High Response Rate in the Phase I/II Study of Meloxicam in Juvenile Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Use of meloxicam as a selective COX-2 inhibitor for treatment of adult rheumatic diseases decreases the frequency of gastrointestinal (GI) side effects in comparison with nonselective COX inhibitors. Up to 50% of children with juvenile rheumatoid arthritis (JRA) also develop GI side effects through nonselective COX inhibitors. In this 12 week Phase I/II study, with an additional open extension lasting up to 52 weeks, the safety, efficacy, and pharmacokinetics of meloxicam in JRA were investigated.

Methods. Meloxicam suspension 0.25 mg/kg once daily was given to 36 patients with JRA who required a nonsteroidal antiinflammatory drug. Safety evaluation and periodic measurement of efficacy were carried out using the Pediatric Rheumatology International Trials Organisation (PRINTO) criteria. Eighteen patients underwent pharmacokinetic (PK) evaluation.

Results. Thirty-one patients completed the study. Four were dropped due to administrative reasons. One patient, who found the drug ineffective, discontinued participation. A response was seen according to PRINTO outcome criteria in 44% of the patients at Week 4, 62% at Week 12, and 74% at Week 52. Drug related adverse events were observed in 5 patients. PK evaluation showed that the maximum plasma concentration C_{max} of –34% and $AUC_{0-\infty}$ of –28% tended to be lower in younger children (2–6 years) versus older children. Plasma elimination half-life (13 h) was similar in all patients.

Conclusion. Meloxicam suspension 0.25 mg/kg once daily seems to be effective and safe for treating active JRA over a period of 52 weeks. (J Rheumatol 2002;29:1079–83)

Key Indexing Terms:
COX-2 INHIBITOR
COX-1 INHIBITOR
CHILDREN
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Cyclooxygenase-2 (COX-2) inhibitors are gaining acceptance in the treatment of adult patients with rheumatic diseases. The main advantage in this population seems to be the more selective inhibition of COX-2 in inflamed joints, and decreased inhibition of COX-1 in the gastrointestinal (GI) system, which seems to be the main reason for GI side effects of the classical nonselective COX inhibitors.

Meloxicam is a selective COX-2 inhibitor[1-4] with a COX-2/COX-1 ratio of 10 in whole blood assay[1,4]. Selective inhibition of COX-2 relative to COX-1 has consistently been described for meloxicam in various *in vitro* test systems[2-4]. In human *ex vivo* studies meloxicam at doses of 7.5 mg and 15 mg did not affect platelet aggregation[5-8]. With once daily dosage, meloxicam has shown efficacy in osteoarthritis[9,10], rheumatoid arthritis[11,12], and ankylosing spondylitis[13]. Meloxicam in daily doses of 7.5 mg to 15 mg has been reported to be as effective as traditional nonsteroidal antiinflammatory drugs (NSAID) such as diclofenac and piroxicam[14-23] with a favorable GI adverse event profile[10,13-15,24-26].

No selective COX-2 inhibitor has been studied in a pediatric patient population, although nearly all children with juvenile rheumatoid arthritis (JRA) receive an NSAID at some point of their disease course and up to 50% of children may develop GI complaints during therapy with classical NSAID[27].

We evaluated the efficacy and safety of meloxicam suspension in children with JRA. Plasma concentrations of meloxicam were determined to assess pharmacokinetics in children.

MATERIALS AND METHODS

This was a Phase I/II open trial to investigate the efficacy and safety of meloxicam in children with JRA over a period of 52 weeks. The study included a pharmacokinetic phase after a single dose in some of the patients. We used the American College of Rheumatology classification system.

All patients or their parents or legally authorized representatives gave written informed consent before participation in the trial. The study

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protocol and procedures were approved by the respective ethics committees of the 3 participating centers. The trial was performed according to the principle of good clinical practice [Federal Register, May 9, 1997 (62 FR 25692) and the Declaration of Helsinki].

Patients. Male and female patients aged between 2 and 16 years were eligible for participation in the trial if they were diagnosed with oligoarticular or polyarticular type JRA[28] and required NSAID therapy. Not eligible for study were those patients with systemic onset of JRA, other rheumatic and nonrheumatic conditions, concomitant therapy with other NSAID (including topical formulations), concomitant therapy with corticosteroids at a dose exceeding 0.3 mg/kg/day, change in disease modifying drugs (including corticosteroids) within the past 3 months, intraarticular injections of corticosteroids during the last 3 months, abnormal clinically relevant laboratory values and concomitant diseases, pregnancy or breast feeding, history of bleeding disorders or active peptic ulcer within the past 6 months, known or suspected hypersensitivity to the trial drug or its excipients, asthma, nasal polyps, angioneurotic edema or urticaria following administration of aspirin or NSAID, surgical procedures planned during the course of the trial, previous participation in this trial, known drug abuse, or inability to understand and follow the trial procedures.

