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Research article

Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review

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Abstract

Background: Rofecoxib is a cyclo-oxygenase 2 selective inhibitor. This systematic review of rofecoxib in acute pain examined studies in adults of analgesic efficacy over six hours, the amount and quality of the evidence on extended duration of analgesia, and the quality and quantity of evidence on adverse events.

Methods: Cochrane Library (issue 4, 2001), Biological Abstracts (March 2002), MEDLINE (March 2002) and PubMed (March 2002) were searched using rofecoxib as a free text term. The area under the pain relief versus time curve was dichotomized using validated equations to derive the proportion of patients on rofecoxib 50 mg or placebo with at least 50% pain relief over six hours. This was used to calculate the number needed to treat for at least 50% pain relief over six hours for rofecoxib compared with placebo. Information on duration of analgesia and adverse events was also collected.

Results: Five included trials investigated 1,118 patients, of whom 211 received placebo and 464 received rofecoxib 50 mg. The NNT for rofecoxib 50 mg was 2.3 (95% confidence interval 2.0 to 2.6). The weighted mean remedication time was 1.9 hours for placebo (126 patients), 7.4 hours for ibuprofen 400 mg (97 patients) and 13.6 hours for rofecoxib 50 mg (322 patients).

Conclusion: Rofecoxib at 2–4 times the standard daily dose for chronic pain is an effective single dose oral analgesic in acute pain. Limitations in trial reporting constrain conclusions about longer duration of analgesia and adverse event profile.

Background

Acute pain has been studied in single dose designs first proposed by Beecher and colleagues [1,2] and formalized by Houde and Wallenstein [3]. The problem with single trials is that while they can demonstrate statistical superiority of analgesic over placebo, variation because of random chance means that, if small, they provide a poor estimate of the size of the analgesic effect [4]. Combining results from clinically homogeneous trials in a meta-analysis gives an accurate estimate of the extent of the analgesic effect when sufficient numbers of patients have been randomized [4,5].

Clinical trials in acute pain normally last four to six hours, because that is the duration of effect for most analgesics, whether injected or as tablets, and for simple analgesics, NSAIDs or opioids. Meta-analysis in acute pain has concentrated on the use of the area under the total pain relief

versus time curve (TOTPAR), dichotomized into at least 50% pain relief or not [6]. It is not necessarily the only measure available or the most relevant. The precedent exists at a primary research level for adopting remedication as an outcome. Bullingham and colleagues [7] and Gibb and colleagues [8] explored the measure of re-medication in post-surgical patients subject to multiple dosing. A 'rescue factor' design was refined to demonstrate both analgesic efficacy and assay sensitivity). [9]. Farrar and colleagues [10] extrapolated from re-medication data in an effort to both define and demonstrate analgesic efficacy.

Despite these efforts, time to remedication has never become a standard outcome in analgesic trials. One reason for this might simply be the similarity in duration between commonly used analgesics. For rofecoxib, this might be different. In arthritis 12.5 mg or 25 mg of rofecoxib is given as a single dose once a day to control pain. The acute pain dose of 50 mg is claimed to have prolonged analgesic activity [11].

The purpose of this systematic review and meta-analysis of rofecoxib in acute pain was threefold. First to examine all acute pain studies of analgesic efficacy in adults over six hours for comparison with other analgesics in acute pain. Second to examine the amount and quality of the evidence presented on extended duration of analgesia. Third to examine the quality and quantity of evidence on adverse events.

Methods

QUORUM guidelines were followed [12]. Possible studies for inclusion were sought through searching the Cochrane Library (issue 4, 2001), Biological Abstracts (March 2002), MEDLINE (March 2002) and PubMed (March 2002) using rofecoxib as a free text term. The search strategy used is detailed in Additional File 1. Abstracts were examined for possible inclusion if they were randomized trials conducted in an acute pain setting, used rofecoxib and a placebo or active comparator. Reference lists and review articles were examined for possible additional references, and in-house databases were also searched for papers.

Criteria for inclusion for postoperative pain were: full journal publication, randomized controlled trials which included single dose treatment groups of oral rofecoxib and placebo, double blind design, baseline postoperative pain of moderate to severe intensity, patients over 15 years of age, at least 10 patients per group, and the pain outcome measures of total pain relief (TOTPAR) or summed pain intensity difference (SPID) over 4–6 hours or sufficient data to allow their calculation. Pain measures allowed for the calculation of TOTPAR or SPID were a standard five point pain relief scale (none, slight, moderate, good, complete), a standard four point pain intensity scale (none, mild, moderate, severe) or a standard visual analogue scale (VAS) for pain relief or pain intensity. Also of interest was information on the time to remedication. For adverse events, the primary outcome sought was the proportion of patients experiencing any adverse event, with secondary outcomes of patients experiencing particular adverse events. Although adverse events are often reported inconsistently in acute pain trials [13], the outcome of any patient experiencing any adverse event was the least inconsistently reported.

