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Individual patient meta-analysis of single-dose rofecoxib in postoperative pain

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Abstract

Background: Individual patient meta-analysis to determine the analgesic efficacy and adverse effects of single-dose rofecoxib in acute postoperative pain.

Methods: Individual patient information was available from 14 trials; 13 in dental and one in postsurgical pain. For each patient the percentage of maximum possible pain relief (%maxTOTPAR) was determined at different time points. The proportion of patients with at least 50% maxTOTPAR, and number-needed-to-treat (NNT) for at least 50% maxTOTPAR, were then calculated, with time when 50% of patients had remedicated (TTR_{50}) and number-needed-to-harm (NNH) for adverse effects.

Results: In dental pain, for rofecoxib 50 mg (1330 patients) compared with placebo (570 patients) the NNT was 1.9 (95% confidence interval 1.8 to 2.1) for six hours, 2.0 (1.8 to 2.1) at eight, 2.4 (2.2 to 2.6) at 12, and 2.8 (2.5 to 3.1) at 24 hours. The TTR_{50} was 15.5 hours. Adverse effects were uncommon, though post-extraction alveolitis (dry socket) occurred more often with rofecoxib 50 mg than with placebo, NNH 24 (14 to 80). For postsurgical pain in one trial (163 patients), the NNT for rofecoxib 50 mg for six hours was 3.9 (2.6 to 7.8), the TTR_{50} was 5.8 hours, and multiple-dose adverse effects over five days occurred at similar rates with rofecoxib 50 mg and placebo.

Conclusions: Single-dose rofecoxib 50 mg is an effective treatment with long-lasting analgesia and few adverse effects in dental pain. More information is required to confirm efficacy in postsurgical pain.

Background

Cox-2 selective inhibitors (coxibs), like rofecoxib, have been developed to provide better gastrointestinal tolerability than conventional non-steroidal anti-inflammatory drugs (NSAIDs). Relatively low rates of gastrointestinal adverse effects allow the use of higher doses of coxibs in the acute pain setting. These high doses may have the additional advantage of longer duration analgesia with extended dosing intervals.

Conventionally, trials in acute pain have been conducted over 4–6 hours because that was how long analgesia lasted for most drugs. Validated methods exist to allow the conversion of mean pain intensity or pain relief outcomes into dichotomous form (the proportion of patients

with at least 50% pain relief) over 4–6 hours [1-4], but methods have not yet been developed to do this beyond six hours. For rofecoxib, a meta-analysis of mean pain outcome data from published trials in postoperative (dental or postsurgical) pain showed a good analgesic response with rofecoxib 50 mg over six hours, and relatively long duration of action (defined in the analysis by time to remedication) [5].

When information is available from individual patients in a trial we do not have to rely on mean values. Since actual pain measurements are available at all time points for each patient, it is possible to calculate for each patient the percent of maximum pain relief (%maxTOTPAR), the number of patients with at least 50% maxTOTPAR and, hence, the number-needed-to-treat (NNT) for at least 50% pain relief at different durations.

The previous analysis [5] was limited to information from five published trials and outcomes over six hours. The objectives of this individual patient meta-analysis were to extend the previous analysis to include more trials and patients, and to calculate NNTs for different durations up to 24 hours.

Methods

QUOROM guidelines for reporting meta-analyses were followed where appropriate [6]. Merck Research Laboratories, Rahway, New Jersey, provided individual patient data from 14 Phase III trials of rofecoxib in postoperative (dental or postsurgical) pain. All completed (July 2002) Phase III trials of rofecoxib meeting pre-specified criteria for inclusion in the meta-analysis were provided. This included information from five published trials in postoperative pain in a previous review [5], but excluded information from one Phase II study [7] which used a different formulation of rofecoxib. The Phase II trial had been included in a previous meta-analysis using published mean data [5].

Trials

The trials were randomised and double blind, and compared single, oral doses of rofecoxib with an active control and placebo in adults with moderate to severe postoperative pain. Dental studies were conducted over 24 hours. One postsurgical study was a multiple dose trial for which information for the first dose was available over 12 hours. In all trials, pain intensity and pain relief were measured using a standard four-point categorical pain intensity scale (0 none, 1 mild, 2 moderate, 3 severe) and a five-point point pain relief scale (0 none, 1 a little, 2 some, 3 a lot, 4 complete). Pain measurements were collected using patient diaries. Patients were assessed at baseline, then at least hourly for eight hours, and again at 12 and 24 hours. In some studies additional assessments were conducted between eight, 12 and 24 hours. The exact time at which a patient requested remedication (rescue analgesic), if required, was recorded. Adverse effects were recorded as the number of patients with any adverse effect(s), or of particular adverse effects. Table 1 shows the study treatments, dosing and number of patients for the individual trials.