Study design and endpoints. *Medication*. After a washout period of one to 3 days depending on previous NSAID, a meloxicam suspension was administered at 0.25 mg/kg body weight in a single dose per day for up to 52 weeks in an open design.

Pharmacokinetics. Meloxicam plasma concentrations were measured in 18 patients before the first dose of meloxicam and up to 72 h afterwards. Analysis of plasma concentrations in steady state was carried out at Weeks 2 and 4 pre- and post-dosage. Drug concentrations were determined by a validated high performance liquid chromatography-ultraviolet method and pharmacokinetic variables were analyzed by noncompartmental procedures.

Efficacy and safety. Clinical efficacy was evaluated by criteria shown in Table 1: assessment of disease activity by investigator; parent's global assessment of well being, parent's global assessment of arthritis, each on a horizontal 100 mm visual analog scale; number of active joints defined as swollen or with a limitation of motion, warm, painful or tender; joints with limited range of motion; and assessment of functional disability by the Childhood Health Assessment Questionnaire (CHAQ)[29,30] and the self-administered Facial Affective Scale[31]. Also applied were the change in functional classification according to the Steinbrocker scale and the final global assessment by investigator and parents on a verbal rating scale (rated: good, satisfactory, not satisfactory, bad). In addition, erythrocyte sedimentation rates (ESR) and the platelet count were determined. Responders were assessed according to the Pediatric Rheumatology International Trials Organisation (PRINTO) definition of improvement of JRA[32].

Safety was assessed by recording adverse events occurring during the trial as well as routine laboratory controls of differential blood count, liver enzymes, and serum creatinine. Evaluations of efficacy and safety were performed at the pre-drug baseline and after 2, 4, 6, 8, 12, 24, 36, and 52 weeks of therapy. Global parent and investigator assessment of tolerability and efficacy was obtained only at Weeks 12 and 52.

Statistical analysis. *Pharmacokinetics*. Pharmacokinetic measures after single dose treatment were obtained by established noncompartmental procedures. Meloxicam plasma concentrations in steady state measured at Weeks 2 and 4 were compared to the concentrations expected from the single dose data.

Efficacy and safety. Patients' responses were analyzed according to the PRINTO criteria[32]. For all other efficacy variables pretreatment and endpoints of treatment data were analyzed (baseline vs Weeks 12 and 52) using the Wilcoxon test.

Safety data were analyzed descriptively by tabulating the adverse events reported according to the WHO body system organ class. Laboratory data were analyzed descriptively by comparing pretreatment and endpoints of treatment values.

RESULTS

Thirty-six patients were included in the trial. One patient was excluded at Week 4 due to noncompliance with the protocol and another was lost to followup after Week 1. Both patients were excluded from the analysis of the core efficacy endpoints, because a minimum treatment period of 6–8 weeks was required. Thirty-four patients completed the 12 week pharmacodynamic phase of the trial. All these patients could also be included in the safety expansion period. One patient who felt a lack of effect in the safety expansion phase discontinued after Week 24 and 2 patients were lost to followup. Thirty-one patients completed the trial extension period of 52 weeks.

Patient characteristics are shown in Table 2. Twenty-four patients had an oligoarticular and 12 a polyarticular disease course. The mean age at entry was 8.4 ± 3.7 years and the median disease duration was 1.7 years (range 0 months to 9 years). The median number of affected joints at study entry was 4.0 (range 1–30). Eighty-six percent of patients were taking an NSAID before entry into the study. Meloxicam treatment was only started after an appropriate washout period depending on the previous NSAID. Fifty percent of

Table 1. Measures for determining efficacy (n = 34).