Each report which could possibly be described as a randomized controlled trial was read independently by at least three authors and scored using a commonly-used three item, 1–5 score, quality scale [14]. Consensus was then achieved. The maximum score of an included study was 5 and the minimum score was 2. Authors were not blinded because they already knew the literature.

For each trial, mean TOTPAR, SPID, VASTOTPAR or VASSPID values for each treatment group were converted to %maxTOTPAR by division into the calculated maximum value [15]. The proportion of patients in each treatment group who achieved at least 50%maxTOTPAR was calculated using valid equations [16–18]. The number of patients randomized was taken as the basis for calculations, to produce an intention to treat analysis. The number of patients with at least 50%maxTOTPAR was then used to calculate relative benefit and NNT for rofecoxib versus placebo. The same methods were used for adverse events.

Relative benefit and relative risk estimates were calculated with 95% confidence intervals using a fixed effects model [19]. Heterogeneity tests were not used as they have previously been shown to be unhelpful [20,21], though homogeneity was examined visually [22]. Publication bias was not assessed using funnel plots as these tests have been shown to be unhelpful [23,24]. The number needed to treat or harm (NNT and NNH) with confidence intervals was calculated by the method of Cook and Sackett [25] from the sum of all events and patients for treatment and placebo. Cumulative calculation of NNT [5] was performed by adding studies by year of publication, and alphabetically within a year.

Relative benefit or risk was considered to be statistically significant when the 95% confidence interval did not include 1. NNT or NNH values were only calculated when the relative risk or benefit was statistically significant, and are reported with the 95% confidence interval. Calculations were performed using Microsoft Excel 2001 on a Power Macintosh G4.

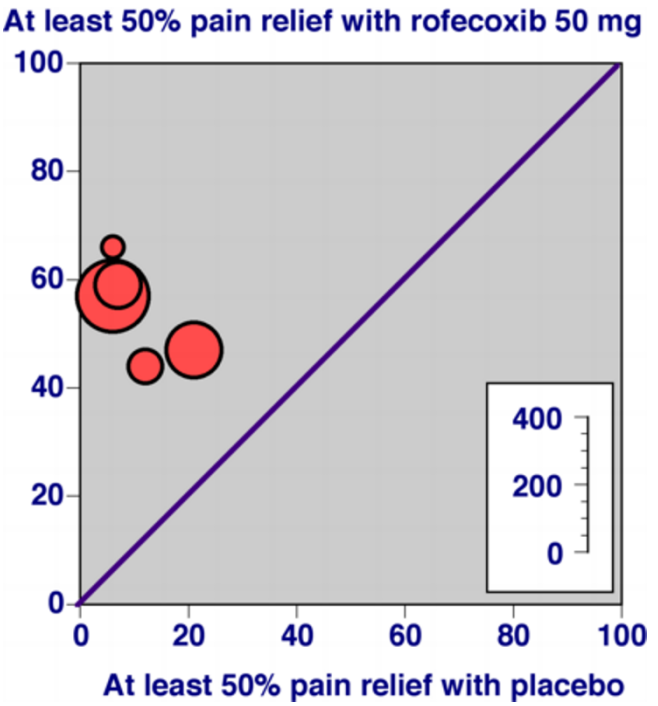

Figure 1
L'Abbe plot of percent of patients with 50% pain relief in placebo controlled trials of rofecoxib 50 mg

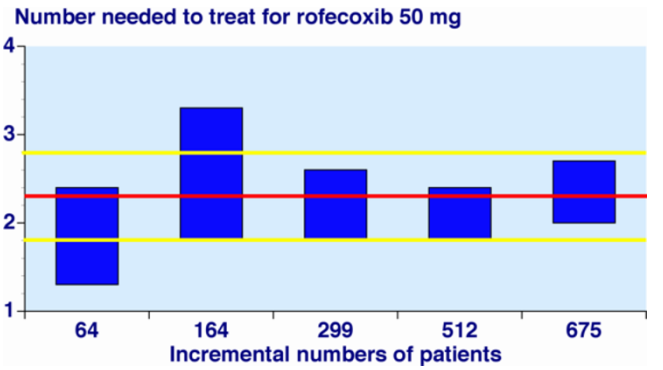

Figure 2
Cumulative meta-analysis of placebo controlled clinical trials of rofecoxib 50 mg

