Oxaceprol – a randomised, placebo-controlled clinical study in osteoarthritis with a non-conventional non-steroidal anti-inflammatory drug

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Abstract

Objective

To evaluate efficacy of therapy with oxaceprol in the treatment of symptomatic osteoarthritis of knee or hip.

Methods

A 3-week prospective, multicentric, randomised, double-blind, placebo-controlled study with 167 patients aged between 40 and 75 years with painful and radiologically confirmed knee or hip osteoarthritis. Patients were randomly assigned to receive oxaceprol 1200 mg/day or placebo for 3 weeks. At inclusion, osteoarthritis symptoms were minimum pain following exercise (standardised as pain after climbing 12-15 stairs) of 40 to 90 mm on a 100 mm pain scale and difficulties in climbing stairs. Efficacy criteria were changes in pain shown in a visual analogue scale (VAS), in the Lequesne index, and in assessments of joint limitation, joint complaint and therapeutic success. The primary end point was the pain following exercise. The confirmatory analysis was based on the Full Analysis data set using the t-test for independent samples.

Results

Baseline characteristics of both groups were comparable. In the primary endpoint a clinically relevant and statistically significant superiority of oxaceprol as compared to placebo could be demonstrated (mean improvement in pain following exercise was 16.6 mm in the oxaceprol and 4.5 mm in the placebo group, p = 0.002). The safety and tolerability was good, showing no statistically significant difference between oxaceprol and placebo.

Conclusion

A statistically significant and clinically relevant efficacy of oxaceprol was shown. The good safety and tolerability of oxaceprol was confirmed.

Key words

Oxaceprol, non-steroidal anti-inflammatory agents, placebo, efficacy, osteoarthritis, knee, hip, pain, drug safety.

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Chephasaar GmbH is the sponsor of the study and the manufacturer of the study medication. Reimbursement was made according to the time spent on the study and within the general framework.

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Introduction

Oxaceprol (INN) is an amino acid derivative, which has been used for decades for the symptomatic treatment of degenerative and inflammatory joint disease in Europe (e.g. AHP 200®, Germany; Jonctum 200 mg gélule, France) (1, 2). Oxaceprol has anti-inflammatory and analgesic efficacy comparable to the conventional non-steroidal anti-inflammatory drugs (NSAIDs) but has a different mode of action. Instead of inhibiting the synthesis of prostaglandins oxaceprol prevents leukocyte infiltration into the joints, thus inhibiting an early step of inflammatory cascade and presenting a novel class of anti-inflammatory agents (3). The limitations of NSAIDs in clinical therapy of joint disease have become obvious during the last 2 years. Beginning with the COX-selective NSAIDs, also the safety profile of the classical NSAIDs has been reassessed, revealing cardiovascular risk in addition to the already known serious risks like gastrointestinal bleeding or renal damage. As a consequence, the interest in therapeutic alternatives has increased.

Oxaceprol could be such an alternative. There are promising results in the preclinical studies (3, 4). Clinical equivalence with diclofenac in recent clinical studies has been shown (5, 6). Due to a potentially strong placebo effect in osteoarthritis, current European requirements additionally ask for placebo control in this indication as a proof of efficacy (7-9). Therefore, the aim of the present study was to determine whether oxaceprol would be superior to placebo in the treatment of osteoarthritis.

Materials and methods

Study design

This study was a double-blind, randomised, multicentric clinical trial in 15 orthopaedic or rheumatologic ambulatory centres in Germany comparing parallel groups. Duration of treatment was 3 weeks with 4 visits: 1st visit screening/start of wash-out, 2nd visit start of intake of study medication, 3rd visit therapy results after 1 week, and 4th visit therapy results after 3 weeks/ end of study. The first patient was enrolled on 19th November 2003; the last patient completed on 16th June 2004.

The study was conducted in accordance with the German Drug Law, the Guidelines for Good Clinical Practice and with the Declaration of Helsinki. The study concept was approved by all necessary ethics committees before starting patient recruitment.

