) in the diclofenac group. The type and incidence of adverse events were comparable between the two groups, with GI system disorders being reported most frequently (26.6% of meloxicam patients and 27.7% of diclofenac patients), followed by respiratory tract complaints (13% and 11.4% respectively). In general, adverse events occurred earlier in the diclofenac group and later with meloxicam. The majority of events in both groups were classified as mild or moderate in severity. However, severe events (as judged by the investigator) were reported by somewhat more patients in the diclofenac group than in the meloxicam group (22% vs 15.8% of patients with adverse events). Similarly, 31 patients (18.7%) in the diclofenac group compared with 21 patients (12.4%) in the meloxicam group were withdrawn due to adverse events, the majority of which were associated with the GI tract (Table III).

Ten adverse events were considered serious, three in the meloxicam group (renal calculi, constipation and rectal bleeding, and brain tumour) and seven in the diclofenac group (melaena, deep vein thrombosis, renal calculi, radical mastectomy, incisional hernia and circumcision), one of which was fatal (myocardial infarction and pulmonary oedema). The relationship to study treatment was judged by the investigator as 'doubtful' in all cases with the exception of melaena which was considered 'possibly' related to treatment with diclofenac.

Both study treatments were well tolerated throughout the study. At the end of the study, the mean global tolerance did not differ significantly between the treatment groups (19.5 and 18.7 mm on the VAS for meloxicam and diclofenac respectively).

There were no clinically relevant changes in blood pressure or pulse rate in either group. Similarly, there were only minor changes in laboratory parameters in the meloxicam group, none of which were considered clinically relevant. In contrast, diclofenac was associated with a number of significant abnormalities in haematology (reduced haemoglobin and white blood cell count in one patient), urea (increased urea in one patient) and liver function parameters (increased AST, ALT, \( \gamma \)GT and/or bilirubin in four patients).

### DISCUSSION

The NSAIDs are well established for the treatment of OA, reducing both pain and stiffness and therefore improving the patient's ability to function normally. One of the most widely used agents is diclofenac, which has proved effective in OA and other rheumatic conditions. It shows at least comparable analgesic and...
anti-inflammatory activity to a wide range of other NSAIDs, and its long-term efficacy has been established in a substantial patient population [7-10]. In addition, diclofenac has been shown to be one of the best tolerated NSAIDs with regards to the incidence of GI haemorrhage [11, 12]. The current large, 6 month, multicentre study provides valuable information on the efficacy and safety of the new NSAID, meloxicam, in comparison with this established treatment for OA.

Meloxicam 7.5 mg/day and diclofenac 100 mg/day both showed good long-term efficacy and safety for treatment of OA of the knee or hip. There were no significant differences between the groups with respect to overall pain, pain on movement, global efficacy or quality-of-life scores at the end of treatment, all of which showed good levels of improvement. Duration of stiffness after immobility was reduced more in the meloxicam group than in patients treated with diclofenac (−43 vs −33 min), although again this difference did not achieve statistical significance.

A meloxicam dose of 7.5 mg/day has previously proved effective in a large, multicentre, placebo-controlled study conducted in patients with OA of the knee [5]. Doses of 7.5 and 15 mg were significantly more effective than placebo in reducing pain on movement and in terms of global efficacy. Similarly good results were demonstrated in a study of patients with OA of the hip who were treated with meloxicam 15 mg/day or piroxicam 20 mg/day [13]. Although there were no significant differences between the treatments, there was a consistent trend in favour of meloxicam in terms of pain on movement, pain at rest, global efficacy and index of severity.

Although the efficacy of the NSAIDs in the treatment of OA is well established, their main limitation is the relatively high incidence of GI adverse events associated with their use, due to inhibition of the cyclooxygenase (COX) enzyme involved in prostaglandin biosynthesis [14]. COX exists in two isoforms, COX-1, which is involved in normal physiological processes, and COX-2, which is induced by inflammatory mediators in pathological conditions [15]. Much research has been directed towards production of a NSAID which combines good efficacy with less gastric irritation and it has been suggested that selective inhibition of COX-2 over COX-1 could provide the key [15]. Preclinical studies suggest that meloxicam may be a selective inhibitor of COX-2. In a guinea-pig peritoneal macrophage system, meloxicam was shown to be a more potent inhibitor of COX-2 than of COX-1. In contrast, diclofenac inhibited COX-1 and COX-2 to a similar degree, whereas piroxicam, indomethacin, tenoxicam and tenidap inhibited COX-1 more strongly than COX-2 [3].

Both meloxicam and diclofenac were well tolerated throughout the current study, with a similar frequency and pattern of adverse events. However, severe adverse events, treatment withdrawals for safety reasons and clinically significant laboratory abnormalities all occurred more frequently with diclofenac than in the meloxicam group. In a short-term (3 week) clinical study, the tolerability of meloxicam 7.5 and 15 mg once daily was shown to be comparable to that of placebo [5]. In addition, diclofenac is thought to be one of the most well tolerated NSAIDs currently available [11, 12], and the fact that meloxicam was associated with somewhat fewer severe adverse events than diclofenac in the present study suggests that meloxicam has a very promising safety profile.

In conclusion, meloxicam 7.5 mg once daily and diclofenac 100 mg slow release once daily showed comparable efficacy in the treatment of OA, although diclofenac was associated with a somewhat higher incidence of severe adverse events, treatment withdrawals and laboratory test abnormalities. Thus, meloxicam will be a beneficial addition to the choice of treatments available for patients suffering from this chronic and disabling condition and demonstrates a better safety profile over diclofenac 100 mg.

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