TOLERABILITY OF MULTIPLE ADMINISTRATION OF INTRAMUSCULAR MELOXICAM: A COMPARISON WITH INTRAMUSCULAR PIROXICAM IN PATIENTS WITH RHEUMATOID ARTHRITIS OR OSTEOARTHRITIS

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SUMMARY
This multicentre, randomized, open controlled study compared the local and overall tolerability of i.m. meloxicam with i.m. piroxicam in 211 patients with rheumatoid arthritis (RA) (n = 95) or osteoarthritis (OA) (n = 116). Of these, 210 patients were randomized (2:1) to receive meloxicam 15 mg (n = 144) or piroxicam 20 mg (n = 66) for 7 days. Local tolerability of meloxicam was significantly better than piroxicam with respect to occurrence of redness after the first injection (P = 0.03) and global assessment after the first and final injections (P < 0.05). No rise in creatinine phosphokinase levels (a marker of muscle fibre damage) was observed with meloxicam, in contrast to piroxicam (P = 0.0001). The overall tolerability of both treatments was good. Significant differences in favour of meloxicam were observed for global efficacy assessed by the patient in RA (P < 0.05) and for overall pain intensity in OA patients (P = 0.02). In conclusion, i.m. meloxicam is safe and effective for the treatment of acute rheumatic pain and shows some superiority over piroxicam.

KEY WORDS: Meloxicam, Piroxicam, Tolerability, Intramuscular, Osteoarthritis, Rheumatoid arthritis, Non-steroidal anti-inflammatory drugs, Creatinine phosphokinase.

INTRODUCTION
Non-steroidal anti-inflammatory drug (NSAID) formulations are used in some centres for the treatment of acute rheumatoid and osteoarthritis (RA and OA). They are especially useful for the treatment of patients who experience difficulties in taking oral formulations. In these patients an i.m. NSAID with a rapid onset of action and good local and overall tolerability is required. However, many NSAIDs are poorly tolerated when administered via the i.m. route, resulting in local tissue irritation and necrosis, often in association with systemic adverse events. Clinical evidence indicates that meloxicam is associated with a favourable gastrointestinal (GI) safety profile [1], and large phase III studies with oral formulations have revealed good efficacy and tolerability in a range of rheumatic conditions including OA [2, 3] and RA [4, 5]. Intramuscular meloxicam (5-30 mg) has previously been shown to be well tolerated, with maximum plasma levels achieved within 1 h of dosing compared to 6-8 h after oral dosing [6]. There is also a linear relationship between plasma concentration and dose [6].

The aim of the present study was to compare the local and overall tolerability of i.m. meloxicam 15 mg/day with i.m. piroxicam 20 mg/day—a standard NSAID with proven efficacy and safety—in patients with OA or RA.

PATIENTS AND METHODS

Patients
Patients, aged between 18 and 75 yr, with RA (based...
and the second 24 h after the last injection. The primary endpoint was the local tolerability of the injections as assessed by the patient and the clinician. Local tolerability was assessed daily by the patient within 1 h of injection on a four-point verbal rating scale (very good, rather good, rather bad, very bad). Local tolerability was assessed by the clinician by recording absence or presence of reddening, swelling, heat or pain on pressure at the site of injection. A global assessment of local tolerability was recorded by the clinician on the same four-point verbal rating scale as the patient.

Secondary endpoints included overall tolerability, assessed by the patient and the clinician on the same four-point verbal rating scale as above. Other tolerability endpoints included the rate of withdrawals due to safety reasons; the number, nature and severity of adverse events; creatinine phosphokinase (CPK) levels; and other laboratory investigations. Efficacy endpoints included global efficacy assessed by the patient and clinician at the second visit on the four-point verbal rating scale; overall pain intensity assessed by the patient before drug administration and at the second visit on a 100 mm visual analogue scale (0 mm = no pain, 100 mm = unbearable pain); and the consumption of paracetamol.

### Statistical methods

The confidence intervals for local tolerability, overall tolerability and overall efficacy were calculated. Treatment differences were determined using Fisher's exact test. A two-sample t-test was performed on the assessment of pain intensity. Since the normal ranges were not identical for all the laboratories taking part in this multicentre study, the analysis of laboratory parameters was based on transformed values. Changes in laboratory parameters from baseline to the final assessment (transformed values) were evaluated descriptively. Tests were considered significant if \( P \leq 0.05 \). A sample size of 200 patients was chosen to collect sufficient safety data especially for local tolerability assessment.