The study design was based on current European recommendations on the conduction of clinical studies in osteoarthritis (7-9). The quality of the study conduction was assured by audits of independent experts.

Patients

Outpatients were included who suffered from radiologically confirmed osteoarthritis of knee or hip. Further inclusion criteria were age 40-75 years, difficulties in climbing stairs, minimum pain following exercise of 40 to 90 mm on a 100 mm pain scale. In case of osteoarthritis of more than one joint, the joint with the most severe symptoms was investigated. Exclusion criteria were known secondary osteoarthritis (e.g. with trauma, dysplasia), rheumatoid arthritis, neurological disorders of the locomotor system, serious adipositas or other diseases with influence on osteoarthritis symptoms (e.g. gout), therapies which could interfere with the study, surgery of the investigated joint during the last 6 months or planned surgery within the next 2 years, patients with surgery of the lower limbs during the last year, periarticular or intraarticular injection (especially corticoids) or punctation during the last 3 months, hypersensitivity to the investigational product, pregnancy (screening test before inclusion) or lactation. Before inclusion all patients gave their written, informed consent.

Drug administration/treatment

Following a wash-out period of at least 5 times the plasma half life of previously administered analgesic or antiphlogistic medication, patients were randomly assigned to treatment for 3 weeks with 2 x 200 mg three times daily, i.e. 1200 mg/day, oxaceprol film-coated tablets or placebo of identical appearance. The study medication was made by Chephasaar GmbH, Germany.

During the study analgesic or antiphlogistic co-medication was excluded. Rescue medication was acetaminophen tablets (0.5 g). Intake was permitted if necessary due to pain but not 48 hours before visits. It was recorded daily by the patient in the diary and checked by the physician at each visit (pill counting of rescue medication and study medication).
Ongoing physiotherapy was allowed if there was no change during the study. It was documented at each visit.

Efficacy variables
The primary end point was pain following exercise after 3 weeks of treatment. It was standardised as pain after climbing 12-15 stairs documented by patient using a 100 mm visual analogue scale (VAS) in the patient's diary (0 = no pain, 100 = maximum pain) at the same time of day. The documentation was checked and documented in the case report form (CRF) by the physician at each visit.
Secondary endpoints were pain at rest (VAS, 0 = no pain, 100 = maximum pain), the Lequesne joint function index (0-24 points, 0 = no functional restriction, 24 = highest functional restriction) (10), patient's and physician's global assessment of joint disability and joint complaint (VAS, 0 = no disability/complaint, 100 = maximum disability/complaint), patient's and physician's global assessment of efficacy and safety of therapy (VAS, 0 = no efficacy/safety, 100 = maximum efficacy/safety), as well as acetaminophen consumption and drop-out due to lack of efficacy.

Safety variables
Adverse events (AEs) were recorded at each visit. Laboratory variables (haematology, clinical chemistry and urine status) were measured at the beginning and end of the study.

