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Intravenous parecoxib for acute postoperative pain in adults

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and adverse effects of single dose parecoxib in studies of acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

BACKGROUND

In the clinical development of analgesics, the first step is to demonstrate that they take away pain. This can only be done by testing them in people with established moderate or severe pain, and experience has shown that this must be clinical, rather than experimentally-induced, pain. To show that the analgesic is working it is necessary to use placebo (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, also called rescue analgesia, if the pain has not diminished after about an hour. This is fair, because not all participants given an analgesic will have significant pain relief, and about 18% of participants given placebo will have significant pain relief (Moore 2006).

The demonstration that a drug is an analgesic after a single dose in an acute pain situation is important. In itself, such demonstration does not determine the utility of the tested drug in any particular situation. However, because drugs that work well in one pain condition generally work well in others, with a similar relative efficacy, acute pain trials provide useful information relevant to many other pain conditions. Knowing the relative efficacy of

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CONTRIBUTIONS OF AUTHORS RL and SD, will perform searching, data extraction, and analysis, including assessment of study quality. RAM and HJM will help with analysis and act as arbitrator. All review authors will contribute to the writing of the protocol and will contribute to the writing of the final review.
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DECLARATIONS OF INTEREST RAM, HJM and SD have received research support from charities, government and industry sources at various times, but no such support was received for this work. RAM and HJM have consulted for various pharmaceutical companies. RAM, and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions.

NOTES The original published protocol was withdrawn from publication on the 8th February 2007 due to contact loss of the author who intended to write the full review - Jose Gomez-Leon. The protocol had minor revisions in June 2008 to update it and bring it in line with a series of reviews of single dose analgesics in acute postoperative pain.

different analgesic drugs at various doses can be helpful. An example is the relative efficacy in the third molar extraction pain model (Barden 2004).

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity or pain relief scales immediately before the intervention, over the following four to six hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. Patients with inadequate pain relief after 60 to 120 minutes are given rescue medication. For these patients it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and in flammation is a critical component of patient care. Clinicians prescribe non-steroidal anti-inflammatory drugs (NSAIDs) to their patients on a routine basis for various types of mild-to-moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999).

Cyclooxygenase (COX) activity has been found to be associated with at least two distinct isoenzymes: COX-1 and COX-2. COX-1 was hypothesized to be involved in the maintenance of physiologic functions such as gastric protection and haemostasis; COX-2 was thought to be involved in pathophysiologic processes such as inflammation, pain and fever. These hypotheses led to the development of the selective COX-2 inhibitors, such as celecoxib, rofecoxib and etoricoxib. These agents have analgesic efficacy comparable with conventional NSAIDs. In addition, they have no anti-platelet activity at therapeutic doses, and therefore may be associated with reduced gastrointestinal adverse effects compared with conventional NSAIDs such as ibuprofen. Concerns about cardiovascular safety in long term use have led to the withdrawal of rofecoxib, and in some countries lumiracoxib.

The most common route for postoperative analgesia is oral, but when patients are unable to swallow, for instance perioperatively, parenteral administration (e.g., intramuscular, intravenous, intrathecal) may be preferred. Some NSAIDs can be administered intramuscularly (e.g., diclofenac, ketoprofen and ketorolac) but this route can be painful in itself. Diclofenac and ketorolac can be administered intravenously, but ketorolac is contraindicated for patients receiving heparin and those who might be susceptible to bleeding from gastrointestinal ulcers or who have renal impairment.

Parecoxib is the first COX-2 that can be administered parenterally. It is a prodrug (the parent drug is inactive) that is rapidly hydrolysed in vivo to its active form, valdecoxib. Clinical trials have indicated that parecoxib is effective in treating postoperative pain resulting from oral surgery, orthopedic surgery and abdominal hysterectomy pain (Barden 2003). Other studies have demonstrated no significant effects on platelet function or upper gastrointestinal mucosa (Graff 2007; Harris 2004; Noveck 2001;Stoltz 2002). As a result, parecoxib sodium has been approved in European countries for the treatment of postoperative pain. In the UK, for example, parecoxib 20 mg or 40 mg powder (and solvent for solution for injection) is licensed for the short-term treatment of postoperative pain.

In 2002 concerns were raised about the potential for serious adverse effects from parecoxib because of reactions experienced by some patients to valdecoxib, the active metabolite of parecoxib sodium. These effects included anaphylaxis, angioedema, and serious skin reactions such as toxic epidermal necrolysis (EMEA 2002), and led to withdrawal of valdecoxib in 2005. As a result, parecoxib is contraindicated in patients who have a history of sensitivity to sulphonamides (a type of antibiotic used to treat infections) because of the risk of severe adverse effects.

A previously published systematic review (Barden 2003) assessed the evidence for the effectiveness of parecoxib for treating postoperative pain from four randomised controlled trials (620 participants) and concluded that parecoxib is an effective analgesic in the postoperative setting. Since then, new studies have been published, and it is hoped that they will provide additional data for more robust estimates of the benefits and harms of parecoxib.

