REGIONAL DRUG AND THERAPEUTICS CENTRE
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RAPID APPRAISAL

Name of Trial: Patient preferences for placebo, acetaminophen (paracetamol) or celecoxib efficacy studies (PACES): two randomised, double blind, placebo-controlled, crossover, clinical trials in patients with knee or hip osteoarthritis.

Reference: Ann Rheum Dis 2004;63:931-39

Question: Which is more effective for the management of osteoarthritis, celecoxib or paracetamol and how do they compare with placebo? Which treatment do patients prefer?

Did the study ask a clearly focussed question?

Yes. This paper reports on two separate manufacturer (Pfizer) sponsored trials, PACES-a and PACES-b, both of which investigated the effectiveness of celecoxib, paracetamol and placebo in the treatment of osteoarthritis (OA) and which treatment patients preferred.[1] The primary endpoints for efficacy were assessed by two separate validated measures: total Western Ontario McMaster (WOMAC™) OA Index score and pain score via 100 mm visual analogue scale (VAS).[2] Patient preference was assessed using a general questionnaire.

Inclusion criteria for both trials were aged ≥45yrs, radiographic Kellergren-Lawrence grade 2-4, pain VAS 40-90 mm and the patient was a candidate for a long-term Cox II inhibitor or other analgesic.
Exclusion criteria included significant medical co-morbidities, rheumatoid or inflammatory arthritis, acute joint trauma, corticosteroids within 2 months, or intra-articular hyaluronic acid injections within 9 months.

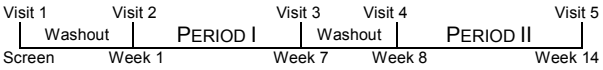

fig 1

After a 3 to 7 day wash out phase, patients were randomised to one of six treatment groups (tables 1 and 2) and given celecoxib 200 mg daily, paracetamol 1000 mg four times daily or placebo for 6 weeks (period I). Following a second wash out phase, patients were crossed over to one of the other two agents and treated for a further six weeks (period II). A weighting of approximately 2:1 was given to the active treatment arms.

Table 1: PACES-a (n randomised = 524)

Period I	n entering period I	Period II	n entering period II
Placebo	55	Paracetamol	39
	106	Celecoxib	81
Paracetamol	105	Celecoxib	85
	54	Placebo	42
Celecoxib	59	Placebo	49
	116	Paracetamol	86

Was the study design appropriate?

Yes. PACES-a and -b had identical study designs; both were multicentre, two-period, double blind, double dummy, crossover trials.

Table 2: PACES-b (n randomised = 556)

Period II	n entering period I	Period II	n entering period II
Placebo	58	Paracetamol	47
	111	Celecoxib	88
Paracetamol	117	Celecoxib	95
	57	Placebo	39
Celecoxib	61	Placebo	49
	124	Paracetamol	98

This type of trial is vulnerable to carry-over effects (which were tested for and not found to be significant) and order effects, seen in that the baseline VAS pain scores were uniformly lower for period II compared with period I. However, this potential bias was adjusted for in the analysis of covariance.[3] It could be argued that paracetamol is not an appropriate comparator in a population in whom 70% were already receiving NSAIDs.

Were participants appropriately allocated to intervention and control groups?

Yes. The trial was randomised from baseline, although the randomisation method was not specified. Baseline characteristics of the groups showed no statistically significant differences, with the exception of the WOMAC score in PACES-a (p=0.031). The paracetamol-celecoxib group had the 'worst' WOMAC score and the celecoxib-placebo group had the 'best' score. This result may also adversely affect the primary end point.

Were participants, staff and study personnel 'blind' to participants study group?

Yes. The trials were double blind, double dummy studies. Mean pain VAS scores were relatively uniform at baseline and no visits were scheduled during the 6-week treatment periods (unless a patient withdrew from the study) reducing the possibility of investigator un-blinding.

Were all of the participants who entered into the trial accounted for at its conclusion?

No. The study tells us that only 73% of patients in PACES-a and 74% of PACES-b completed the study. Dropout rates were ranged relatively evenly across the groups from 2% to 7% in period I and from 23% to 29% in period II, with the exception of the paracetamol groups in period II where the dropout rate was 8%. No information on the

reasons for patients leaving the study is provided or why so many dropped out in period II. It is stated that the results were analysed by the intention-to-treat principle, except for the patient preference results, which are analysed only for those with complete data for both periods.

Were the participants in all groups followed up and data collected in the same way?

Yes. Patients were assessed in person by study investigators with the appropriate questionnaires on five separate visits over a total of 14 weeks. (*fig.1, page 1*) All patients took part in the efficacy assessments at visit 3 and/or 5. Patients unable to complete a treatment period were given the appropriate efficacy assessment (visit 3 or 5) at the point of drop out. Patients dropping out of period I were offered enrolment into period II.

Was the study large enough?

Probably. For both PACES-a and PACES-b, at least 150 patients would be required in each of the three treatment groups to have at least 90% power, at the 0.05 significance level, for treatment comparisons of the total WOMAC score and the 100 mm VAS for pain during period I.
The paired patient preference comparison would have a power of at least 90% at the 0.05 significance level with at least 100 patients for each of the two sequences for paracetamol before/after celecoxib.
However it is not stated for either test how big a difference would be detected.

How are the results presented and what is the main result?