Statistical analysis
The study was planned as a pivotal study. Pre-study sample size estimation was based on the following assumptions: Error levels of alpha = 0.05, and beta = 0.8; clinically relevant difference in pain measured by VAS = 10 mm with a common standard deviation of 20 mm. 128 evaluable patients would have been required for this approach. 140 patients should be recruited in order to compensate for drop-outs. After inclusion of 40 patients a planned, blinded interim analysis was carried out to check the assumptions of the sample size calculation. Since the drop-out rate was higher than expected, the sample size was increased to totally 160 patients.
Efficacy variables were evaluated on the basis of a full analysis (FA) according to a modified intent-to-treat principle. For sensitivity reasons an additional per protocol (PP) analysis was carried out. The confirmatory analysis was based on the FA data set using the t-test for independent samples. All patients who received at least one dose of study medication entered the safety analysis.
Patient allocation was 1:1, with a block size of 6 patients, resulting in a list of numbers 1 – x (computer programme RANCODE, version 3.6, IDV Gauting; based on random number generator of George Massaghia and T. A. Bray, Mathematics Research Laboratory Boeing Scientific Research Laboratories, March 1968). Study centres received study medication with continuing numbers, recruiting the patients ascending, beginning with lowest number.
Random code was withheld from all persons directly involved in the patient recruitment or involved in statistical analysis. The only deblinding which was possible during the study, was deblinding of specified patients in case of a severe side reaction, which could not be treated adequately without knowledge of the investigational product. Therefore, the doctors and the monitors received sealed envelopes to enable deblinding.
The primary study hypotheses for efficacy focused on "pain following exercise" and were hierarchically ordered a-priori as follows: 1st null hypothesis: The pre-/post-treatment difference (3 weeks versus day 0) is not different in patients treated with oxaceprol and patients treated with placebo. 2nd null hypothesis: The pre-/post-treatment difference (1 week versus day 0) is not different in patients treated with oxaceprol and patients treated with placebo.
The secondary efficacy parameters were evaluated according to the same principles and the same methods as the primary efficacy variables. Nevertheless, significant differences of the secondary parameters had to be interpreted descriptively. All data analyses were carried out using the programme SPSS for Windows, version 12.0.
An analysis of safety was carried out by comparing the incidences of adverse events by Fisher's exact test.

Results
Patient characteristics
Of 167 screened patients, 159 were randomised. One hundred and fifty three received treatment (at least 1 tablet of study medication) and were evaluated for safety analysis (SA data set). 97 patients could be evaluated for efficacy of the primary endpoint after 3 weeks (FA dataset). Based on blind data review 24 patients had to be excluded from efficacy evaluation due to serious protocol violations of inclusion or exclusion criteria (13 VAS < 40 mm or > 90 mm at inclusion; 3 without difficulties in climbing stairs; 3 intraarticular medication; 2 joint surgery; 2 > 80 years; 1 BMI > 40); 22 patients due to serious protocol violations (8 unauthorised analgesic/antiphlogistic medication within 5 plasma half times before visit; 5 study medication for less than 6 calendar days; 3 acetaminophen within 6 hours before visit; 2 wash-out medication during treatment phase; 1 lack of compliance in intake of study medication; 1 lack of efficacy data; 1 attack of gout during the study; 1 start of study 20 days before first intake of study medication) and 10 lack of VAS compliance (8 change of VAS > 40 mm within 24 hours during the first treatment week, 1 VAS improvement > 20 mm during wash-out time, 1 VAS 1 mm at inclusion).
Baseline data of both groups were comparable in the SA data set and in the FA data set (see Table I).

Therapeutic efficacy
In the primary endpoint, pain following exercise, at the end of the study after

Table I. Baseline characteristics of the patients.

Variable	SA data set		FA data set	
	Oxaceprol (n = 77)	Placebo (n = 76)	Oxaceprol (n = 56)	Placebo (n = 41)
Male	25 (32.5%)	28 (36.8%)	20 (35.7%)	11 (26.8%)
Female	52 (67.5%)	48 (63.2%)	36 (64.3%)	30 (73.2%)
Age (years)	59.9 ± 9.8	60.5 ± 9.4	59.4 ± 9.1	59.9 ± 7.8
Height (cm)	167.8 ± 9.0	168.1 ± 7.7	169.1 ± 8.7	167.2 ± 6.6
Body weight (kg)	76.8 ± 14.5	78.7 ± 12.9	79.4 ± 13.8	78.7 ± 9.4
Blood pressure (mmHg)				
Systolic	136 ± 18	139 ± 20	134 ± 15	138 ± 18
Diastolic	84 ± 12	85 ± 11	84 ± 11	84 ± 12
Heart rate (/min)	72 ± 11	73 ± 10	72 ± 12	74 ± 11
Diagnosis				
Gonarthrosis	55 (71.4%)	57 (75.0%)	38 (67.9%)	29 (70.7%)
Coxarthrosis	22 (28.6%)	19 (25.0%)	18 (32.1%)	12 (29.3%)

Values are absolute and relative frequencies or means ± standard deviations.