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**Fig. 1.**—Clinicians' assessment of local tolerability after the first injection of meloxicam or piroxicam.
RESULTS

The demographic data are shown in Table I. One patient was withdrawn before receiving the first injection due to depression and was not analysed. There was a tendency for the duration of knee OA to be longer in the piroxicam group than in patients treated with meloxicam ($P = 0.06$). The groups were well matched in all other parameters.

**Primary endpoints**

Evaluation of local tolerability by the clinician revealed excellent results for both meloxicam and piroxicam, although meloxicam treatment offered an advantage that was statistically significant for a number of parameters. After the first injection, local reddening, swelling, heat and pain on pressure were all observed in more patients in the piroxicam group than in the meloxicam group, the difference achieving statistical significance with respect to local reddening (9.1% vs 2.1%; $P = 0.03$) (Fig. 1). Similarly, global local tolerability as assessed by the physician revealed a statistically significant advantage for meloxicam over piroxicam ($P = 0.045$); treatment was considered 'very good' in 134/144 (93.1%) patients treated with meloxicam and in 55/66 (83.3%) treated with piroxicam. Twenty-four hours after the final injection, patients in the meloxicam group experienced less reddening, swelling, heat and pain on pressure than those in the piroxicam group, although none of the differences achieved statistical significance (Fig. 2). The global local tolerability assessments were more significant with meloxicam than with piroxicam ($P = 0.029$). Global local tolerability was rated as 'very good' in 130/144 (90.3%) patients treated with meloxicam and in 52/66 (78.8%) of those treated with piroxicam.

Local tolerability assessments recorded by the patients in a daily diary and 24 h after the final injection showed similarly good results for both meloxicam and piroxicam; 24 h after the final injection, local tolerability was rated as 'very good' by 121/144 (84.0%) patients receiving meloxicam and by 53/66 (80.3%) receiving piroxicam.

**Secondary endpoints**

**Safety.** Both drugs showed good overall tolerability as assessed by the clinician and the patients. The clinicians rated overall tolerability as 'very good' in 121/144 (84.0%) patients in the meloxicam group and 55/66 (83.3%) in the piroxicam group. The corresponding assessment by the patients revealed 'very good' overall tolerability in 117/144 (81.2%) patients treated with meloxicam and 53/66 (80.3%) treated with piroxicam.

Muscular tolerability, determined by changes in serum CPK from baseline to after the final injection, was significantly better with meloxicam than with piroxicam ($P = 0.0001$). Indeed, there was no mean change in CPK levels in the meloxicam group (0%), while the piroxicam group was associated with a statistically significant increase (59%) from baseline ($P = 0.01$). Moreover, an increase of 30 IU/l or more from baseline was recorded in only 3.8% of patients treated with meloxicam compared with 22.6% in the piroxicam group ($P = 0.0001$) (Table II).

There were no significant differences between the treatment groups with respect to the incidence of adverse events, with 16.7% of patients treated with

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**TABLE II**

| Changes in CPK levels from baseline to the final visit following treatment with meloxicam or piroxicam |
|--------------------------------------------------|--------------------------------------------------|----------------------------------|
| Meloxicam ($n = 131$)                           | Piroxicam ($n = 62$)                              | $P$-value (between groups) |
| Increase of at least 1 IU/l                     | 47 (35.9%)                                       | 40 (64.3%)                     | 0.0005 |
| Increase of at least 10 IU/l                    | 26 (19.9%)                                       | 25 (40.3%)                     | 0.005  |
| Increase of at least 20 IU/l                    | 9 (6.9%)                                         | 18 (29.0%)                     | 0.0001 |
| Increase of at least 30 IU/l                    | 5 (3.8%)                                         | 14 (22.6%)                     | 0.0001 |
meloxicam and 12.1% treated with piroxicam experiencing at least one adverse event (Table III). No serious adverse events were reported in either group. The overall safety profile was similar to that previously observed with this class of drug and consisted mainly of GI events (gastric pain, nausea and diarrhoea), skin reactions (pruritus and rash), and central or peripheral nervous system side-effects (headache and vertigo). Laboratory analyses and cardiovascular parameters showed no clinically significant changes from baseline in either group.

**Efficacy** Assessment of global efficacy by the patients revealed a significant advantage for meloxicam over piroxicam among those with RA (P = 0.007), and a trend towards improvement with meloxicam among those with OA. In patients with RA, global efficacy was rated as 'very good' or 'rather good' by 62/68 (91.2%) of those treated with meloxicam and only 20/27 (71.4%) treated with piroxicam (P = 0.045). The corresponding ratings in patients with OA were achieved by 66/76 (86.6%) of those treated with meloxicam and 32/39 (82.1%) treated with piroxicam. A large number of OA patients rated meloxicam as 'very good' (40.8% of meloxicam-treated patients vs 23.1% of piroxicam-treated patients).