The quality of trials, in terms of their descriptions of randomisation, double blinding and withdrawals or dropouts, was determined using a five point scale [8]. Study validity was determined using a 16-point pain validity scale [9]. These scales are described in Additional file 1.

Meta-analysis

Outcome data were pooled in an intention to treat (number of patients randomised) analysis. For each patient we calculated the area under the pain relief – time curve (TOTPAR) for six, eight, 12 and 24 hours. When a patient remedicated the pain relief score was set to zero for all remaining time points until the end of the observation period. For each patient we then calculated the percentage of the maximum possible TOTPAR for each time point (number of hours of observation multiplied by the maximum possible pain relief of 4; for example,24 for six hours, 32 for eight hours).

When making comparisons, each active analgesic was compared with placebo from those trials in which the active analgesic was used. Efficacy was defined as the number-needed-to-treat (NNT) for at least 50% pain relief. Duration of analgesia was defined as the time when 50% of patients with the same treatment had remedicated (TTR_{50}).

Analyses for comparator treatments were based on information available only from the trials of rofecoxib mentioned in this report, but for most there was insufficient information to be confident of the result [10]. In acute pain studies we need information from at least 500 patients to be sure of an NNT ± 0.5 when the NNT is 2, and many more patients when the NNT is higher. Only ibuprofen 400 mg had sufficient information (601 patients in six trials). While data are provided for other comparators, only information from rofecoxib 50 mg and ibuprofen 400 mg will be discussed. The single postsurgical study was not pooled with dental trials for observations beyond six hours because the only outcome for which we know that these two pain models give the same result is NNT for at least 50% maxTOTPAR for 4–6 hours [11].

Relative benefit (or risk) was calculated using a fixed effects model [12], with no statistically significant difference between treatments assumed when the 95%

Table 1: Trials details

Trial ID	Pain condition	Study drug and dose, number of patients	Design	Observations after 8 hrs	Quality, Validity scores
27	Dental	Rofecoxib 50 mg, 38 Naproxen 550 mg, 39 Placebo, 39	Single oral dose, parallel	12, 24	Q 5 V 16
51	Dental	Rofecoxib 50 mg, 72 Naproxen 550 mg, 49 Placebo, 48	Single oral dose, parallel	12, 24	Q 5 V 16
66	Dental	Rofecoxib 50 mg, 50 Ibuprofen 400 mg, 51 Placebo, 50	Single oral dose, parallel	12, 24	Q 5 V 16
71	Dental	Rofecoxib 50 mg, 50 Ibuprofen 400 mg, 52 Placebo, 50	Single oral dose, parallel	12, 24	Q 5 V 16
84	Dental	Rofecoxib 50 mg, 56 Ibuprofen 400 mg, 56 Placebo, 56	Single oral dose, parallel	12, 24	Q 5 V 16
95	Dental	Rofecoxib 50 mg, 90 Ibuprofen 400 mg, 46 Placebo, 45	Single oral dose, parallel	10, 12, 24	Q 5 V 16
104	Dental	Rofecoxib 50 mg, 151 Ibuprofen 400 mg, 46 Placebo, 45	Single oral dose, parallel	10, 12, 24	Q 5 V 16
111	Dental	Rofecoxib 50 mg, 159 Ibuprofen 400 mg, 53 Placebo, 52	Single oral dose, parallel	10, 12, 24	Q 5 V 16
127	Dental	Rofecoxib 50 mg, 180 Paracetamol 600 mg + Codeine 60 mg, 180 Placebo, 30	Single oral dose, parallel	12, 24	Q 5 V 16
128	Dental	Rofecoxib 50 mg, 182 Paracetamol 600 mg + Codeine 60 mg, 180 Placebo, 31	Single oral dose, parallel	12, 24	Q 5 V 16
152	Dental	Rofecoxib 50 mg, 90 Oxycodone 5 mg + Paracetamol 325 mg, 91 Placebo, 31	Single oral dose, parallel	12, 24	Q 5 V 16
154	Dental	Rofecoxib 50 mg, 91 Oxycodone 5 mg + Paracetamol 325 mg, 89 Placebo, 30	Single oral dose, parallel	12, 24	Q 5 V 16
169	Dental	Rofecoxib 50 mg, 121 Diclofenac 50 mg Q8 hr, 121 Placebo, 63	Single oral dose, parallel	10, 11, 12, 16, 20, 24	Q 5 V 16
72	Postsurgical	Rofecoxib 50 mg, 110 Naproxen 550 mg, 55 Placebo, 53	Multiple with single dose efficacy data, AE 5 days, parallel	12 hrs	Q 5 V 16