Table II. Pain following exercise, at start and after 3 weeks measured by 100 mm VAS Data base: Full Analysis data set (FA).

Groups	Day 0	After 3 weeks	Differences within groups	Difference between groups	95% confidence interval
Oxaceprol	61.8 ± 14.9	45.2 ± 22.2	-16.6 ± 19.8		
n	56	56			
				-12.1	-19.8 to -4.4
Placebo	63.0 ± 13.9	58.5 ± 21.6	- 4.5 ± 17.3		
n	41	41			

Values are means ± standard deviations, confidence interval and "n".

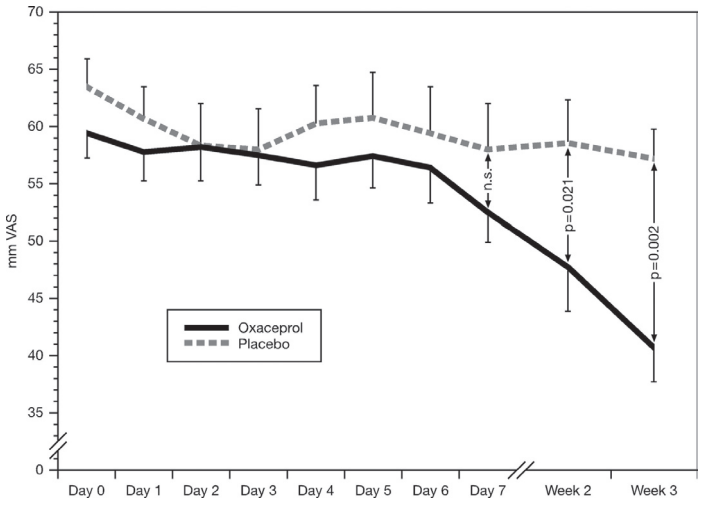

Fig. 1. Mean intensity of the pain following exercise beginning with day 0 for the first week (daily assessment), after 2 and after 3 weeks. Data base: Full Analysis data set (FA). Means and stand error of means.

3 weeks, the improvement on the 100-mm-pain-scale was on average 16.6 mm in the oxaceprol group and 4.5 mm in the placebo group (Table II). A statistically significant superiority of oxaceprol as compared to placebo could be demonstrated (p = 0.002, 95% confidence interval for the end-point difference = -19.8 to -4.4). A clear onset of efficacy is seen beginning from week 2 (p = 0.021) (Fig. 1). The analysis based on the per protocol sample showed a similar result (oxaceprol: -18.6 mm, placebo: -6.4 mm; p = 0.005; 95% confidence interval for the end-point difference = -20.4 to -3.9).

Mean pain at rest improved by 7.6 mm in the oxaceprol group and deteriorated by 3.3 mm in the placebo group. The difference between the groups was significant (p = 0.016). Significant difference was also seen in the physician's assessment of joint complaint at study end (oxaceprol group: 43.2 mm, placebo group: 53.7 mm; p = 0.020).

Statistical trends favouring the oxaceprol group were determined for the mean patient's and physician's assessment of therapeutic success at study end (p = 0.069 and p = 0.095, respectively).

Mean Lequesne index and mean joint limitation clearly improved better in the oxaceprol than in the placebo group (Lequesne index improvement: 2.4 points versus 1.5 points; joint limitation improvement: 9.8 mm versus 5.6 mm). Nevertheless – probably due to relatively low patient number – significance was not reached.

There was low acetaminophen consumption and few drop-outs due to lack of efficacy, so that differences between the groups were not significant in these parameters.

In conclusion, the secondary target parameters confirm the results in favour of oxaceprol. All parameters show clinically relevant improvement under oxaceprol after 3 weeks, even if statistical significance was not met in all parameters.

