Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial

E. Batlle-Gualda M.D., Ph.D., Associate Professor*, J. Román Ivorra M.D., Ph.D., Associate Professor†, E. Martín-Mola M.D., Ph.D., Associate Professor‡, J. Carbonell Abelló M.D., Ph.D.¶, L. F. Linares Ferrando M.D., Ph.D., Associate Professor¶, J. Torneró Molina M.D., Ph.D., Associate Professor#, A. Raber Béjar M.D.†† and J. Fortea Busquets M.D., Ph.D.‡‡

† Rheumatology Unit, Hospital General Universitario, Alicante, Spain
‡ Rheumatology Unit, Hospital Dr. Pesset, Valencia, Spain
¶ Rheumatology Unit, Hospital Universitario La Paz, Madrid, Spain
¶¶ Rheumatology Unit, Hospital del IMAS: Hospitales del Mar y de la Esperança, Barcelona, Spain
# Rheumatology Unit, Hospital General Universitario Virgen de la Arrixaca, Murcia, Spain
†† Medical Department, Almirall, Barcelona, Spain
‡‡ International Medical Department, Almirall, Barcelona, Spain

Summary

Objective: To evaluate the efficacy and tolerability of aceclofenac, 200 mg/day, and paracetamol, 3000 mg/day, in the treatment of osteoarthritis (OA) of the knee.

Methods: This was a double-blind, parallel-group, multicentre clinical trial involving patients with symptomatic OA of the knee, conducted in Spain. Patients were randomly allocated to aceclofenac 100 mg twice daily (n = 82) or paracetamol 1000 mg three times daily (n = 86). Patients were assessed at baseline and 6 weeks. Primary efficacy measures were severity of pain (visual analogue scale, VAS), Lequesne OA knee index, and patient’s and physician’s global assessment of disease activity. Severity of knee pain at rest or walking, stiffness, knee swelling and tenderness, and assessment of health-related quality of life (Health Assessment Questionnaire, Western Ontario and McMaster Universities Osteoarthritis Index, and Short Form 36) were included as secondary endpoints.

Results: Both treatment groups showed significant improvement compared with their baseline values in the four primary endpoints. Mean between-treatment differences favoured aceclofenac over paracetamol on pain (VAS, 7.64 mm [95% confidence interval (CI), 0.44–14.85 mm]), Lequesne OA index (1.41 [95% CI, 0.45–2.36]), and patient’s (0.33 [95% CI, 0.06–0.61]) and physician’s (0.23 [95% CI, 0.01–0.47]) global assessments. Adverse events were similar for both drugs (paracetamol, 29% patients vs aceclofenac, 32%; P = 0.71). Four patients withdrew in each group due to adverse events. Patients tended to prefer aceclofenac to paracetamol (P = 0.001), and more treated with paracetamol withdrew from the study due to lack of efficacy (n = 8 vs n = 1, P = 0.035, for paracetamol and aceclofenac, respectively).

Conclusion: At 6 weeks, patients with symptomatic OA of the knee showed a greater improvement in pain and functional capacity with aceclofenac than paracetamol with no difference in tolerability.

© 2007 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Key words: Aceclofenac, Paracetamol, Osteoarthritis, Controlled clinical trial, Treatment.

Introduction

Osteoarthritis (OA) is a primary cause of morbidity associated with rheumatic diseases. In the near future, the ageing population and the decline in physical function when hips and knees are affected by OA will increase the impact of this condition on health care utilization. In Spain, the Estudio Epidemiológico de la Sociedad Española de Reumatología (EPISER) Study indicated that up to 29% of people >60 years had symptomatic OA of the knee.

