Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review

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CRD summary
The authors concluded that there was weak evidence for the efficacy of paracetamol in patients with inflammatory arthritis, and insufficient disease-specific safety data to draw conclusions. There were some limitations of the review process (only one reviewer was involved), but the authors’ conclusions appear suitably cautious and reliable.

Authors’ objectives
To assess the efficacy and safety of paracetamol (acetaminophen) in the management of pain in inflammatory arthritis.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to May 2010 for studies published in English, Dutch, French, German or Portuguese; search terms were reported. Abstracts from two conferences (named in paper) were handsearched, and reference lists from retrieved articles were checked for additional relevant studies.

Study selection
Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of adults 18 years of age or older with inflammatory arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and spondyloarthritis) were eligible for inclusion. Trials had to compare the effect of paracetamol with placebo or any other analgesic (alone or in combination) on pain improvement. For the evaluation of safety (measured as adverse events and withdrawals due to adverse events), cohort studies, case-control studies and case series with more than 30 participants were also eligible for inclusion. Studies that included a mixed population were only included if data on participants with inflammatory arthritis were reported separately. Studies published in English, Dutch, German, French and Portuguese were included in the review, but studies without an English abstract were excluded.

Most of the included studies described patients with active rheumatoid arthritis, with the remaining studies providing no details on baseline disease activity. Duration of treatment ranged from six hours to 13 weeks. The dates of publication ranged from 1959 to 1993. Dosages of paracetamol ranged from 650mg/day to 7.5g/day. Almost a third of the studies administered paracetamol in combination with non-steroidal anti-inflammatory drugs (NSAID) such as, indomethacin, naproxen or tolmetin. Comparators included placebo, NSAID, or weak opioids. The studies measured pain in various ways (mean % maximum pain relief, scales, 100mm visual analogue scale).

One reviewer selected the studies for inclusion.

Assessment of study quality
Quality of the included studies was assessed using criteria published by the Cochrane Collaboration which included sequence generation, allocation concealment, blinding, outcome data, intention-to-treat analysis and other sources of risk of bias. One reviewer assessed study quality.

Data extraction
Data on outcomes for efficacy (change in pain rating score) and safety (safety rates and withdrawals due to adverse events) were extracted by one reviewer.

Methods of synthesis
The data were presented in a narrative synthesis.

Results of the review
Thirteen studies were included in the review: ten cross-over RCTs (299 patients), two parallel RCTs (194 patients) and one cohort study (5,692 participants). All included trials were considered to have a high overall risk of bias.
Paracetamol versus placebo (three trials): All three trials demonstrated statistically significant effects in favour of paracetamol for mean pain relief over a six hour period.

Paracetamol versus NSAID (four trials): All four trials indicated a benefit of NSAID over paracetamol for pain relief, but the results were not clearly reported by the trial authors.

Paracetamol versus weak opioids (three trials): None of the trials showed a difference between paracetamol and weak opioids for pain relief.

Paracetamol plus NSAID versus placebo plus NSAID (two trials): One trial that evaluated different dosages of indomethacin (NSAID) and found no difference in mean pain or tolerability between the two different treatment groups. Another trial compared paracetamol plus naproxen versus placebo plus naproxen, and found significantly less pain with the combined treatment, but no difference in tolerability.

There were no significant differences in total adverse events or withdrawals due to adverse events between the treatment arms in eight out of ten of the trials that reported safety data. Among the two remaining trials, findings were mixed (reported fully in paper). The cohort trial found no differences in the incidence of serious gastrointestinal events between patients taking different single analgesics (paracetamol, acetylsalicylic acid or ibuprofen). There was an increased rate of serious gastrointestinal events with paracetamol over acetylsalicylic acid or ibuprofen (when used concurrently with corticosteroids and one of the other analgesics).

Authors' conclusions
There was weak evidence for the efficacy of paracetamol in patients with inflammatory arthritis and insufficient disease-specific safety data to draw conclusions.

CRD commentary
The review question and inclusion criteria were clear. Several databases were searched for studies, but it was not clear if unpublished data were sought, which introduced potential for publication bias. Only one reviewer was involved in selecting papers for inclusion, data extraction and quality assessment which increased the risk of reviewer error and bias. A quality assessment of the included studies was undertaken and considered in the analysis.

Due to the poor quality and heterogeneity across studies, it appeared that a narrative synthesis was appropriate. The authors also described the limitations of the evidence base, including the fact that most of the studies were of a cross-over design (potentially increasing bias due to a carryover effect), the trials were not reflective of current practice, the doses of medication were atypical, and the duration of studies were too short for the treatment of a chronic pain condition.

There were some limitations of the review process (only one reviewer was involved), but the authors' conclusions appear suitably cautious and reliable.

Implications of the review for practice and research
Practice: The authors stated that given the relative paucity of information, any recommendations for the use of paracetamol should include expert opinion and may rely on extrapolation from evidence in other chronic pain conditions.

Research: The authors did not state implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.