Safety and tolerability

One hundred and seventy-one adverse events were reported in 68 patients. Most of the adverse events were mild (61%). Two patients in the oxaceprol group and 3 patients in the placebo group dropped out due to adverse events. In each administration group there was one serious adverse event. None of them was seen in the context with the study medication (placebo: fracture of hand after falling off a bicycle; oxaceprol: acute cervical syndrome).

The incidence of symptoms observed in at least 3 patients was not relevantly

Table III. Adverse events: Symptoms. Data base: Safety Analysis data set (SA).

Symptoms[a] ($n_{total} \geq 3$ patients[b])	Oxaceprol	Placebo
Headache	10 (13%)	8 (11%)
Raise of the C-reactive protein	2 (3%)	8 (11%)
Pruritus	4 (5%)	6 (8%)
Impaired appetite	4 (5%)	3 (4%)
Erythrocyte sedimentation rate raised	1 (1%)	6 (8%)
Dyspepsia	3 (4%)	3 (4%)
Increased susceptibility to infections	2 (3%)	4 (5%)
Raise of uric acid in blood	3 (4%)	3 (4%)
Raise of Gamma-GT	1 (1%)	5 (7%)
Activated appetite	3 (4%)	3 (4%)
Dizziness	4 (5%)	1 (1%)
Ructus	1 (1%)	4 (5%)
Redness	4 (5%)	1 (1%)
Epigastric pain	2 (3%)	3 (4%)
Diarrhoea	1 (1%)	3 (4%)
Flatulence	1 (1%)	2 (3%)
Migraine	2 (3%)	1 (1%)
Cold	2 (3%)	1 (1%)
Sum	50	65
Total number of all treated patients	77 (100%)	76 (100%)

Values are absolute and relative numbers of patients.
[a]Preferred Term MedDRA version 7.0.
[b]Further adverse events.

higher in the oxaceprol group than in the placebo group (see Table III). Only in the parameters "raise of the C-reactive protein" and "ESR" (erythrocyte sedimentation rate) almost significant differences (more AEs in the placebo group) were observed, which could be interpreted as an indication of worse inflammatory control under placebo.
In conclusion, the adverse events did not differ significantly in any aspect, neither qualitatively nor quantitatively between the treatment groups. The total rate of adverse drug reactions in this clinical study is low and the rate of side effects in the oxaceprol group is comparable with the placebo group.