Paracetamol has been recommended as the initial therapy for the treatment of pain in knee OA, primarily due to...
its low risk and cost\textsuperscript{2,3}, while non-steroidal anti-inflammatory drugs (NSAIDs) are reserved for those patients who do not improve, who have more severe symptoms, or who have signs of joint inflammation\textsuperscript{4,5}. The published evidence for the efficacy of paracetamol in OA compared with placebo or NSAIDs is quite limited. Table I shows the most relevant trials retrieved after a search strategy including Medline and Cochrane databases with the following descriptors: osteoarthritis, knee/therapy [MeSH]; anti-inflammatory agents, non-steroidal/therapeutic use [MeSH]; paracetamol; acetaminophen; limited to clinical trials, meta-analyses, randomized controlled trials, and reviews. Publications in non-European languages were excluded, and a manual search from retrieved studies was done.

Findings were reported from a parallel-group trial, in which paracetamol (4000 mg/day), diclofenac (150 mg/day), and placebo were assessed for pain relief in knee OA\textsuperscript{6}. In this trial, paracetamol was judged no more efficacious than placebo (P = 0.92) but superior (P = 0.19) weeks. Diclofenac improved pain control from baseline at both 2 and 12 weeks using the WOMAC OA index; however, at 12 weeks, diclofenac was no longer superior to paracetamol or placebo (P = 0.25)\textsuperscript{6}.

Paracetamol was also compared to placebo in two simultaneous, double-blind, double-dummy, two-period crossover trials involving patients with OA of the knee or hip (PACES-a and PACES-b)\textsuperscript{7}. Despite their identical design, PACES-a and PACES-b showed some differences in their results. Paracetamol (4000 mg/day) was more efficacious than placebo, generally P < 0.05, in PACES-a but not in PACES-b (P > 0.05). Celecoxib, 200 mg/day, was more efficacious than paracetamol in both studies. A pooled estimate of these trials found that paracetamol was more effective than placebo for pain relief in OA\textsuperscript{8,9}. Although a third trial was not able to detect any difference between paracetamol and placebo in the treatment of OA knee flares\textsuperscript{10}, its findings have been questioned\textsuperscript{9}.

The remaining published studies assessing the efficacy of paracetamol in OA have involved active comparators, i.e., NSAIDs\textsuperscript{11,12}. Bradley et al.\textsuperscript{11} compared paracetamol (4000 mg/day) with analgesic and anti-inflammatory doses of ibuprofen (1200 mg and 2400 mg/day, respectively). Although the authors concluded that the efficacy of paracetamol was similar to that of ibuprofen, independent of the dosage, only patients treated with ibuprofen had a statistically significant improvement in both walking pain and rest pain, with statistically greater improvement in rest pain in the ibuprofen group compared with paracetamol. In two post hoc analyses of this study, the authors found that neither the intensity of pain nor signs of joint inflammation were able to predict a greater response to ibuprofen than paracetamol\textsuperscript{12,13}.

Williams et al.\textsuperscript{14} compared paracetamol (2600 mg daily) with naproxen (750 mg daily) in a 2-year, randomized, double-blind trial. Between-group comparisons showed naproxen to be superior to paracetamol for only pain at rest. The authors concluded that the efficacy of paracetamol and naproxen was similar, despite an appearance of a better response for naproxen. A meta-analysis\textsuperscript{15}, including both trials\textsuperscript{11,14}, suggested that NSAIDs were slightly more effective than simple analgesia, although paracetamol should be the first treatment for OA pain due to its better cost effective profile.

More recently, Pincus et al.\textsuperscript{15} compared diclofenac plus misoprostol (150 mg and 400 µg/day, respectively) with paracetamol (4000 mg/day) in a double-blind, two-period, crossover trial in patients with hip or knee OA. After 6 weeks, diclofenac/misoprostol provided significantly more improvement in both primary outcomes (pain VAS and WOMAC), compared to paracetamol, although paracetamol was associated with fewer adverse events. Accordingly, more patients, who took both drugs in a random order, rated diclofenac/misoprostol as “better” or “much better” than paracetamol\textsuperscript{15}.