confidence intervals included unity. Number-needed-to-treat (or harm) was calculated using the method of Cook and Sackett [13] using the pooled number of observations. NNT/H is the reciprocal of the absolute risk reduction or increase; for instance, if 75 out of 100 patients benefit with treatment and only 25 out of 100 benefit with placebo, the absolute risk increase is 0.75-0.25 = 0.5, and the NNT is 1/0.5 = 2.

The following terms were used to describe adverse outcomes in terms of harm or prevention of harm:

• When significantly fewer adverse effects occurred with active treatment than with placebo we used the term the number-needed-to-treat to prevent one event (NNTp).

• When significantly more adverse effects occurred with active treatment compared with placebo we used the term the number-needed-to-harm to cause one event (NNH).

Clinical homogeneity of trials was examined graphically [14] since heterogeneity tests and funnel plots have been shown to be unreliable [15,16]. The z test [17] was used to detect statistically significant differences between the NNTs derived for different treatments. Statistical significance was indicated by $p < 0.01$.

Results

All 14 trials scored the maximum of five points for quality and the maximum of 16 points for validity. In all 14 trials (2060 patients) the NNT for at least 50% pain relief over six hours was 2.0 (1.9 to 2.1) for rofecoxib 50 mg compared with placebo in dental plus postsurgical pain.

Dental pain

There were 13 trials in dental pain (studies 27, 51, 66, 71, 84, 95, 104, 111, 127, 128, 152, 154, 169). Patients underwent surgical removal of impacted third molars. Their mean age was 21 years, and 60% were women. Sixty-five percent of patients had moderate and 35% severe pain at baseline. Study treatments were rofecoxib 50 mg (1330 patients), placebo (570 patients), and active comparators of ibuprofen 400 mg in six trials (303 patients), enteric-coated diclofenac sodium 50 mg in one (121 patients), naproxen sodium 550 mg in two (88 patients), paracetamol 600 mg plus codeine 60 mg in two (360

Table 2: NNT for at least 50% pain relief in dental pain

Number of trials	Drug and dose (mg)	Improved with		Relative risk (95% CI)	NNT (95% CI)	Mean percent improved with	
		Active	Placebo			Placebo	Active
Six hours							
13	Rofecoxib 50 mg	832/1330	58/570	5.9 (4.6 to 7.5)	1.9 (1.8 to 2.1)	10	63
6	Ibuprofen 400 mg	159/303	25/298	6.3 (4.2 to 9.2)	2.3 (2.0 to 2.7)	9	53
1	Diclofenac 50 mg	32/121	8/63	2.1 (1.02 to 4.2)	7.3 (4.0 to 42)	13	26
2	Naproxen 550 mg	52/88	9/87	5.7 (3.0 to 11)	2.1 (1.6 to 2.7)	11	59
2	Oxycodone 5 mg + paracetamol 325 mg	30/180	5/61	2.0 (0.8 to 5.0)	nc	8	17
2	Paracetamol 600 mg + codeine 60 mg	102/360	11/61	1.6 (0.9 to 2.7)	nc	18	28
Eight hours							
13	Rofecoxib 50 mg	814/1330	62/570	5.4 (4.3 to 6.9)	2.0 (1.9 to 2.1)	11	61
6	Ibuprofen 400 mg	135/303	25/298	5.3 (3.6 to 7.9)	2.8 (2.4 to 3.4)	8	44
1	Diclofenac 50 mg	32/121	11/63	1.5 (0.8 to 2.8)	nc	17	26
6	Ibuprofen 400 mg	135/303	25/298	5.3 (3.6 to 7.9)	2.8 (2.4 to 3.4)	8	44
2	Naproxen 550 mg	45/88	8/87	5.6 (2.8 to 11)	2.4 (1.9 to 3.4)	10	51
2	Oxycodone 5 mg + paracetamol 325 mg	21/180	4/61	1.8 (0.6 to 5.0)	nc	6	12
2	Paracetamol 600 mg + codeine 60 mg	70/360	10/61	1.2 (0.7 to 2.1)	nc	16	20
Twelve hours							
13	Rofecoxib 50 mg	662/1330	46/570	5.9 (4.5 to 7.8)	2.4 (2.2 to 2.6)	8	50
6	Ibuprofen 400 mg	73/303	19/298	3.8 (2.4 to 6.1)	5.6 (4.3 to 8.2)	6	24
1	Diclofenac 50 mg	No data – doses repeated every 8 hours					
6	Ibuprofen 400 mg	73/303	19/298	3.8 (2.4 to 6.1)	5.6 (4.3 to 8.2)	6	24
2	Naproxen 550 mg	30/88	7/87	4.2 (2.0 to 9.1)	3.9 (2.7 to 7.0)	8	34
2	Oxycodone 5 mg + paracetamol 325 mg	15/180	2/61	2.5 (0.6 to 11)	nc	3	8
2	Paracetamol 600 mg + codeine 60 mg	30/360	8/61	0.6 (0.3 to 1.3)	nc	13	8
Twenty-four hours							
13	Rofecoxib 50 mg	595/1330	49/570	5.1 (3.9 to 6.7)	2.8 (2.5 to 3.1)	9	45
6	Ibuprofen 400 mg	43/303	21/298	2.0 (1.2 to 3.3)	14 (8.3 to 44)	7	14
1	Diclofenac 50 mg	No data – doses repeated every 8 hours					
6	Ibuprofen 400 mg	43/303	21/298	2.0 (1.2 to 3.3)	14 (8.3 to 44)	7	14
2	Naproxen 550 mg	24/88	8/87	3.0 (1.4 to 6.2)	5.5 (3.4 to 14)	9	27
2	Oxycodone 5 mg + paracetamol 325 mg	18/1804	61	1.4 (0.5 to 3.6)	nc	7	10
2	Paracetamol 600 mg + codeine 60 mg	24/360	7/61	0.6 (0.3 to 1.2)	nc	11	7