WOMAC™ SCORES
In PACES-a period I, only differences between celecoxib/placebo were significant (p=0.002) whilst, the differences between celecoxib /paracetamol (p=0.18) and paracetamol/placebo (p=0.08) were not significant. The differences between celecoxib/placebo (p<0.007) and celecoxib/paracetamol (p<0.009) only became significant in period II or when both periods were combined. However, paracetamol/placebo remained non-significant throughout (p=0.08 to 0.60).
In PACES-b period I, the differences between celecoxib/placebo, celecoxib/paracetamol and paracetamol/placebo were all significant (p<0.001 to p=0.027). Significant differences were also seen in all groups across period II and both periods combined except for paracetamol/placebo in period II (p=0.39). Percentage improvements from baseline averaged over all four treatment periods in both trials were 21.6% for celecoxib, 13.0% for paracetamol and 7.9% for placebo.
The minimum clinically important difference in hip and knee OA for the total WOMAC score (on 100 mm VAS) has been shown to be 9.5-10 mm.[4] Applied here, the only total WOMAC scores to achieve this magnitude were celecoxib therapy in PACES-a, period I and PACES-b, periods I & II. However, the important measure is the number of patients reaching this clinically important difference rather than the mean size of the score as presented in this paper. Individual results are not reported.

PAIN VISUAL ANALOGUE SCALE SCORES (100MM)
Pain VAS scores are not presented in full here but were similar to the WOMAC results.[1]

The minimum clinically important difference using the 100 mm pain VAS score in hip OA and knee OA has been shown to be around 17 mm and 28 mm respectively.[4] In this paper hip and knee results were pooled, but no mean changes in VAS for pain reached 28 mm and only 3 results were >17 mm: celecoxib, period I in PACES-a &-b and paracetamol, period I in PACES-a. Again what we are really interested in is the actual number of patients achieving a clinically significant improvement, rather than the mean overall result.

PAIRED PATIENT PREFERENCE
Of the 173 patients in PACES-a who received celecoxib and paracetamol and completed both periods, 52.6% preferred celecoxib, 24.3% preferred paracetamol and 23.1% reported no preference. Odds ratios were 2.07 for preference of celecoxib vs. paracetamol (p<0.001), 2.51 for celecoxib vs. placebo (p<0.001) and 1.21 for paracetamol vs. placebo (p=0.34).
In PACES-b, of the 192 patients who received celecoxib and paracetamol and completed both periods, 49.5% preferred celecoxib, 32.3% preferred paracetamol and 18.3% reported no preference. Odds ratios were 1.47 for preference of celecoxib vs. paracetamol (p=0.009), 2.47 for celecoxib vs. placebo (p<0.001) and 1.68 for paracetamol vs. placebo (p=0.007).

Rescue medication was used by less than 5% of participants.

How safe were the regimens?

Adverse events were reported by 23-29% of patients in the three groups. No statistically significant differences were seen between the groups for gastrointestinal (GI) events or any other adverse events.
In PACES-a 8 adverse events were classed as serious. Of these, one instance each of intestinal obstruction and raised liver enzymes were thought to be related to the study drug, celecoxib. In PACES-b, there were 4 serious adverse events but all were considered unrelated to the study drug.
However, this study was not powered to detect GI or cardiovascular (CV) events and the short duration of celecoxib treatment would be unlikely to show these relatively uncommon adverse effects.[5] The European Agency for the Evaluation of Medicinal Products recently reviewed the safety data for Cox-II inhibitors,[6] resulting in the amendment of the summary of product characteristics (SPC) to reflect the GI, CV and

hypersensitivity reaction risks associated with celecoxib.

How precise are the results?

The inter-group comparisons for period I appear to be robust although no confidence intervals are presented. However, the statistics appear to be overly complex and it is not clear why methods for multiple comparisons differed between PACES-a and PACES-b.

Can the results be applied to the local population?

This study is unlikely to be helpful in providing solutions for a local population for the following reasons. It is not clear whether the patients were recruited from primary or secondary care. The patients in these trials were likely to have had moderately severe disease, reflected by their baseline pain, WOMAC and radiographic scores.[3] The average duration of disease was 8-10 yrs. Around 70% of the randomised patients in both trials had previously been taking NSAIDs for treatment of OA (thus presumably would have already tried paracetamol). No indication is given as to whether patients were included due to a 'flare' or increase in symptoms but mean pain scores post-washout suggest prior benefit from these analgesics. It is also not clear if the results differed between patients previously on NSAIDs and those not and between patients with OA of the hip or of the Knee.

On first presentation of OA, PRODIGY guidance currently recommends that paracetamol should be considered for first line use in pain relief.[7] The evidence presented by the PACES trials does not justify changing paracetamol as a first line agent. Most OA is seen in the elderly population and a significant proportion will present with co-morbidities, some of which will contra-indicate the use of NSAIDs or Cox II inhibitors. Current NICE guidance recommends that if an anti-inflammatory is required for OA then standard NSAIDs should be used except when clearly indicated in patients who may be at high-risk of developing serious GI adverse effects.[8]
The study did not include standard NSAIDs and therefore provides no evidence to use Cox-II inhibitors before standard NSAIDs on efficacy grounds.

Is celecoxib or paracetamol more efficacious in osteoarthritis compared with placebo and which do patients prefer?

In the PACES trials most, but not all, inter-group analyses showed that celecoxib was more effective than paracetamol in the treatment of OA and was more often preferred by patients. Celecoxib and paracetamol are more efficacious compared with placebo in this group of patients. A recent meta-analysis also found other NSAIDs to be more efficacious than paracetamol in the treatment of OA.[9]

In conclusion, although this study demonstrates that celecoxib is marginally more effective than paracetamol, there is not sufficient evidence to support changing the initial management of patients with OA. Paracetamol remains first line treatment and where this is unsuccessful, and an NSAID is indicated, this study does not present any evidence to suggest that celecoxib should be used in preference to other NSAIDs on efficacy grounds.

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KEY: RCT - randomised controlled trial, MA-meta analysis, R-review, E-editorial, G-Guidance

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