Similarly good results were observed for the clinician's assessment of global efficacy, with a significant benefit for meloxicam over piroxicam among patients with RA (P = 0.002) and OA (P = 0.02). Among patients with RA, global efficacy ratings were considered 'very good' or 'rather good' in 62/68 (91.2%) treated with meloxicam and 20/27 (74.1%) treated with piroxicam (P = 0.045). In the OA group, 67/76 (88.2%) patients treated with meloxicam and 32/39 (82.0%) treated with piroxicam experienced 'very good' or 'rather good' global efficacy (Table IV).

The overall pain intensity experienced with RA and OA at baseline was significantly reduced after the final injection of both meloxicam and piroxicam (P = 0.0001). Among patients with OA, the decrease in pain intensity was significantly greater in the meloxicam group (−34.8%) than in the group treated with piroxicam (−22.1%) (P = 0.02). A similar trend was observed among patients with RA, although this did not achieve statistical significance (−32.1% vs −23.3%).

Concomitant paracetamol treatment was limited in both treatment groups but was greater among patients with RA than among those with OA. The mean daily dose was constantly <600 mg in patients with RA and 300 mg for those with OA. There were no significant differences between the treatment groups with respect to paracetamol consumption. Among patients with RA, 52.2% on meloxicam and 48.1% on piroxicam took paracetamol at least once during the study; the corresponding figures for patients with OA were 24.0% and 31.6% respectively.

**DISCUSSION**

NSAIDs are the most commonly prescribed therapy for rheumatoid disorders, and although chronic treatment can be given orally, acute pain may necessitate a rapid onset of effect which can best be achieved with i.v. or i.m. administration. The current study was undertaken to compare the local and overall tolerability of an i.m. formulation of meloxicam with i.m. piroxicam, an established treatment for rheumatic conditions which shows good local tolerability [10].

Local tolerability was good in both treatment groups, however, meloxicam was significantly better than piroxicam for a number of parameters, including presence of redness after the first injection and global local tolerability after the first and final injections.

Any changes in serum CPK levels are an important factor in the evaluation of local tolerability since CPK is an indicator of muscle fibre damage [11, 12]. It is well recognized that i.m. injections can result in elevated CPK [13], which in turn may be due to a number of factors including direct muscle trauma, chemotoxicity or stimulation of histamine release [14]. Previous studies with NSAIDs injected i.m. have reported mean increases from baseline of 922% with diclofenac and 147% with piroxicam [13]. These changes tend to occur ~6–12 h after injection and may persist for 3 or 4 days [14]. In the present study, there was no mean increase in serum CPK levels in the meloxicam group, while piroxicam was associated with a 59% increase; this difference was statistically significant and emphasizes the good local tolerability profile of meloxicam.
The overall safety of both drugs was good. Assessments of 'very good' were achieved by 84.0% of patients treated with meloxicam and 83.3% treated with piroxicam following evaluation by the clinician; the corresponding percentages following assessment by the patient were 81.2% and 80.3% respectively. The incidence of systemic adverse events was similar in both treatment groups and there were no serious events or clinically relevant changes in laboratory parameters.

Assessments of efficacy, which were performed separately for OA and RA, revealed that the global efficacy of meloxicam was significantly better than that of piroxicam in patients with RA and that overall pain intensity was improved to a significantly greater extent with meloxicam than with piroxicam in patients with OA.

The results of this study are in accordance with animal studies of local tolerability of i.v., i.m., dermal and ocular formulations of meloxicam, all of which showed excellent local and systemic tolerability [15]. When the tolerability of i.m. meloxicam was compared with diclofenac and piroxicam in rabbits, diclofenac caused considerably more tissue reddening than either of the other two drugs. Both diclofenac and piroxicam, but not meloxicam, resulted in the development of necrotic areas in the muscle of the animals [15].

In conclusion, the local and overall tolerability of i.m. meloxicam in patients with RA and OA was good. Assessment of local tolerability showed an advantage in favour of meloxicam over piroxicam which attained statistical significance for a number of parameters, a finding that was confirmed by muscular tolerability as determined by changes in CPK. In addition, the efficacy of meloxicam was superior to that of piroxicam. Thus, meloxicam is suitable for i.m. administration in the management of acute rheumatic pain, showing an advantage in local tolerability and somewhat better efficacy than the well-established NSAID, piroxicam, in RA.

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