Finally, Geba et al.\textsuperscript{16} compared the efficacy of rofecoxib (12.5 and 25 mg/day), celecoxib (200 mg/day), and paracetamol (4000 mg/day) in a 6-week, double-blind clinical trial. Rofecoxib, at 25 mg daily, provided greater therapeutic benefits than paracetamol in all prespecified endpoints, whereas celecoxib at the lower dose and celecoxib were not proven to have any advantage over paracetamol. Two meta-analyses including data from COX-2 inhibitors showed that NSAIDs were consistently superior to paracetamol in pain relief across the evaluated studies with a trend for improved safety favouring paracetamol\textsuperscript{17,18}. Prolonged use of non-selective NSAIDs can lead to significant mortality and morbidity from gastrointestinal (GI) bleeding, ulceration, and perforation, whereas paracetamol has a very low incidence of GI side-effects\textsuperscript{19}. By contrast, COX-2 selective NSAIDs appear to have an incidence of GI ulceration comparable to placebo, and a reduced risk of complicated and symptomatic ulcers compared to conventional NSAIDs\textsuperscript{19}. The advantages leading to suggest these more selective NSAIDs as a first-line treatment for OA of the knee have been offset by its increased risk of cardiovascular events including heart attacks and strokes\textsuperscript{20}. Additional concerns have been raised about the cardiovascular safety related to the more classical non-selective NSAIDs\textsuperscript{21,22}.

Aceclofenac is a phenylacetic acid derivative structurally related to diclofenac that has shown a higher therapeutic index than other NSAIDs with similar analgesic and anti-inflammatory activity in animal models\textsuperscript{23}. Aceclofenac (100 mg) exhibits a sustained block of COX-2 in vivo, but only a minor inhibition of COX-1, compared with 75 mg diclofenac\textsuperscript{24}. Controlled clinical trials have

Table I

<table>
<thead>
<tr>
<th>Authors</th>
<th>Joint</th>
<th>Design</th>
<th>Treatment arms, n (mg/day)</th>
<th>Trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley, 1991\textsuperscript{11}</td>
<td>Knee</td>
<td>Parallel</td>
<td>Paracetamol; ibuprofen; ibuprofen; 61(4000); 62(1200); 62(2400)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Williams, 1993\textsuperscript{13}</td>
<td>Knee</td>
<td>Parallel</td>
<td>Paracetamol; Naproxen; 89(2600); 90(750)</td>
<td>2 years</td>
</tr>
<tr>
<td>Pincus, 2001\textsuperscript{15}</td>
<td>Knee (78%), hip (22%)</td>
<td>Crossover</td>
<td>Paracetamol; Diclofenac; 180(4000 mg); 180(150 mg)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Geba, 2002\textsuperscript{16}</td>
<td>Knee</td>
<td>Parallel</td>
<td>Paracetamol; Celecoxib; Rofecoxib; 94(4000); 97(200); 96(12.5); 95(25)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Case, 2003\textsuperscript{14}</td>
<td>Knee</td>
<td>Parallel</td>
<td>Paracetamol; Diclofenac; Placebo; 29(4000); 25(150); 28(–)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Pincus, 2004 (PACES)</td>
<td>Knee (85%), hip (15%)</td>
<td>Crossover</td>
<td>Paracetamol; Celecoxib; Placebo; 114(4000); 121(200); 115(–)</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>
demonstrated that aceloferac is effective and well tolerated in patients with OA, rheumatoid arthritis, and ankylosing spondylitis. Aceloferac is one of the most widely used NSAIDs in Spain. Due to the paucity of data about paracetamol in OA of the knee, and of direct comparative data vs aceloferac in particular, we assessed the efficacy of aceloferac (200 mg/day) compared to paracetamol (3000 mg/day) in the treatment of patients with symptomatic knee OA in a 6-week, multicentre, parallel, double-blind, randomized clinical trial.

