Rofecoxib for dysmenorrhoea: meta-analysis using individual patient data

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CRD summary

This review used individual patient data to investigate the efficacy and safety of rofecoxib in treating pain caused by dysmenorrhoea. It concluded that a single dose of rofecoxib 50 mg is as effective as a single dose of naproxen sodium 550 mg in controlling pain, and it causes few adverse effects. The small number of trials and lack of individual trial results make it difficult to verify these conclusions.

Authors' objectives

To conduct an individual patient data (IPD) meta-analysis to determine the efficacy and duration of analgesic activity of single-dose rofecoxib in the treatment of dysmenorrhoea, and to evaluate any adverse effects.

Searching

Data were provided by Merck Research Laboratories, and all relevant studies completed by July 2002 were made available to the researchers. PubMed was also searched up to January 2004 to identify other studies.

Study selection

Study designs of evaluations included in the review

Double-blind, randomised controlled trials were eligible for inclusion.

Specific interventions included in the review

Studies comparing oral rofecoxib with placebo, which provided efficacy data for single-dose treatment, were eligible for inclusion. The included studies evaluated: single-dose rofecoxib at 25 or 50 mg; multiple-dose rofecoxib at 50 mg as required, or 50 mg followed by 25 mg daily as required; ibuprofen 400 mg; and naproxen sodium 550 mg every 12 hours.

Participants included in the review

The included studies involved women with moderate to severe pain due to dysmenorrhoea. The mean age of the women was 31 years. Sixty-six per cent of women suffered moderate pain at baseline and 34% suffered severe pain. The women were assessed over three or four menstrual cycles.

Outcomes assessed in the review

The outcomes available in the original trials were pain relief, pain intensity, time to remedication (use of rescue analgesic), and adverse effects.

How were decisions on the relevance of primary studies made?

Studies were obtained through contact with the manufacturer of rofecoxib (Merck).

Assessment of study quality

It was not reported whether any attempts were made to check the accuracy of data included in the IPD meta-analysis; instead, the authors used the original trial reports to assess trial quality. Each trial was assigned a score of between 0 and 5 according to the Jadad scale (a 5-point scale covering randomisation, blinding and loss to follow-up). An additional 16-point validity scale was also used to assess quality. Eligible studies were identified using the Jadad score, where studies had to score a minimum of 2 points (one each for randomisation and blinding). One study was excluded as it had an open design.

Data extraction

Pain intensity and relief were measured with 4- or 5-point categorical scales, respectively, ranging from zero (none) to 3 or 4 (the maximum). The patients were assessed at baseline, then hourly for 8 hours, and again at 12 hours. The proportion of patients with at least 50% pain relief was derived at 6, 8 and 12 hours. Use of rescue medication was derived as the proportion of patients remedicating at 6, 8 and 12 hours after the initial dose.

Methods of synthesis

How were the studies combined?

Pooled relative risks (RRs) were calculated using a fixed-effect model. Analyses were conducted on an intention-to-treat basis. The number-needed-to-treat (NNT) was calculated from the pooled results. Mean adverse event rates were also calculated, weighted by the size of the treatment group.

How were differences between studies investigated?

Differences between the studies were assessed graphically.

Results of the review

Three trials (n=231), of which two were crossover trials (n=182) and one was a parallel-group trial (n=49), were included.

All three trials were of a high quality and scored a maximum of 5 on the Jadad scale and more than 13 on the 16-point scale.

All the active analgesics were significantly more effective than placebo, with more patients experiencing at least 50% pain relief. The RR for improvement in pain after 6 hours was 1.5 (95% CI: 1.1, 2; based on 303 patients) for rofecoxib 25 mg, 2 (95% CI: 1.6, 2.5; based on 451 patients)for rofecoxib 50 mg, 3 (95% CI: 1.7, 5.4; based on 96 patients) for ibuprofen, and 2 (95% CI: 1.6, 2.5; based on 359 patients) for naproxen sodium. The corresponding NNTs were 5 (95% CI: 3.7, 7.8), 3.2 (95% CI: 2.4, 4.5), 2.4 (95% CI: 1.7, 4.2) and 3.1 (95% CI: 2.4, 4.4), respectively. The results were similar for pain relief after 8 and 12 hours.

The proportions of patients remedicating within 12 hours of the first dose were 29% (rofecoxib 25 mg), 28% (rofecoxib 50 mg), 29% (naproxen sodium), 41% (ibuprofen) and 50% (placebo).

Few adverse events were reported. Those reported were mostly nausea and somnolence, and none were serious. In the single-dose trial, the proportions of patients reporting an adverse event were 10% with rofecoxib 25 mg, 8% with rofecoxib 50 mg, 12% with ibuprofen, and 6% with placebo. For the two multiple-dose trials, these proportions were 23% (rofecoxib 25 mg), 24% (naproxen sodium) and 18% (placebo).

Authors' conclusions

Based on information from three trials, a single dose of rofecoxib 50 mg is as effective as a single dose of naproxen sodium 550 mg in controlling the pain associated with dysmenorrhoea, and it causes relatively few adverse effects.

CRD commentary

This review had a clear objective, and clear inclusion criteria with respect to study design and treatments. It was funded by Merck, the manufacturers of rofecoxib, who also provided the raw data. Efforts to locate other relevant studies were limited to searching one database, so it is possible that other studies (published or unpublished) might have been missed. Trial inclusion was based on the Jadad quality score, although it was not reported how many reviewers assessed inclusion. One trial was excluded and the reason for this was reported. The authors did not state if they undertook any additional checking to determine the validity of the raw data.

The results of the individual trials or of the graphical assessment of heterogeneity were not presented, therefore it is not possible to judge the appropriateness of the meta-analysis methods. Details of how the outcome of at least 50% pain relief was derived from the categorical pain scale data were also not provided, which makes it difficult to assess the rationale behind its choice as the main pain outcome. The authors' conclusion, that single doses of rofecoxib and

naproxen sodium have similar efficacy for pain relief, seems overstated given that the results presented are for comparisons with placebo and the results of the two trials that directly compared these two drugs were not presented.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future trials should examine a range of short-term analgesics and longer outcomes such as interference with daily living or absence from work or school. Future individual patient analyses of trials should be able to examine the efficacy of analgesics in women with heavy menstrual loss or women who used combined oral contraceptive pills.

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