Measure	Baseline	Week 6	Week 12	Week 52
Investigator's assessment of disease activity, VAS, mm	34 ± 23	17 ± 15**	16 ± 17**	10 ± 16**
Parent's global assessment of overall well being, VAS, mm	35 ± 23	29 ± 19	29 ± 22	18 ± 18**
No. of joints with active arthritis	7.5 ± 8.5	3.2 ± 4.0*	2.5 ± 3.9**	3.3 ± 8.8**
No. of joints with limited range of motion	10.5 ± 13	9.7 ± 13	7.6 ± 11	5.7 ± 9.0*
CHAQ score	0.97 ± 0.66	0.79 ± 0.68	0.68 ± 0.65	0.56 ± 0.70*
ESR, mm/h	29 ± 20	27 ± 17	25 ± 18	21 ± 12
Parent's global assessment of arthritis, VAS, mm	46 ± 27	33 ± 22*	33 ± 23*	18 ± 19**
Facial Affective Scale	0.46 ± 0.31	0.35 ± 0.29	0.26 ± 0.27*	—

* $p < 0.05$, ** $p < 0.001$ (difference to baseline). CHAQ: Childhood Health Assessment Questionnaire.

Table 2. Patient characteristics (n = 36).

Mean age, yrs ± SD	8.4 ± 3.7
Age group, %	
2–6 yrs	9 (25)
7–16 yrs	27 (75)
Sex, %	
Male	14 (38.9)
Female	22 (61.1)
Mean weight, kg ± SD	27.19 ± 11.80
Median duration of disease, yrs (range)	1.7 (0 to 9)
Median number of affected joints (range)	4 (1 to 30)
JRA onset type, %	
Oligoarticular	24 (66.7)
Polyarticular	12 (33.3)
Concomitant treatment for JRA, %	17 (50)
Methotrexate	11 (33)
Corticosteroids	7 (25)
Other *	2 (5.6)
Previous medication with other NSAID, %	31 (86.1)

* One patient each treated with sulfasalazine or hydroxychloroquine.

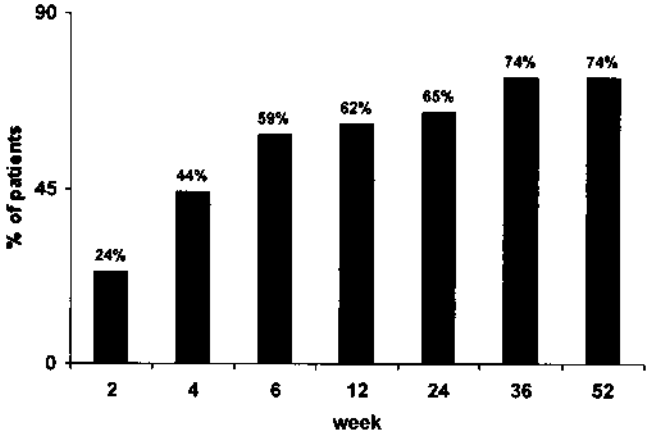

Figure 1. Response rate over time according to the PRINTO assessment criteria[32].

patients received a second-line treatment and/or corticosteroids, 33% methotrexate, 6% other second-line drugs (hydroxychloroquine, sulfasalazine), and 25% corticosteroids.

Pharmacokinetic characteristics. The maximum plasma concentration of meloxicam C_{max} (–34%) and $AUC_{0-\infty}$ (–28%) tended to be lower in younger children (ages 2 to 6 years, mean 3.4; n = 7) compared to older children (7 to 14 years, mean 10.8; n = 11), while weight-normalized clearance appeared to be higher in younger children. In comparison with adults, plasma concentrations were more similar in older children and adults. Plasma elimination half-life (13 h) in children tended to be shorter than in adults (15–20 h). Meloxicam plasma concentrations in steady state measured at Weeks 2 and 4 were within the range expected from single dose data.

Efficacy. Following the PRINTO outcome criteria[32], 44% of the patients responded at Week 4, 62% at Week 12, and 74% after 52 weeks (Figure 1). Changes in PRINTO outcome criteria measures, children's classification of discomfort, and parents' final global assessment from baseline to Weeks 6, 12 and 52 are shown in Table 1. All efficacy measures improved markedly, but no changes in ESR or platelet count were observed.

Global efficacy as judged by the parents was good or satisfactory in 92% (n = 36) of patients after 12 weeks and in 91% (n = 34) of patients after 52 weeks.

Safety. Adverse events occurred in 65% of patients within 12 weeks and in 72% within 52 weeks of treatment. Systemic disorders were most frequently reported (44%), followed by disorders of the respiratory system (39%) and GI system (39%).