Patients and methods

PATIENT POPULATION

Outpatients, aged 30–75 years, with primary knee OA (patients with radiological chondrocalcinosis were allowed), degrees II or III according to Kellgren–Lawrence classification, history of knee pain for at least 3 months in the last year, current knee pain >30 mm on a visual analogue scale, and American College of Rheumatology (ACR) functional classes I–III, were recruited from six Spanish rheumatology units. Patients were excluded for the following reasons: if they had any other kind of arthritis or connective tissue disease; knee trauma within the last 3 months; previous open intervention in the knee or being on a waiting list for joint replacement surgery; pregnancy or lactation; renal (creatinine >1.5 mg/dl) or hepatic disease; concomitant use of anticoagulants, aspirin, corticosteroids, lithium, phenytoin, ticosteroid in the past 3 months; concomitant use of oral anticoagulants, aspirin, corticosteroids, lithium, phenytoin, thyroxine or probenecid. Female patients with childbearing potential who were not practising adequate contraceptive measures and patients enrolled in any other clinical trial potential who were not practising adequate contraceptive measures and patients enrolled in any other clinical trial.

TREATMENT ASSIGNMENT AND CONCEALMENT

Patients were randomly allocated to either aceloferac or placebo treatments, in balanced blocks of four within each centre, by computer generated random numbers. Sealed sachets were concealed in opaque sealed envelopes. Active and placebo tablets, as well as active and placebo sachets, were identical in appearance to preserve the double-dummy design. Medication was packaged in sachets containing 1000 mg of paracetamol and tablets of 100 mg of aceloferac presented in blister packs. Patients in the aceloferac group received one 100 mg tablet and one placebo sachet in the morning, one placebo sachet at noon, and one 100 mg tablet with one placebo sachet at night. Those in the paracetamol group received one sachet of 1000 mg with one tablet of placebo in the morning, one sachet of 1000 mg at noon, and one sachet of 1000 mg with one tablet of placebo at night.

Patients remained at the same dose during the 6 weeks of the trial. Study medications were taken after meals. Tablet and sachet counts were performed to account for compliance. During the trial, antacid, anti-H2 or proton pump inhibitors were allowed. Concurrent corticosteroid injection was not permitted. Patients were encouraged to keep the same level of physical activity and physical therapy.

MEASURES OF HEALTH-RELATED QUALITY OF LIFE

Two specific and one generic questionnaire were used to characterize the perceived impact of knee OA on patients' health-related quality of life.
The HAQ is a rheumatoid disease-specific, health-related questionnaire, which includes 20 items on daily living activities related to physical function. The final score is the sum of the worst score from each category, divided by the number of categories explored (usually 8). The previously validated Spanish version of the HAQ disability index was used for this study. Scores pertaining to lower-extremity function were analysed as a subset of the HAQ.

The WOMAC Universities Osteoarthritis Index is a specific questionnaire for OA of the knee and hip which contains 24 items concerning pain, stiffness, and physical function. The Likert version of this questionnaire (WOMAC LK 3.0), transculturally adapted to Spanish people, was used in this study. Each item is scored from 0 (none) to 4 (extreme). The total WOMAC score was calculated by the most common approach, the simple summation of the 24 component item scores. Although the validity of this overall score has not been completely established, this score has been reported in several trials and we included it here among the secondary efficacy variables.

The SF-36 is a generic health status questionnaire that comprises 36 items which are summed and transformed according to standard algorithms in order to obtain a final score from 0 (poor health) to 100 (good health).

SAFETY AND TOLERABILITY

Safety and tolerability were based on history, physical exam, laboratory testing, at baseline and end of trial, and reporting of adverse events. Number of patients with adverse events, and number of patients withdrawn due to adverse events were the primary outcomes of tolerability. Type and severity of adverse events were also evaluated. Adverse events were rated by the patients as mild, moderate, or severe. The investigators determined whether adverse events were possibly related, related or not related to the study medication.

