Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics

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Authors' objectives
To assess the safety and effectiveness of oral tramadol.

Searching
The trials were made available by Grunenthal GmbH (Aachen, Germany) and the Robert Wood Johnson Pharmaceutical Research Institute, (Pennsylvania, USA). In addition, the in-house database of Searle UK was searched, as were MEDLINE (from 1960 to 1995) and the Oxford Pain Relief Database (from 1950 to 1995) (see Other Publications of Related Interest no.1). ‘Tramadol’ was used as a free text term.

Study selection

Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs). In practice, all the included studies were double-blind, single-dose RCTs. Randomisation in all studies was by computer-generated code stratified for pre-treatment pain intensity.

Specific interventions included in the review
Studies of single oral doses of tramadol were eligible for inclusion in the review. In the included studies, tramadol (50, 75, 100 or 150 mg) was compared with placebo, codeine, aspirin (650 mg) plus codeine (60 mg) combined, or acetaminophen (paracetamol; 650 mg) plus propoxyphene (100 mg) combined.

Participants included in the review
Studies of patients with acute painful conditions were eligible for inclusion in the review. The patients had to have moderate or severe pain and their condition had to be appropriate for management with a centrally acting analgesic and acetaminophen. All the studies included in the review were of patients aged 18 to 70 years, who were suffering post-operative pain or pain following dental extraction.

Outcomes assessed in the review
Only studies that had data from categorical pain relief scales, which allowed the percentage of maximum pain relief obtained by individual patients to be calculated, were included in the review. Adverse events volunteered by the patient were recorded, regardless of any rescue medication used.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, although it appears that they looked for studies that had been conducted to the same high standard as the ones supplied by the Robert Wood Johnson Pharmaceutical Research Institute. The authors do not state how many of the reviewers performed the selection.

Assessment of study quality
The quality of the RCTs was assessed using the scale of Jadad et al. (see Other Publications of Related Interest no.2). The authors do not report how the accuracy of the data, the integrity of the randomisation or the completeness of the follow-up were assessed. The authors do not state if or how the IPD from each study were checked for validity.

Data extraction
The IPD for the included studies were supplied by Grunenthal GmbH (Aachen, Germany) and the Robert Wood Johnson Pharmaceutical Research Institute (Pennsylvania, USA). The categories of data extracted were identifier, drug
administered, the number of patients in each arm of the study, and results. For each patient, the area under the curve of pain relief (categorical scale) against time was calculated (TOTPAR) for 6 hours after the study drug was given. The percentage of the maximum possible for this summary measure (%maxTOTPAR) was then calculated (see Other Publications of Related Interest no.3).

**Methods of synthesis**

How were the studies combined?
The IPD were combined in a meta-analysis. The number of patients on each treatment who achieved more than 50% of the %maxTOTPAR was determined. The relative risk (RR) with 95% confidence intervals (CIs) were calculated for each individual trial using a fixed-effect model (see Other Publications of Related Interest no.4), and the number-needed-to-treat (NNT) was calculated as described by Cook and Sackett (see Other Publications of Related Interest no.5). The RR and NNT were calculated for both tramadol and the other analgesics, as all the studies compared tramadol with another analgesic as well as with placebo. In addition, significance testing for dose-response of tramadol was performed.

How were differences between studies investigated?
The authors report that the protocols for the included studies were essentially identical. A statistical test for homogeneity in the meta-analysis was not reported. There was a prior hypothesis that the response to analgesic drugs is different post-dental extraction than it is postsurgery. Therefore, it was planned to analyse these conditions separately.

**Results of the review**
A total of 18 studies (n=3,453) were included in the review.

Dental.

Among the dental studies all treatments, except for codeine 60 mg, showed significantly greater pain relief than with placebo. There was a clear dose-response for tramadol.

For tramadol 50 mg, the RR was 2.9 (95% CI: 1.6, 5.2) and the NNT was 9.1 (95% CI: 6.1, 18.8).