Results

Searches identified twelve papers that were excluded. The references and reasons for exclusion are given in Additional File 2. Five studies were included [11,26–29]. Details of the design, numbers of patients, outcomes, analgesic results, adverse events and quality scores are given in Additional File 3. Four of the five included trials were in a dental pain setting after third molar extraction, and one [29] was after orthopaedic surgery. The five trials studied 1,118 patients, of whom 211 received placebo and 464 received rofecoxib 50 mg. Comparator analgesics included ibuprofen 400 mg (117 patients in three trials), celecoxib 200 mg (91 patients in one trial), paracetamol 600 mg plus codeine 60 mg (180 patients in one trial) and naproxen sodium 550 mg (55 patients in one trial). Quality scores were 4 for four trials and 5 for one. All the included studies were funded by Merck, the manufacturer of rofecoxib.

At least 50% pain relief

All five trials gave or allowed the calculation of six-hour TOTPAR and the derivation of the number of patients with at least 50%maxTOTPAR. There was good agreement between the five studies (Figure 1). Overall 252/464 patients (54%) given rofecoxib 50 mg had at least 50% maxTOTPAR over six hours, compared with 24/211 patients (11%) with placebo. The NNT for one patient to have at least half pain relief over six hours was 2.3 (2.0 to 2.6) (Table 1). Cumulative meta-analysis of the five trials (Figure 2) shows that the 95% confidence interval of the calculated NNT fell within ± 0.5 NNT of the overall mean (1.8 to 2.8) when 500 patients had been randomized.

Table 1: Number, number-needed-to-treat/harm and relative benefit/risk estimate for placebo controlled clinical trials of rofecoxib 50 mg

		Number/total (%) with the outcome with			
Outcome	Number of trials	Rofecoxib 50 mg	Placebo	Relative benefit/risk (95% CI)	NNT/H (95% CI)
At least 50% pain relief	5	(56)	(11)	4.8 (3.3 to 7.2)	2.3 (2.0 to 2.6)
Any adverse event	2	(28)	(33)	0.69 (0.44 to 1.08)	Not calculated
Nausea	3	(7)	(17)	0.48 (0.26 to 0.88)	-11 (-6 to -40)
Vomiting	3	(4)	(12)	0.36 (0.16 to 0.79)	-12 (-7 to -46)

Table 2: Rofecoxib 50 mg numbers-needed-to-treat compared with common analgesics

Drug and dose	Number of patients in the comparison	NNT (95%CI)
Rofecoxib 50 mg	675	2.3 (2.0 to 2.6)
Diclofenac 50 mg	738	2.3 (2.0 to 2.7)
Ibuprofen 400 mg	4703	2.4 (2.3 to 2.6)
Morphine 10 mg (IM)	946	2.9 (2.6 to 3.6)
Paracetamol 1000 mg	2759	3.8 (3.4 to 4.4)
Paracetamol 600/650 mg + codeine 60 mg	1123	4.2 (3.4 to 5.3)
Aspirin 600/650 mg	5061	4.4 (4.0 to 4.9)

Compiled from published and unpublished systematic reviews

Remedication time

Onset of analgesia with rofecoxib 50 mg appeared to be generally the same as with comparator analgesics. Trials tried to discourage remedication within 90 minutes, and two patients in one trial were excluded because they remedicated within 90 minutes, one on placebo and one on rofecoxib 50 mg [26]. This was not reported consistently (Additional File 3). The percentage of patients remedicating within two hours was given in one study [26], and within 24 hours in two [11,27]. Only one study (.([27] gave cumulative remedication rates over the duration of the study. Median time to remedication was given in three studies [11,27,28], and this allowed the calculation of a mean of the three trials weighted by the number of patients. For placebo the weighted mean time to remedication from 126 patients in three trials was 1.9 hours. For rofecoxib 50 mg the weighted mean time to remedication from 322 patients in three trials was 13.6 hours. For ibuprofen 400 mg the weighted mean time to remedication from 97 patients in two trials was 7.4 hours.

Adverse events

Adverse events were not reported consistently (Additional File 3). Two trials reported the proportion of patients having any adverse event. An adverse event was reported by 33% of patients on placebo and 28% of those on rofecoxib 50 mg (not significantly different, Table 1). Nausea and vomiting were reported separately in three dental trials, and both occurred significantly less frequently with rofecoxib 50 mg than with placebo (Table 1). For both there were negative numbers needed to harm (-11 and -12 respectively), showing that for every 11 or 12 patients given rofecoxib, one fewer was nauseous or vomited than with placebo. There were few events, though, with only 44 nauseated patients and only 27 who vomited in the three trials of rofecoxib 50 mg comparable with 34 nauseated patients and only 22 who vomited in the two trials of ibuprofen 400 mg.