STATISTICAL ANALYSIS

We calculated the sample size required to detect a mean difference of 12 mm for severity of pain on VAS between patients treated with aceclofenac and paracetamol, with an estimated standard deviation of 22, an alpha level of 0.05 (two-tailed), and a power of 90%. With these assumptions and estimating a dropout rate of 15%, we obtained a final sample size of at least 80 patients per treatment group.

The following clinical assessments were considered, a priori, as primary efficacy measures: (1) severity of pain (VAS), (2) Lequesne OA knee index, (3) patient’s global assessment of disease activity, and (4) physician’s global assessment of disease activity. Efficacy was assessed with an intention-to-treat analysis; the safety population included all patients who were randomized and who received at least one dose of study medication. Thus, the same population was used for both efficacy and safety analyses. For those patients who withdrew for any reason before the end of the trial, the baseline observations were carried forward.

Categorical data were compared by the chi-square, Mantel–Haenszel, or Fisher’s exact test. Continuous variables were evaluated using the unpaired t test or, for within-group comparisons (i.e., final vs baseline values), the paired t test. Between-group comparisons of the relative change from baseline were performed with one-way analyses of variance. Treatment differences for efficacy variables are presented as mean with 95% confidence interval.

Patient’s and physician’s global assessment of the clinical efficacy of aceclofenac and paracetamol at the end of the trial was compared with the Cochran-Armitage trend test. Primary efficacy analyses were also adjusted for multiple comparisons with the Hochberg step-up procedure. All tests of significance were two-sided, and a P value < 0.05 was considered to be significant. Statistical analyses were performed using SAS (SAS Institute, Cary, NC).

RESULTS

STUDY PATIENTS

A total of 169 patients were randomized in this study (Fig. 1). After the exclusion of one patient, who never took the study medication, valid data for efficacy and safety intention-to-treat analyses was available for 168 patients (86 on paracetamol, 82 on aceclofenac). Demographic, disease characteristics, and clinical assessments at the start of the trial were similar between both treatment groups (Tables II and III). The only exception was a higher diastolic blood pressure in the aceclofenac group (P = 0.031). About 75% of all subjects were overweight (median BMI, 31 kg/m² [interquartile range, 28 to 33 kg/m²]).

WITHDRAWAL FROM THE STUDY

More patients withdrew in the paracetamol group compared with the aceclofenac group (17/86 [19.8%] vs 5/82 [6.1%], P = 0.011, for paracetamol vs aceclofenac, respectively) (Fig. 1). The main reasons included lack of efficacy (n = 8 vs n = 1; P = 0.035, for paracetamol and aceclofenac, respectively) and adverse events (n = 4 in each group). Five patients, all in the paracetamol group, withdrew for reasons unrelated to study medication (personal reasons, n = 3; lost to follow-up, n = 1; and protocol violation, n = 1).

COMPLIANCE

There was no difference between the two groups in the number of tablets or sachets taken during the study. Patients took a mean [median; interquartile range] of 76% [94%; 63–98] of the prescribed active sachets and 79% [95% confidence interval (CI); 85–98] of the placebo sachets (P = 0.55), compared with 76% [95% CI; 64–99] of the prescribed placebo tablets and 79% [95% CI; 75–99] of the active tablets (P = 0.57).