nc: not calculated because relative risk showed no statistically significant difference between active and placebo. Naproxen was given as the sodium salt

patients), and oxycodone 5 mg plus paracetamol 325 mg in two (180 patients). Enteric-coated diclofenac sodium 50 mg was given every eight hours and efficacy estimates were therefore calculated only at six and eight hours for this drug.

Efficacy in dental pain

Table 2 shows the efficacy results for all active treatments compared with placebo over six, eight, 12 and 24 hours in dental pain. Using pooled data from 13 trials, the proportion of patients with at least 50% pain relief with rofecoxib 50 mg was 63% (832/1330 patients) over six

Table 3: Time to remedication

Pain model	Drug & dose (mg)	Number of trials	Number of patients	TRR_{50}(hrs)
Dental	Rofecoxib 50 mg	13	1330	15.5
	Ibuprofen 400 mg	6	303	7.1
	Diclofenac 50 mg	1	121	1.6
	Ibuprofen 400 mg	6	303	7.1
	Naproxen 550 mg	2	88	9.3
	Oxycodone 5 mg + paracetamol 325 mg	2	180	3.1
	Paracetamol 600 mg + codeine 60 mg	2	360	3.8
	Placebo	13	570	1.6
Postsurgical	Rofecoxib 50 mg	1	110	5.8
	Naproxen 550 mg	1	55	5.9
	Placebo	1	53	2.8

Naproxen was given as the sodium salt

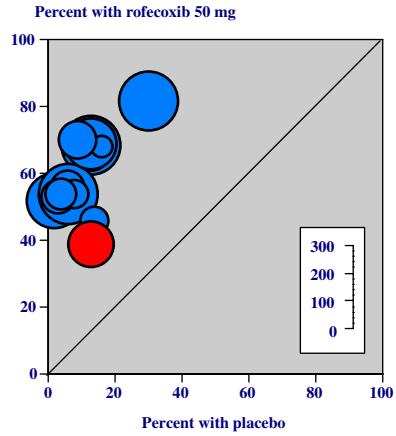

Figure 1
Percent with at least 50% pain relief with rofecoxib 50 mg over six hours

hours (Figure 1), 61% (814/1330) over eight hours, 50% (662/1330) over 12 hours and 45% (595/1330) over 24 hours. The proportions of patients with at least 50% pain relief with placebo at six, eight, 12 and 24 hours were 10% (58/570; Figure 1), 11% (62/570), 8% (46/570), and 9% (49/570). Rofecoxib 50 mg was significantly more effective than placebo at all time points. For rofecoxib 50 mg compared with placebo, the NNT for at least 50% pain relief was 1.9 (1.8 to 2.1) over six hours, 2.0 (1.9 to 2.1) over eight hours, 2.4 (2.2 to 2.6) over 12 hours and 2.8 (2.5 to 3.1) over 24 hours. Rofecoxib 50 mg was statistically superior to ibuprofen 400 mg at eight ($z = 3.75$, $p = 0.0002$), 12 ($z = 7.16$, $p = <0.00006$) and 24 hours ($z = 9.43$, $p = <0.00006$).

