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Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial[1,2]

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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.

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[1].

Paracetamol has been recommended as the initial therapy for the treatment of pain in knee OA, primarily due to

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its low risk and cost[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[3–5]. 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[6]. In this trial, paracetamol was judged no more efficacious than placebo at 2 ($P = 0.92$) and 12 ($P = 0.19$) weeks. Diclofenac provided 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 ($P = 0.25$)[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)[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 periods in both studies. A pooled estimate of these trials found that paracetamol was more effective than placebo for pain relief in OA[8,9]. Although a third trial was not able to detect any difference between paracetamol and placebo in the treatment of OA knee flares[10], its findings have been questioned[9].

The remaining published studies assessing the efficacy of paracetamol in OA have involved active comparators, i.e., NSAIDs[4,5]. Bradley *et al.*[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[12,13].

Williams *et al.*[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[4], including both trials[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.*[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[15].

Finally, Geba *et al.*[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 rofecoxib 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[8,17].

The debate about when to use paracetamol and when to use NSAIDs in patients with OA has been ongoing for at least 20 years[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[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[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[20]. Additional concerns have been raised about the cardiovascular safety related to the more classical non-selective NSAIDs[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[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[24]. Controlled clinical trials have

Table I
Controlled clinical trials comparing paracetamol and NSAIDs in knee OA

Authors	Joint	Design	Treatment arms, *n* (mg/day)	Trial duration
Bradley, 1991[11]	Knee	Parallel	Paracetamol; Ibuprofen; Ibuprofen; 61(4000); 62(1200); 62(2400)	4 weeks
Williams, 1993[14]	Knee	Parallel	Paracetamol; Naproxen; 88(2600); 90(750)	2 years
Pincus, 2001[15]	Knee (78%), hip (22%)	Crossover	Paracetamol; Diclofenac; 180(4000 mg); 180(150 mg)	6 weeks
Geba, 2002[16]	Knee	Parallel	Paracetamol; Celecoxib; Rofecoxib; Rofecoxib; 94(4000); 97(200); 96(12.5); 95(25)	6 weeks
Case, 2003[6]	Knee	Parallel	Paracetamol; Diclofenac; Placebo; 29(4000); 25(150); 28(−)	12 weeks
Pincus, 2004[7] (PACES)	Knee (85%), hip (15%)	Crossover	Paracetamol; Celecoxib; Placebo; 114(4000); 121(200); 115(−)	6 weeks