The time to onset and overall analgesic efficacy of rofecoxib 50 mg: a meta-analysis of 13 randomized clinical trials


CRD summary
This review aimed to determine the time to onset of pain relief in patients given rofecoxib after wisdom tooth extraction. The authors concluded that 50 mg rofecoxib led to pain relief in approximately 30 minutes. Because of incomplete reporting, the presence of publication bias and other potential sources of bias, the authors' conclusions should be treated with caution.

Authors' objectives
To determine the time of onset of analgesia for rofecoxib based on a patient-level meta-analysis of randomised, placebo-controlled, post-operative oral surgery pain studies.

Searching
MEDLINE was searched from January 1993 to February 2003 using the term 'rofecoxib'. This was supplemented by a search of the manufacturer's (Merck) data on file and by checking the reference lists of retrieved studies.

Study selection
Study designs of evaluations included in the review
Individual patient data from placebo-controlled, double-blind, randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies were included if they evaluated the effects of a single dose of rofecoxib 50 mg. The review compared rofecoxib with placebo. It also assessed non-selective non-steroidal anti-inflammatory drug treatments (NSAIDs; ibuprofen 400 mg and naproxen sodium 550 mg) that were part of the rofecoxib versus placebo studies.

Participants included in the review
Studies of patients experiencing moderate to severe pain after the surgical extraction of at least 2 third molars, at least one of which was a mandibular impaction, were included in the review. The mean age of the patients in the included studies was 21 years, and 60% were female.

Outcomes assessed in the review
To be included in the meta-analysis, studies reporting time to onset of analgesia had to use the two stopwatch method. Time to onset of analgesia, duration of analgesia, overall analgesic efficacy and safety were measured in the included studies. The primary outcome measures in the included studies were total pain relief after 6 and 8 hours (TOPAR6 and TOPAR8, respectively).

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data.
Methods of synthesis
How were the studies combined?
The analysis of time to onset of analgesia and time to use of rescue analgesic medication was performed using the log-rank test and Kaplan-Meier product limit estimates of the median time to event and 95% confidence intervals (CIs). A logistic regression was used to combine studies for the outcomes of analgesic efficacy and incidence of clinical adverse experiences. TOPAR8 scores were analysed using a parametric analysis of variance (ANOVA) model with factors relating to trial, treatment and baseline pain intensity (moderate or severe).

How were differences between studies investigated?
The likelihood ratio test of trial-by-treatment interaction in a Cox proportional hazards model was used to assess heterogeneity of effect in trials measuring time to onset of analgesia and/or time to use of rescue analgesic medication. The logistic regression test of interaction between treatment and trial was used to assess the homogeneity of odds ratios (ORs) across trials of analgesic efficacy. The ANOVA test of interaction between trial and treatment was used to assess homogeneity across TOPAR8 outcomes.

Results of the review
A total of 13 studies were included in the efficacy analysis of rofecoxib versus placebo (n=1,900). Eleven of these were included in the meta-analysis of onset and duration (n=1,703).

Eight of the RCTs also included a non-selective NSAID treatment arm and were included in the analyses of non-selective NSAIDs (n=391).

Onset of efficacy.
Rofecoxib showed a median time to onset of analgesia of 34 minutes (95% CI: 31, 38) compared with over 4 hours for placebo (P<0.001). Six studies of non-selective NSAIDs showed a similar median time to onset of analgesia (30 minutes, 95% CI: 28, 37). Similar values were observed for the median time to perceptible pain relief.

Onset of analgesia was achieved by 77% (range: 64, 88) of rofecoxib patients, 76% (range: 63, 87) of non-selective NSAID patients and 23% (range: 11, 43) of placebo patients. The OR was 10.9 (95% CI: 8.4, 14.2) for rofecoxib versus placebo and 11.5 (95% CI: 7.8, 16.8) non-selective NSAID versus placebo. A similar pattern of results was observed for the achievement of perceptible pain relief.

Duration of analgesia.
Median time to rescue medication was 9 hours 16 minutes (9:16) in placebo patients (95% CI: 6:56, 17:21) versus more than 24 hours for rofecoxib patients (range: 10:22, >24), (P<0.001 for the difference). The results for non-selective NSAIDs were not given.

Overall analgesic efficacy.
The mean TOPAR8 score was 17.4 (95% CI: 16.9, 18) for rofecoxib and 4.4 (95% CI: 3.7, 5.2) for placebo. The difference between groups was significant (P<0.001). The mean TOPAR8 score for non-selective NSAIDs was similar to rofecoxib (15.2, 95% CI: 14.3, 16.1). Similar results were observed for patient global assessment of response to therapy at 24 hours.

Safety.
Significant differences between the groups in terms of drug-related adverse experiences, serious adverse experiences, and discontinuations due to adverse experiences were not observed. Compared with placebo, rofecoxib was associated with significantly less headaches, nausea and vomiting, but significantly more postextraction alveolitis (dry socket). There were no significant differences between non-selective NSAIDs and placebo.
The authors did not report any statistical heterogeneity between the trials for any comparison.

**Authors' conclusions**
The clinical characteristics of rapid onset of analgesia combined with sustained effectiveness of rofecoxib 50 mg supports its utilisation in the treatment of acute pain.

**CRD commentary**
Although this review answered a focused question that was largely supported by relevant inclusion criteria, there were several aspects of the conduct of the review that limit confidence in its conclusions. The validity of the included studies was not assessed, nor was it clear whether more than one reviewer was involved to minimise error and bias at any stage of the review process. Only MEDLINE, the drug manufacturer's database and study references were searched; there was no attempt to identify published or unpublished data from any other sources. This might have introduced publication bias. In fact, upon closer inspection of the included studies, it becomes apparent that many of the studies share authors in common with one another as well as with the review itself. The remaining studies were referred to as 'data on file', with the exception of what appears to be a Food and Drug Administration submission for the study drug. Consequently, it appears that virtually all of the studies included in the meta-analysis were sponsored by the drug manufacturer.

Average values for each treatment arm (rofecoxib, placebo, non-selective NSAIDs) were reported for most outcomes, but direct statistical comparisons were only made between rofecoxib and placebo. The review only included non-selective NSAID data from treatment arms in identified RCTs comparing refecoxib versus placebo, and this raises the possibility of selection bias. No statistical comparisons with other NSAIDs were reported.

Because of incomplete reporting, the presence of publication bias and other potential sources of bias, the authors' conclusions should be treated with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that the clinical characteristics of rapid onset of analgesia combined with sustained effectiveness of rofecoxib 50 mg supports its utilisation in the treatment of acute pain.

**Research:** The authors did not state any implications for future research.

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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.