Time to remedication in dental pain

Results for time to remedication are shown in Table 3. Duration of analgesia was longer with rofecoxib 50 mg than with other active comparators used in the trials. The TTR_{50} was 15.5 hours with rofecoxib 50 mg, 1.6 hours with placebo, and 7.1 hours with ibuprofen 400 mg.

Adverse effects in dental pain

Results for adverse effects are shown in Table 4. There was no statistically significant difference in the number of patients reporting any adverse effects with rofecoxib 50 mg (35%, 459/1330 patients) compared with placebo (231/570, 41%), relative risk 0.9 (0.8 to 1.0).

Post-extraction alveolitis (dry socket) was reported significantly more often with rofecoxib 50 mg (179/1330, 13%) than with placebo (52/570, 9%), relative risk 1.5 (1.1 to 2.1). The NNH was 24 (14 to 80). The other most commonly reported adverse effects were dizziness, nausea, and vomiting. Significantly fewer events were reported with rofecoxib 50 mg compared with placebo for some adverse effects. The NNTps to prevent one event were 43 (24 to 253) for dizziness, 18 (11 to 41) for nausea, and 19 (13 to 38) for vomiting.

Ibuprofen 400 mg was not associated with significantly increased or decreased rates of patients with any adverse effect or particular adverse effects. One case of gastrointestinal bleeding was reported with ibuprofen 400 mg, otherwise no adverse effects were described as serious for any intervention.

Postsurgical pain

In one trial (study 72) following major orthopaedic surgery (total hip or knee replacement or femoral fracture repair with open reduction and internal fixation), the

Table 4: Adverse effects in dental pain

Number of trials	Drug and dose	Adverse effects with active		Adverse effects with placebo		Relative risk (95% CI)	NNH/NNTp (95% CI)
		Number	Percent	Number	Percent		
Any adverse event							
13	Rofecoxib 50 mg	459/1330	35	231/570	41	0.9 (0.8 to 1.0)	nc
6	Ibuprofen 400 mg	102/303	34	122/298	41	0.8 (0.7 to 1.0)	nc
1	Diclofenac 50 mg*	72/121	60	31/63	41	1.2 (0.9 to 1.6)	nc
6	Ibuprofen 400 mg	102/303	34	122/298	41	0.8 (0.7 to 1.0)	nc
2	Naproxen 550 mg	27/88	31	25/87	29	1.1 (0.7 to 1.7)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	116/180	64	29/61	48	1.4 (1.02 to 1.8)	5.9 (3.2 to 39)
2	paracetamol 600 mg + codeine 60 mg	146/360	41	24/61	39	1.0 (0.7 to 1.4)	nc
Post-extraction alveolitis							
13	Rofecoxib 50 mg	179/1330	13	52/570	9	1.5 (1.1 to 2.1)	24 (14 to 80)
6	Ibuprofen 400 mg	23/304	8	31/298	10	0.7 (0.4 to 1.2)	nc
1	Diclofenac 50 mg*	9/180	5	3/63	5	1.0 (0.3 to 3.8)	nc
6	Ibuprofen 400 mg	23/304	8	31/298	10	0.7 (0.4 to 1.2)	nc
2	Naproxen 550 mg	13/88	15	8/87	10	1.6 (0.7 to 3.4)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	20/180	11	7/61	11	0.9 (0.4 to 2.2)	nc
2	Paracetamol 600 mg + codeine 60 mg	27/360	8	3/61	6	1.3 (0.5 to 3.9)	nc
Dizziness							
13	Rofecoxib 50 mg	30/1330	2	25/570	5	0.5 (0.3 to 0.9)	**43 (24 to 253)**
6	Ibuprofen 400 mg	7/304	**3**	13/298	5	0.6 (0.3 to 1.4)	nc
1	Diclofenac 50 mg*	9/180	8	5/63	8	0.6 (0.2 to 1.8)	nc
6	Ibuprofen 400 mg	7/304	**3**	13/298	5	0.6 (0.3 to 1.4)	nc
2	Naproxen 550 mg	1/88	2	1/87	1	0.9 (0.2 to 9.3)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	44/180	24	6/61	10	2.5 (1.1 to 5.6)	6.9 (4.1 to 21)
2	Paracetamol 600 mg + codeine 60 mg	19/360	1	1/61	2	3.3 (0.5 to 24)	nc
Drowsiness							
13	Rofecoxib 50 mg	8/1330	0.6	1/570	0.6	0.9 (0.3 to 3.1)	nc
6	Ibuprofen 400 mg	1/304	0.7	0/298	0.5	1.3 (0.2 to 11)	nc
1	Diclofenac 50 mg*	5/180	3	0/63	0	3.5 (0.2 to 64)	nc
6	Ibuprofen 400 mg	1/304	0.7	0/298	0.5	1.3 (0.2 to 11)	nc
2	Naproxen 550 mg	0/88	0	0/87	0	0.9 (0.0 to 16)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	6/180	4	1/61	2	2.2 (0.3 to 18)	nc
2	Paracetamol 600 mg + codeine 60 mg	7/360	2	1/61	2	1.2 (0.2 to 9.2)	nc
Nausea							
13	Rofecoxib 50 mg	112/1330	8	80/570	14	0.6 (0.5 to 0.8)	**18 (11 to 41)**
6	Ibuprofen 400 mg	38/304	12	51/298	17	0.7 (0.5 to 1.08)	nc
1	Diclofenac 50 mg*	21/180	12	10/63	16	0.7 (0.4 to 1.5)	nc
6	Ibuprofen 400 mg	38/304	12	51/298	17	0.7 (0.5 to 1.08)	nc
2	Naproxen 550 mg	4/88	5	3/87	3	1.3 (0.3 to 5.7)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	61/180	34	10/61	17	2.0 (1.1 to 3.5)	6.0 (3.5 to 19)
2	Paracetamol 600 mg + codeine 60 mg	70/360	19	6/61	10	2.0 (0.9 to 4.4)	10 (5.5 to 92)