For tramadol 75 mg, the RR was 2.7 (95% CI: 1.1, 6.5) and the NNT was 9.1 (95% CI: 5.1, 64.5).

For tramadol 100 mg, the RR was 3.8 (95% CI: 2.4, 5.8) and the NNT was 4.6 (95% CI: 3.6, 6.4).

For tramadol 150 mg, the RR was 4.8 (95% CI: 2.1, 11.1) and the NNT was 4.2 (95% CI: 2.9, 7.3).

For codeine 60 mg, the RR was 1.3 (95% CI: 0.8, 2.1) and the NNT was 50 (95% CI: 16.3, infinity).

For aspirin 650 mg plus codeine 60 mg, the RR was 3.8 (95% CI: 2.2, 6.8) and the NNT was 6.3 (95% CI: 4.5, 9.8).

For acetaminophen 650 mg plus propoxyphene 100 mg, the RR was 4.0 (95% CI: 1.7, 9.4) and the NNT was 5.3 (95% CI: 3.4, 11.4).

Postsurgical.

All treatments showed statistically significantly superior analgesia compared with placebo. There was a clear dose-response for tramadol.

For tramadol 50 mg, the RR was 2.4 (95% CI: 1.4, 4.4) and the NNT was 7.1 (95% CI: 4.6, 17.9).

For tramadol 75 mg, the RR was 2.4 (95% CI: 1.7, 3.5) and the NNT was 4.5 (95% CI: 3.1, 7.0).

For tramadol 100 mg, the RR was 3.2 (95% CI: 1.8, 5.6) and the NNT was 4.8 (95% CI: 3.4, 8.2).

For tramadol 150 mg, the RR was 3.5 (95% CI: 2.5, 4.9) and the NNT was 2.4 (95% CI: 2.0, 3.1).
For codeine 60 mg, the RR was 1.9 (95% CI: 1.3, 2.7) and the NNT was 9.1 (95% CI: 6.0, 23.4).

For aspirin 650 mg plus codeine 60 mg, the RR was 5.8 (95% CI: 2.1, 15.9) and the NNT was 3.6 (95% CI: 2.5, 6.3).

For acetaminophen 650 mg plus propoxyphene 100 mg, the RR was 2.7 (95% CI: 1.9, 3.8) and the NNT was 5.3 (95% CI: 3.0, 5.7).

Overall, there was a clear dose-response for tramadol (p<0.0001, Kruskal-Wallis test).

Adverse events. There was also a dose-related effect for adverse effects in dental extraction patients, but not postsurgical patients.

**Authors' conclusions**
Tramadol is an effective analgesic in post-operative pain. All doses of tramadol were statistically superior to placebo in both surgical and dental pain, and there was a significant dose-response. Single oral doses of tramadol (75 to 150 mg) had analgesic efficacy that was equivalent to combinations of acetaminophen plus propoxyphene and aspirin plus codeine.

**CRD commentary**
This systematic review addressed a relevant question with fairly well-defined inclusion and exclusion criteria. Essentially, however, this review summarised only the studies from a single research programme and, therefore, might have been subject to some undetermined bias. Only two electronic databases were searched, and although one was a specific pain database it is possible that studies might have been missed. The details of the review methodology were not well reported in the review. The methods were not as rigorous as would be expected from a meta-analysis of IPD, for example, the authors took data from summary reports rather than rigorously checking and reanalysing the data. There was no mention of contacting the primary study investigators with regard to queries. The details of the individual studies were adequately presented, albeit briefly. The pooling of the tramadol data was appropriate, although homogeneity was assumed rather than confirmed. The calculation of the RRs and NNTs for drugs other than tramadol is questionable, as the search for studies of other drugs was not systematic or even wide ranging, and only very limited data for these other analgesics were included in this review.

The authors' conclusions regarding the efficacy of tramadol relative to placebo are fully supported by the findings of this review. However, the use of calculated RRs and NNTs to compare the efficacy of tramadol with that of standard analgesics constitutes an indirect comparison and should, therefore, be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors state that 'Tramadol is an effective analgesic in postoperative pain'.

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

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