Of the 5 patients with abdominal pain, 2 experienced pain during diarrhea and one shortly after diarrhea. Most adverse events were classified as mild (64%) or moderate (47%) during the 52 weeks. Most side effects are considered as adverse events, which normally occur in this age group. Adverse events considered to be related to meloxicam therapy occurred in 4 patients (11%) after 12 weeks and in 5 patients (14%) after 52 weeks. These adverse events were abdominal pain (one patient), diarrhea (2 patients), nausea (2 patients), and hepatic enzymes or increasing blood urea nitrogen (one patient each) (Table 3). No perforation, ulceration, or bleeding from the upper GI tract was observed. No patient discontinued the study medication due to a drug related adverse event. Serious adverse events were reported in 4 patients (11%): worsening of arthritis, malformation of the foot, abdominal pain, and bronchitis. The investigators

Table 3. Types of adverse events experienced at least once in 36 patients.

Adverse Event	Number of Patients (%) from Week 1 to 12*	Number of Patients (%) from Week 1 to 52*
Pharyngitis	10 (27.8)	10 (27.8)
Influenza-like symptoms	4 (11.1)	10 (27.8)
Fever	3 (8.3)	6 (16.7)
Bronchitis	3 (8.3)	4 (11.1)
Bacterial infection	1 (2.8)	3 (8.3)
Parasitic infection	1 (2.8)	2 (5.6)
Headache	1 (2.8)	2 (8.3)
Diarrhea	7 (19.4)	7 (19.4)
Abdominal pain	3 (8.3)	5 (13.9)
Food poisoning	3 (8.3)	3 (8.3)
Gastroenteritis	2 (5.6)	3 (8.3)
Nausea	2 (5.6)	2 (5.6)
Aggravated arthritis	1 (2.8)	3 (8.3)
Nail disorder	2 (5.6)	2 (5.6)

* Analysis of adverse events was performed for the first 12 weeks and for the whole trial (52 weeks, including Weeks 1-12).

judged that no causal relationship existed between the study medication and any serious adverse event.

Global patient tolerance was rated good or satisfactory by the investigator in 83% (n = 36) at Week 12 and in 94% (n = 34) at Week 52.

DISCUSSION

In this open study, the selective COX-2 inhibitor meloxicam seemed to be effective and safe at a dose of 0.25 mg/kg/day over 52 weeks in children with JRA. The oral meloxicam suspension[33] is a suitable alternative as a regimen that can be dosed according to body weight, especially in children.

Meloxicam given once daily exhibited a broad efficacy in treatment of signs and symptoms of JRA throughout the day. Clinically relevant improvement was observed after 2 weeks of therapy, with a plateau at Week 6 and a further moderate increase in efficacy up to 12 and even 52 weeks, indicating that a treatment duration of 8 to 12 weeks may be necessary to assess efficacy in this clinical setting[34]. The number of joints with limited range of motion and CHAQ score improved significantly at Week 52 in comparison with baseline, while improvement had already been observed at Week 12. The ESR did not change significantly, which may be explained by the mean ESR at baseline already being 29 (± 20) mm/h, thus almost within the normal range. Treatment effectiveness was also reflected by the significant change in the parents' global assessment (of the children's classification of discomfort). At Week 12 almost 62% and at Week 52, 74% of the patients were "responders" according to the PRINTO outcome criteria at the end of the trial.

The clinical efficacy of the meloxicam suspension in JRA indicates that once-daily dosage is sufficient in children, although the plasma elimination half-life of 13 h tended to be shorter in children than in adults. The phenomenon of higher rate of clearance in younger children has been reported for a number of other NSAID including ibuprofen[35,36], diclofenac[37], piroxicam[38], indomethacin[39], and tiaprofenic acid[40], leading to dose adjustments in some cases[37].

Meloxicam was well tolerated in the pediatric population investigated. No adverse event required hospitalization or discontinuation of treatment. Abdominal pain occurred in 8.3% of the patients after 12 weeks, and in 13.9% after 52 weeks, which seems lower than in a recent retrospective chart review[27]. In 3 of 7 patients abdominal pain was associated with diarrhea. The other treatment adverse events were primarily typical infections seen in this age group.

Meloxicam seemed effective and was well tolerated in this pediatric patient population. A comparative, double blind controlled Phase III/IV study is in progress. Depending on the results of the Phase III/IV study, meloxicam may become a reasonable alternative to classical NSAID, especially considering the convenient once-daily dosage regimen as a suspension, which increases compliance in patients and acceptance by parents.

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