Table 4: Adverse effects in dental pain *(Continued)*

Vomiting							
13	Rofecoxib 50 mg	51/1330	4	51/570	9	0.4 (0.3 to 0.6)	**19 (13 to 38)**
6	Ibuprofen 400 mg	25/304	8	36/298	12	0.7 (0.4 to 1.1)	nc
1	Diclofenac 50 mg*	6/180	3	7/63	11	0.3 (0.1 to 1.0)	nc
2	Naproxen 550 mg	1/88	2	1/87	2	0.9 (0.1 to 9.3)	nc
2	Oxycodone 5 mg + paracetamol 325 mg	35/180	19	3/61	6	3.4 (1.2 to 9.8)	7.2 (4.6 to 18)
2	Paracetamol 600 mg + codeine 60 mg	58/360	16	4/61	7	2.46 (0.9 to 6.5)	10 (5.9 to 44)

***NB:** Diclofenac was taken every eight hours during the study. Naproxen was given as the sodium salt Bold type: NNTp to prevent one event (significantly fewer events occurred with rofecoxib 50 mg compared with placebo

mean age of patients was 65 years, 58% were women, and 82% had moderate pain at baseline. Rofecoxib 50 mg (110 patients) was compared with naproxen sodium 550 mg (55 patients) or placebo (53 patients). Single-dose efficacy data were available from this five-day study; efficacy data were not available for multiple doses. Multiple dose adverse effects were collected over five days and are described below.

Efficacy in postsurgical pain

Results are shown in Table 5. No data were available at 24 hours. The mean event rates (proportion of patients with at least 50% pain relief) with rofecoxib 50 mg over six, eight, and 12 hours were 39% (43/110 patients, Figure 1), 40% (44/110), and 35% (38/110). With naproxen sodium 550 mg the mean event rates were 36% (20/55), 33% (18/55), and 25% (14/55) and with placebo were 13% (7/53) (Figure 1), 11% (6/53), and 4% (2/53).

Rofecoxib 50 mg was significantly more effective than placebo at all time points. For rofecoxib 50 mg compared with placebo, the NNT for at least 50% pain relief was 3.9 (2.6 to 7.8) over six hours, 3.5 (2.4 to 6.9) over eight hours, and 3.3 (2.4 to 4.9) over 12 hours. Naproxen sodium 550 mg was significantly more effective than placebo at all time points. For naproxen sodium 550 mg compared with placebo, the NNT for at least 50% pain relief was 4.3 (2.6 to 13) over six hours, 4.7 (2.7 to 16) over eight hours, and 4.6 (2.9 to 11) over 12 hours.

Time to remedication in postsurgical pain

TTR_{50} with rofecoxib 50 mg was similar to that of naproxen sodium 550 mg (Table 3). It was 5.8 hours with rofecoxib 50 mg, 5.9 hours with naproxen sodium 550 mg, and 2.8 hours with placebo.