EFFICACY

Primary efficacy variables

Changes in clinical efficacy assessments at the end of the trial are shown in Table III. After 6 weeks, patients with symptomatic knee OA who received aceclofenac (200 mg/day) had significantly greater improvement than patients treated with paracetamol (3000 mg/day) in all primary efficacy measures (VAS, mean treatment difference, 7.64 mm [95% CI, 0.44–14.85 mm], P = 0.037), Lequesne OA index (mean treatment difference, 1.41 [95% CI, 0.45–2.36], P = 0.004), and patient’s (mean treatment difference, 0.33 [95% CI, 0.06–0.61], P = 0.017) and physician’s (mean treatment difference, 0.23 [95% CI, 0.01–0.47], P = 0.041) global assessments. These differences remained significant (P < 0.05) after controlling for multiple comparisons with the Hochberg step-up procedure.
Furthermore, although both treatment groups demonstrated significant clinical improvement from their baseline values at end of trial, the percent improvement in patients treated with acetylsalicylic acid was almost double that of patients treated with paracetamol (21% vs 9%), patient’s global assessment (26% vs 17%), Lequesne OA index (21% vs 9%), physician’s global assessment (20% vs 13%). At the end of the trial, both patient’s and physician’s global assessments of the clinical efficacy of the treatment were generally more favourable for acetylsalicylic acid. None of the remaining secondary efficacy variables, including the eight domains of the SF-36 questionnaire, were significantly different between the acetylsalicylic acid and paracetamol treatment groups.

**Safety and tolerability**

Both paracetamol and acetylsalicylic acid were well tolerated, and the incidence of patients reporting adverse events did not show any improvement in the duration of morning stiffness, and the HAQ disability score (P > 0.05). Total WOMAC (mean treatment difference, 4.28 [95% CI, 0.75–7.82], P = 0.018), WOMAC physical function (mean treatment difference, 3.14 [95% CI, 0.66–5.61], P = 0.013), full HAQ (mean treatment difference, 0.11 [95% CI, 0.01–0.22], P = 0.031), and lower extremities HAQ (mean treatment difference, 0.15 [95% CI, 0.01–0.29], P = 0.037) showed mean treatment effects in favour of acetylsalicylic acid. None of the remaining secondary efficacy variables, including the eight domains of the SF-36 questionnaire, were significantly different between the acetylsalicylic acid and paracetamol treatment groups.

### Table II

*Patient’s characteristics at the start of the trial*  

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol, 3000 mg/day (n = 86)</th>
<th>Acetylsalicylic acid, 200 mg/day (n = 82)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year, mean ± SD</td>
<td>62.5 ± 6.8</td>
<td>62.2 ± 6.7</td>
<td>0.752</td>
</tr>
<tr>
<td>Female (%)</td>
<td>73 (85)</td>
<td>67 (82)</td>
<td>0.581</td>
</tr>
<tr>
<td>Education level, year, mean ± SD</td>
<td>5.6 ± 3.8</td>
<td>5.4 ± 3.9</td>
<td>0.709</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>30.5 ± 2.8</td>
<td>30.9 ± 3.7</td>
<td>0.457</td>
</tr>
<tr>
<td>Duration of OA, symptomatic, selected knee, year, mean ± SD</td>
<td>8.5 ± 6.5</td>
<td>8.4 ± 6.4</td>
<td>0.914</td>
</tr>
<tr>
<td>ACR functional class (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>32 (37.2)</td>
<td>31 (37.8)</td>
<td>0.466</td>
</tr>
<tr>
<td>II</td>
<td>34 (39.5)</td>
<td>24 (29.3)</td>
<td>0.232</td>
</tr>
<tr>
<td>III</td>
<td>20 (23.3)</td>
<td>27 (32.9)</td>
<td>0.598</td>
</tr>
<tr>
<td>Radiological Classification, selected knee (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>29 (33.7)</td>
<td>35 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>57 (66.3)</td>
<td>47 (57.3)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.7 ± 15.0</td>
<td>75.4 ± 14.7</td>
<td>0.321</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>147.2 ± 21.1</td>
<td>150.5 ± 21.6</td>
<td>0.032</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84.6 ± 10.5</td>
<td>88.0 ± 9.9</td>
<td></td>
</tr>
</tbody>
</table>

*Between-group comparisons were analyzed with unpaired t test.
†Chi-square.
‡Mantel–Haenszel test.