Discussion

The five included studies were of generally high reporting quality (quality scores of 4 or 5), known to be associated with minimal reporting bias [30,31]. They all had a placebo control, used standardized pain intensity and relief scores in adult patients with established pain of moderate or severe intensity, and measured outcomes over at least six hours. The pain models, third molar dental extraction and orthopaedic surgery, are commonly used in research and choice of model does not appear to influence results in single-dose analgesic studies when patients are able to take oral medication [13]. Comparison of rofecoxib 50 mg with other analgesics over six hours is legitimate, because the same outcome was measured in the same way in the same patients over the same period of time, and with same comparator.

Compared with placebo, the NNT for at least 50% pain relief over six hours was 2.3 (2.0 to 2.6). Table 2 collects NNTs for a number of common oral analgesics and intramuscular morphine from recent meta-analyses [32,13] and unpublished updates of other published Cochrane reviews [33,34]. Rofecoxib 50 mg is comparable with other doses of oral NSAIDs and intramuscular morphine.

For rofecoxib 50 mg this may not fully reflect its efficacy compared with these other analgesics, because rofecoxib 50 mg may have a longer duration of action. In the five included trials duration was inconsistently reported, however, with median remedication times in three trials (but without dispersion) and percentage remedicated at two hours in one trial and 24 hours in two trials. This disparity in reporting allowed only the crudest analysis of weighted mean remedication time. This was 1.9 hours for placebo, 7.4 hours for ibuprofen 400 mg and 13.6 hours for rofecoxib 50 mg. The figures of 7.4 hours for ibuprofen 400 mg and 1.9 hours for placebo is in agreement with a larger unpublished analysis (Barden et al, unpublished observations). The extended time to remedication for rofecoxib

50 mg may represent a real clinical advantage where the problem is not a lack of effective analgesics, but rather effective analgesics ineffectively delivered [35], and given that using a relatively large dose has no disadvantages.

The efficacy of rofecoxib in these five classical clinical analgesic assays is in contrast to two randomized comparisons of rofecoxib with placebo when given before the operation in adults [36] and children [37]. The methodological difficulties and lack of effect of preemptive analgesia have been pointed out previously [38,39]. In these two trials additional difficulties were the large between-individual variation in morphine consumption in adults [36], and the use of a novel (unlicensed) syrup formulation of rofecoxib in children [37]. Lack of a demonstrable analgesic effect in preemptive studies does not negate a substantial postoperative effect when patients both have pain and can swallow.

There was no consistent pattern of adverse event reporting in the five included trials. Two trials had information on any patient with any adverse event (Table 1), with no difference between rofecoxib 50 mg and placebo. In three trials information on patients suffering nausea and vomiting was available, showing that these adverse events occurred less frequently with rofecoxib 50 mg than placebo. The amount of information (number of patients randomized) was insufficient to make any authoritative statement about adverse events, or compare the adverse event profile of rofecoxib 50 mg in single doses with other single dose analgesics. Adverse events in single-dose studies are often poorly reported, and of limited value [40].

In clinical practice, NSAIDs are associated with acute renal failure in patients with impaired renal function [41,42] and with congestive heart failure in older people with a prior history of heart disease [43]. Acute renal failure after surgery occurs in 1 patient in 1000 after major surgery [44], though it is not clear how much of this is specifically due to the NSAID. For coxibs, especially at high doses, similar caution should be used in patients with pre-existing renal or cardiac conditions as apply to the use of NSAIDs. The slope of the adverse event dose-response may be steeper than for analgesia.

These published reports were insufficiently detailed for calculation of numbers needed to treat for durations longer than six hours. Some information was available for TOTPAR calculated to eight hours, but not in a dichotomous format. TOTPAR is not normally distributed, and mean values are not meaningful [45]. For times longer than six hours, and for duration of analgesia and adverse event profiles, more detailed information from individual patients would be required.

Conclusions

Rofecoxib at a dose 2–4 times the standard daily dose for chronic pain is an effective single dose oral analgesic in acute pain. Limitations in trial reporting constrain conclusions about longer duration of analgesia and adverse event profile.

Competing interests

RAM has been a consultant for MSD. RAM & HJM have consulted for various pharmaceutical companies. RAM, HJM & JE have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times, but no such support was received for this work. No author has any direct stock holding in any pharmaceutical company.

Authors' contributions

JB was involved with searching, data extraction, quality scoring, analysis and writing. JE was involved with searching, data extraction, quality scoring and writing. HJM was involved in analysis and writing. RAM was involved in data extraction, quality scoring, analysis and writing.

Additional material

Additional file 1

Search strategy
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Additional file 2

Excluded studies
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Additional file 3

Included Studies
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