Adverse effects in postsurgical pain

Information on adverse effects was collected over five days for multiple doses of study treatments; single dose information was not available. The most commonly reported adverse effects were fever, constipation, and nausea. No adverse effects were serious. There were too few patients to analyse reliably particular adverse effects like dizziness or nausea.

There was no statistically significant difference in the reported incidence of patients with any adverse effect with rofecoxib 50 mg (42/54 patients, 78%) compared with placebo (41/53, 77%), relative risk 1.0 (0.8 to 1.2). With naproxen sodium 550 mg 37/55 patients (67%) reported adverse effects, again with no significant difference compared with placebo, relative risk 0.9 (0.7 to 1.1).

Discussion

Individual patient data is the gold standard in meta-analysis and has been performed only rarely in acute pain, with tramadol [18], and tramadol plus paracetamol [19]. This review is therefore the first individual patient data analysis for NSAIDs and coxibs in acute pain. For rofecoxib, individual patient information was available from fourteen trials in postoperative pain. The trials were of high quality and validity, scoring the maximum for both. The same methods and outcomes were used in all trials, thus ensuring clinical homogeneity. Since trials were conducted over 24 hours in dental pain and 12 hours in postsurgical pain, and because only for six hour TOTPAR can we be confident that there is no difference between pain models [11], the prior decision was to analyse these two pain models separately.

Historically, single-dose analgesic trials for most treatments have been conducted over 4–6 hours since this is typically how long pain relief has lasted. Trials of coxibs, like rofecoxib and valdecoxib [20], have been conducted over 12–24 hours. Because of the long duration of analgesia at the doses given, the potential existed to use trials of rofecoxib to calculate single dose efficacy estimates over durations up to 24 hours in dental pain and 12 hours in postsurgical pain. This would not have been possible without individual patient information because methods to convert mean summary data into dichotomous form exist only for 4–6 hours [2-4]. Examination of efficacy estimates over longer durations allowed examination of the duration of analgesic effect, the caveat being that in

Table 5: NNT for at least 50% pain relief in postsurgical pain

Time (hours)	Drug and dose (mg)	Improved with		Relative risk (95% CI)	NNT (95% CI)	Mean percent improved with	
		Active	Placebo			Placebo	Active
6	Rofecoxib 50 mg	43/110	7/53	3.0 (1.4 to 6.1)	3.9 (2.6 to 7.8)	13	39
	Naproxen 550 mg	20/55	7/53	2.8 (1.3 to 6.0)	4.3 (2.6 to 13)	13	36
8	Rofecoxib 50 mg	44/110	6/53	3.5 (1.6 to 7.8)	3.5 (2.4 to 6.9)	11	40
	Naproxen 550 mg	18/55	6/53	2.9 (1.2 to 6.7)	4.7 (2.7 to 16)	11	33
12	Rofecoxib 50 mg	38/110	2/53	9.2 (2.3 to 37)	3.3 (2.4 to 4.9)	4	35
	Naproxen 550 mg	14/55	2/53	6.8 (1.6 to 28)	4.6 (2.9 to 11)	4	25

Naproxen was given as the sodium salt

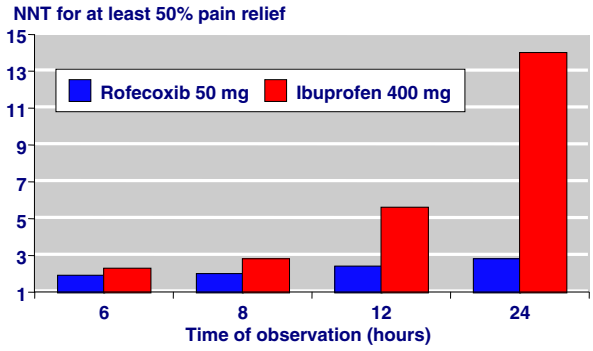

Figure 2
Comparison of NNTs of rofecoxib 50 mg and ibuprofen 400 mg over different times

some studies there was only one additional observation beyond 12 hours.

In dental pain the six-hour NNTs for rofecoxib 50 mg and ibuprofen 400 mg were similar at about two. This means that for every two patients treated one would obtain at least 50% pain relief with active treatment who would not have done with placebo. For rofecoxib 50 mg the NNTs were similar (all below 3) at six, eight, 12 and 24 hours, whereas for ibuprofen 400 mg the NNTs increased (drug less effective) with time (Figure 2). This comparison of rofecoxib 50 mg with ibuprofen 400 mg at longer times is the only one we have with adequate numbers of patients. External, or indirect, comparisons are only available over six hours. Table 6 shows a comparison for coxibs, NSAIDs, and simple analgesics over six hours after third molar surgery [20,21]. Oral rofecoxib 50 mg and valdecoxib 20 mg and 40 mg all have mean NNT values below 2, and have overlapping confidence intervals. Standard doses of diclofenac and ibuprofen have similar, if slightly higher, NNTs, while standard doses of paracetamol and aspirin have considerably higher (worse) NNTs.