### Table III

*Intention-to-treat analysis for primary efficacy measures at baseline, changes at 6 weeks, and treatment effect for all study patients, by treatment group (mean ± SD)*  

<table>
<thead>
<tr>
<th></th>
<th>Baseline*</th>
<th>Change at 6 weeks (within-group comparisons)</th>
<th>Treatment difference (between-group comparisons)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol, 3000 mg/day (n = 86)</td>
<td>Acetylsalicylic acid, 200 mg/day (n = 82)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Pain, VAS, 0–100</td>
<td>62.40 ± 16.97</td>
<td>62.19 ± 20.09</td>
<td>−10.70 ± 22.31</td>
</tr>
<tr>
<td>Lequesne index, 0–24</td>
<td>11.11 ± 3.24</td>
<td>11.15 ± 3.75</td>
<td>-0.97 ± 3.11</td>
</tr>
<tr>
<td>Patient global assessment, Likert scale, 1–5</td>
<td>2.48 ± 0.66</td>
<td>2.55 ± 0.77</td>
<td>-0.33 ± 0.85</td>
</tr>
<tr>
<td>Physician global assessment, Likert scale, 1–5</td>
<td>3.17 ± 0.62</td>
<td>3.23 ± 0.81</td>
<td>-0.40 ± 0.69</td>
</tr>
</tbody>
</table>

*At baseline all between-group differences were not significant at P = 0.05; unpaired t test.
†Positive changes favour acetylsalicylic acid, P values from ANOVA.
‡P < 0.001 vs baseline.
§P < 0.01 vs baseline.
Altogether, four patients in each treatment group were withdrawn owing to an adverse event. Among the patients treated with paracetamol, adverse events that led to early discontinuation were as follows: rash (n = 2), abdominal distension with meteorism (n = 1), and epigastralgia associated with myalgia (n = 1). Among the patients who received acelofoxacin, adverse events that led to withdrawal were as follows: epigastric pain (n = 2), abdominal distension with meteorism (n = 1), and an allergic reaction with urticaria (n = 1).

Discussion

This study shows that patients with symptomatic OA of the knee treated for a period of six weeks with acelofoxacin, 200 mg/day, had a significantly greater improvement than patients treated with paracetamol, 3000 mg/day, for four primary endpoints covering pain, function and overall assessment. There were also significant improvements in favour of acelofoxacin on several health-related quality of life measures, including WOMAC functional capacity (P = 0.013), total WOMAC score (P = 0.018), full HAQ (P = 0.031), and lower-extremity HAQ (P = 0.037). These results are consistent with the findings of three recently published trials indicating superior efficacy of NSAIDs (ro fecoxib, 25 mg/day; celecoxib, 200 mg/day; and diclofenac 150 mg/day + misoprotol 400 μg/day), compared with paracetamol 4000 mg/day.

Moreover, although both groups realized significant improvements compared with their baseline values, the percent improvement in the four primary efficacy variables for patients treated with acelofoxacin was greater than with paracetamol, in some cases twice as large (e.g., patients’ global assessment, 26% vs 13%; Lequesne OA index, 21% vs 9%). In addition, more patients in the paracetamol

Table IV

<table>
<thead>
<tr>
<th>Patient’s and physician’s global assessment of the clinical efficacy of the treatment at the end of the trial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient*</td>
</tr>
<tr>
<td>Paracetamol, 3000 mg/day (n = 86)</td>
</tr>
<tr>
<td>A lot better</td>
</tr>
<tr>
<td>Fairly better</td>
</tr>
<tr>
<td>Little better</td>
</tr>
<tr>
<td>Same</td>
</tr>
<tr>
<td>Little worse</td>
</tr>
<tr>
<td>Fairly worst</td>
</tr>
<tr>
<td>A lot worst</td>
</tr>
<tr>
<td>Not available</td>
</tr>
</tbody>
</table>

*Cochran – Armitage trend test, both patient and physician, P = 0.001, for paracetamol vs acelofoxacin.
group withdrew from the study due to lack of efficacy compared with those receiving aceclofenac (eight vs one patient, P = 0.035), with no difference in the number of patients who discontinued the trial due to adverse events.