Discussion

The data presented here clearly show the superiority of oxaceprol as compared to placebo in the treatment of osteoarthritis. Compared to previous placebo-controlled studies (11) the present study was planned confirmatory in accordance with current European requirements (7-9) and is therefore highly relevant for the proof of efficacy of oxaceprol. The efficacy indices were chosen in line with the EMEA recommendations for osteoarthritis clinical studies: pain attributed to the target joint is recommended as primary endpoint for symptom-modifying drugs for osteoarthritis, functional disability is an important additional primary endpoint. VAS or Likert scales are methods recommended to assess pain. Functional disability should be assessed by the Western Ontario Mac Master University osteoarthritis index (WOMAC) or the Lequesne index (9). All these indices are validated and give patient relevant information. In this study the pain VAS was chosen as the primary endpoint. The Lequesne index, which had already been established in previous studies with oxaceprol, was used as secondary endpoint. Although current publications tend to assess responder criteria due to their patient-derived perspective [e.g. the WOMAC index contributed to the development of proposed definitions for responder criteria (12, 13)], at the time of the set-up of the study response criteria required additional validation (13) and were therefore not regarded as sufficiently validated parameters at that time. Therefore, the results were expressed at a group level as mean changes.
In the primary endpoint oxaceprol was significantly ($p = 0.002$) more effective than placebo after 3 weeks. The pain following exercise improved by 16.6 mm in the oxaceprol group and by 4.5 mm in the placebo group. Regarding the group mean, the net oxaceprol effect (minus placebo effect) is an improvement of 12.1 mm. This difference is clearly clinically relevant taking into consideration that already a difference of 10 mm on 100 mm VAS is clinically relevant (12). Additionally, the comparison of the results in this study with Falgarone *et al.'s* patient-derived parameters Low Disease Activity State (LDAS) and pain killer intake level (15) shows that in the oxaceprol group the VAS pain value at the beginning of the study (61.8 ± 14.9 mm) was a clear high disease level (50^{th} percentile of LDAS 36) and there was a need for intake of pain killer (50^{th} percentile of the pain killer intake level 48). There was a clear improvement at the end (45.2 ± 22.2 mm). A comparison with NSAID studies confirms this result. After 2 weeks of treatment in patients with knee osteoarthritis, Kivitz reports a net effect of Valdecoxib 20 mg/day and Naproxen 2 x 500 mg/day of 10.88 mm and 9.84 mm respectively (16). Williams reports a net effect of Celecoxib 100 mg BID and Celecoxib 200 mg QD of 10.1 mm and 8.7 mm, respectively (17).
In previously published studies the equivalence of therapeutic efficacy of oxaceprol and diclofenac was demonstrated. Bauer *et al.* proved the efficacy of oxaceprol (3 x 200 mg/day orally) in comparison with the standard therapy diclofenac (3 x 25 mg/day orally) in 150 patients with activated painful osteoarthritis of hip or knee (5). The biometric testing was a confirmatory test of equivalence. The main efficacy parameter of the study, the Lequesne index (reflecting pain and function), showed significant and clinically relevant improvement after 20 days of treatment (4 points in the oxaceprol and 3.4 points in the diclofenac group). Also the secondary parameters, e.g. weight-bearing pain improved clearly (oxaceprol by 3 of 10 points, diclofenac by 3.2 points). In conclusion, the study shows that oxaceprol in the low dosage of 3 x 200 mg/day is equivalent to the standard therapeutic diclofenac in the low dosage of 3 x 25 mg/day. The study published by Herrmann *et al.* also showed

the equivalence of oxaceprol with diclofenac in a comparable study design but with higher dosage (diclofenac 3 x 50 mg/day orally and oxaceprol 3 x 400 mg / day orally) (6). The Lequesne index improved by 2.5 points in the oxaceprol and by 2.8 points in the diclofenac group. The weight-bearing pain also improved clearly (oxaceprol –2.2 of 10 points, diclofenac –2.3 of 10 points).

As compared to the present study, the improvement in these active comparator studies seems to be slightly higher (in the present study improvement by 16.6 of 100 mm VAS). This might be due to higher basic effect of physiotherapy, since the studies of Bauer *et al*. and Herrmann *et al*. were performed with inpatients receiving physiotherapy. The present study was performed with outpatients; only 28.6% of the patients in the oxaceprol group and 31.7% of the patients in the placebo group received physiotherapy.

In our study the tolerance of oxaceprol was comparable to placebo confirming the results of previously published studies. Bauer reports on a statistical significance level that oxaceprol is better tolerated than diclofenac (5).

The main risk of NSAIDs results from the inhibition of the production of prostaglandins, which have a crucial role in protection mechanisms of gastrointestinal and cardiovascular system. Oxaceprol does not inhibit prostaglandin synthesis (4). The anti-inflammatory and analgesic effect results from an inhibition of leukocyte infiltration (4). In an *in vitro* leukocyte adhesion model oxaceprol was shown to inhibit selectively the adhesion of leukocytes to endothelial cells (18). The effects on leukocyte adherence and extravasation were also shown *in vivo* in hamsters (19), in the carrageenan-induced paw oedema of the rat (4), in the adjuvant arthritis model in the rat and in the model of antigen-induced arthritis in mice (4, 20).

In conclusion, oxaceprol presents a well-established drug for symptomatic treatment of joint disease. Recent preclinical and clinical publications demonstrate that it is a novel class of anti-inflammatory agents with better safety profile than classical NSAIDs. The present study completes the clinical proof of efficacy showing superiority of oxaceprol as compared to placebo.

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