In this analysis, time for 50% of patients to have remedicated was calculated for each drug and for placebo from individual patients. The results showed that in dental pain the duration of analgesia was longer with a single dose of rofecoxib 50 mg than for other comparator drugs (at the doses used in the trials). In the postsurgical trial TTR_{50} was shorter at 5.8 hours. The difference in TTR_{50} values for dental compared with postsurgical pain may be due to the different pain context (more major orthopaedic than dental surgery), the more elderly population in the postsurgical study (mean age 65 years versus 21 years in the dental trials), and that results were simply not robust in the postsurgical study because they were based on too little information. Oral valdecoxib 20 mg or 40 mg has comparable duration of analgesia to rofecoxib 50 mg in dental studies [20], though in many fewer patients.

Overall, efficacy results for rofecoxib 50 mg from this individual patient meta-analysis were similar to those derived using published mean summary data [5]. There were minor differences. For instance, the NNT for at least 50% pain relief over 4–6 hours from five published trials with 675 patients in the comparison was 2.3 (2.0 to 2.6) in dental plus postsurgical pain. Here, in all 14 trials with 2060 patients it was 2.0 (1.9 to 2.1) in dental plus postsurgical pain. Again, the previous estimate for duration of analgesia using time to remedication calculated from weighted mean values was 13.6 hours, and here it was 15.5 hours measured from individual patients (though in dental pain only).

Adverse effects are also important, though in single dose trials they are both uncommon and inadequately reported

Table 6: Comparison of NNTs for oral analgesics in dental pain. NNT are for at least 50% pain relief compared with placebo over six hours

Drug and dose	Number of patients in comparison	NNT (95% CI)
Rofecoxib 50 mg	1900	1.9 (1.8 to 2.1)
Valdecoxib 40 mg[1]	473	1.6 (1.4 to 1.8)
Valdecoxib 20 mg[1]	204	1.7 (1.4 to 2.0)
Diclofenac 50 mg[2]	367	2.1 (1.8 to 2.6)
Ibuprofen 400 mg[2]	3402	2.2 (2.1 to 2.4)
Paracetamol 975/1000 mg[2]	1038	3.7 (3.1 to 4.7)
Paracetamol 600/650 mg[2]	1265	4.2 (3.6 to 5.2)
Aspirin 600/650 mg[2]	3635	4.7 (4.2 to 5.4)

1. Barden et al. BMC Anesthesiol. 2003 3:1 2. Barden et al, BDJ, in press.

[22]. Information from many patients is required to determine NNH reliably even for relatively common, minor, events like dizziness or nausea [23]. Adverse effects were uncommon with single doses of rofecoxib 50 mg, and rates of particular adverse effects were low. There is no obvious reason for post-extraction alveolitis with rofecoxib; the incidence with rofecoxib 50 mg (13%) was similar to that with comparator NSAIDs (5–15%, Table 4). Central nervous system and gastrointestinal effects would be expected with the opioid combination comparators, though results were based on few patients and NNHs were not robust.

Surveys have shown that acute pain is often not managed well [24]. Potential exists for better pain management since drugs with fast onset and long-lasting analgesic action are available. Information on remedication in trials may help demonstrate duration of analgesia with different treatments, since patients are meant to remedicate only when they have inadequate pain relief. Longer duration analgesics may be of importance, not only as part of a multimodal approach to analgesia in the perioperative period [25]. A recent survey of French general practitioners found acute pain at home after hospital discharge to be a major problem [26].

Conclusions

Single dose rofecoxib 50 mg in dental pain had comparable analgesia to ibuprofen 400 mg over six hours, but was superior at eight and 12 hours. Adverse effects were uncommon. Results for postsurgical pain were not robust because of limited patient numbers.

Competing interests

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Authors' contributions

JE performed the analysis and wrote the draft manuscript. RAM checked all analyses. JE, RAM and HJM contributed equally to the design, writing and reviewing of the paper.

Additional material

Additional File 1

Quality and validity scales. This file describes in detail the scales for trial quality and trial validity that have been used in the analysis.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2253-4-3-S1.pdf]

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