Although the absolute magnitude of the observed treatment differences in this study were small, the degree of improvement in each of the four primary endpoints was between 9% and 17% for patients treated with paracetamol, and between 20% and 29% for patients receiving aceclofenac. This degree of improvement is consistent with ranges reported in other clinical trials assessing NSAID for OA of the knee, which often do not exceed 30%.[5] The improvements, in functional capacity with aceclofenac, when assessed by both the HAQ and the WOMAC questionnaires, was also consistent with other studies reporting improvement in function among patients receiving NSAIDs[11,15,16,36]. The patient preference for aceclofenac vs paracetamol was also in agreement with previous reports,[15,42] probably due to a greater satisfaction with the degree of symptomatic relief associated with NSAIDs.

The good safety profile of aceclofenac was consistent with that reported in other studies.[42–46] A case—control study of patients with a primary diagnosis of upper GI bleeding admitted to 10 hospitals in Spain and eight hospitals in Italy, represented 10,734,897 person-years of experience found that the odds ratio of GI bleeding associated with aceclofenac exposure was 1.14% (95% CI 1.06, 3.3), compared to control subjects matched according to age, sex, and centre.[46] Similarly, good results for tolerability were reported in a longitudinal study of patients presenting with haematemeses, melena, or both, in conjunction with an endoscopic diagnosis of upper GI bleeding, and admitted to two Spanish hospitals.[47]

Aceclofenac had the lowest incidence rate of upper GI bleeding among 13 NSAIDs evaluated (1.7 incidents per 1000 person-years treatment). This was in contrast to the highest reported rate of 25.8 incidents per 1000 persons-years treatment for ketorolac.[47] Concerns about the cardiovascular effects of the new COX-2 specific NSAIDs have raised uncertainties about the cardiovascular risk related with more classical NSAIDs, as aceclofenac/diclofenac. This is a short trial, not aimed to detect differences in cardiovascular morbidity/mortality. More studies are needed to weigh the potential cardiovascular and GI risks/benefits of the less COX-2 selective NSAIDs such as aceclofenac.

In this study, unlike previously published trials, the dose of paracetamol used (3000 mg/day) was less than the maximum recommended dose (4000 mg/day). During the planning stages for this trial, European League Against Rheumatism recommendations[48] for the management of OA of the knee had not yet been published and we decided to use the lower (3000 mg/day) recommended dose proposed by the ACR to represent more accurately the situation in daily clinical practice. Although it is possible that a maximum dose of paracetamol (4000 mg/day) could have improved the response in the paracetamol group, results of two large published trials do not support this argument[15,16]. Furthermore, recent reports have suggested an increase of serious GI complications when using paracetamol >2000 mg/day[59,50], although these observations have been questioned[51].

There are some issues related to generalizability of the results of this study. Patients were selected from a population with OA of the knee attended by rheumatologists, and thus may differ from patients who consult primary care physicians. It has been suggested that NSAIDs may be more effective for patients with more severe disease.[15] It would also be inappropriate to generalize the results of this trial for periods longer than 6 weeks. However, for purposes of comparison, it should be noted that most data discussed above are from trials with a duration of between 2 and 12 weeks.

In conclusion, our results provide some additional information to the relatively few data existing comparing NSAIDs with paracetamol in the management of OA. In this 6-week study aceclofenac was superior to paracetamol in pain reduction and functional improvement in symptomatic patients with OA of the knee, with no significant difference in tolerability. Our findings give additional support to the notion that NSAIDs may be more effective than simple analgesics in OA patients, especially when used at short term.

Acknowledgments

The authors thank Dra Merche Pintos, Mrs Anna Román and Mr Ramon Esbri, from Almirall Prodesfarma, for their dedicated collaboration in the study. We acknowledge Dr Cristina Alcañiz and Dr Joaquim Esteve for their contribution. We are also grateful to the patients who participated and thereby made this clinical trial possible.

References