This review is one of a series of reviews examining the efficacy (and to some extent safety) of single doses of oral analgesics in typical acute pain situations. The studies will have been performed principally for registration purposes, to demonstrate analgesia rather than to show how best to control postoperative pain. Trials will typically be of short in duration, rarely over 12 hours, and the numbers will be small, so that no reliable conclusions can be drawn about safety. The aim of this series of reviews is to present evidence for relative analgesic efficacy through indirect comparisons, with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level.

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Recent reviews include Lumiracoxib (Roy 2007) and Celecoxib (Derry 2008), and will include updates of existing reviews like Ibuprofen (Collins 2002) and Aspirin (Edwards 2000).

OBJECTIVES

To assess the efficacy and adverse effects of single dose parecoxib in studies of acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

METHODS

Criteria for considering studies for this review

Types of studies—Studies will be included if they are double blind trials of single dose parecoxib compared with placebo for the treatment of moderate to severe postoperative pain in adults with at least ten participants randomly allocated to each treatment group. Multiple dose studies will be included if appropriate data from the first dose are available. Cross-over studies will be included provided data from the first arm are presented separately. No language restriction will be applied to the search for studies.

The following will be excluded:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies where pain relief is assessed only by clinicians, nurses or carers (i.e., not patient-reported);
- studies of less than four hours duration or studies that fail to present data over four to six hours post-dose.

For postpartum pain, studies will be included if the pain investigated is due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; studies investigating pain due to uterine cramps alone will be excluded.

Types of participants—Studies of adult participants (at least 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery will be included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity will be equated to greater than 30 mm (Collins 1997).

Types of interventions—Parecoxib or matched placebo administered as a single parenteral dose for postoperative pain.

Types of outcome measures—Data will be collected on the following outcomes:

- Participant characteristics;
- Patient reported pain at baseline (physician, nurse or carer reported pain will not be included in the analysis);

- Patient reported pain relief expressed at least hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both);
- Time to use of rescue medication;
- Number of participants using rescue medication;
- Number of participants with one or more adverse events;
- Number of participants with serious adverse events;
- Number of withdrawals (all cause, adverse event)

Search methods for identification of studies

To identify studies for inclusion in this review, the following electronic databases will be searched:

- Cochrane CENTRAL
- MEDLINE via Ovid
- EMBASE via Ovid
- Oxford Pain Relief Database (Jadad 1996a)

Please see Appendix 1 for the MEDLINE search strategy, all other database search strategies will be adapted from this search. Additional studies will be sought from the reference lists of retrieved articles, textbooks and reviews.

Language—No language restriction will be applied.

Unpublished studies—The manufacturing pharmaceutical company will not be contacted for unpublished trial data.

Data collection and analysis

Selection of studies—Two review authors will independently assess and agree the search results for studies that might be included in the review.

Quality assessment—Two review authors will independently assess the included studies for quality using a five-point scale (Jadad 1996b) that considers randomisation, blinding, study withdrawals and dropouts.

Data management—Data will be extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling will be entered into RevMan 5.

Data analysis—For each study, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID (Appendix 2) values for active and placebo will be converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The proportion of participants in each treatment group who achieved at least 50%maxTOTPAR will be calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These

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proportions will then be converted into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. Information on the number of participants with at least 50%maxTOTPAR for active and placebo will then be used to calculate relative benefit/relative risk, and number-needed-to-treat-to-benefit (NNT).

Pain measures accepted for the calculation of TOTPAR or SPID will be:

- five-point categorical pain relief (PR) scales with comparable wording to “none, slight, moderate, good or complete”;
- four-point categorical pain intensity (PI) scales with comparable wording to “none, mild, moderate, severe”;
- visual analogue scales (VAS) for pain relief;
- VAS for pain intensity;
- five-point categorical global scale with comparable wording to “poor, fair, good, very good, excellent” (Collins 2001)

The number of participants reporting treatment-emergent adverse effects will be extracted for each treatment group. Relative benefit/risk estimates will be calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT/Number-needed-to-treat-to-harm (NNH) and 95% CI will be calculated using the pooled number of events using the method devised by Cook and Sackett (Cook 1995). A statistically significant difference from control will be assumed when the 95% CI of the relative risk/relative benefit does not include one. Homogeneity will be examined visually using L’Abbe plots (L’Abbe 1987).

Sub-group analyses are planned to determine the effect of dose, presenting condition (pain model), and high versus low (two or fewer versus three or more) quality trials. A minimum of two trials and 200 participants must be available in any sensitivity analysis (Moore 1998).

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Internal sources

- Pain Research Funds, UK.

External sources

- NHS Cochrane Collaboration Programme Grant scheme, UK.

Appendix 1. MEDLINE search strategy

Search strategy for MEDLINE (via Ovid)

1. parecoxib [single term MESH]
2. dynastat
3. OR/1-2

4. PAIN, POSTOPERATIVE [single term MeSH]
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")) [in title, abstract or keywords]
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$))[in title, abstract or keywords]
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")) [in title, abstract or keywords]
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)) [in title, abstract or keywords]
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$"))[in title, abstract or keywords]
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$"))
11. OR/4-10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized controlled trials.sh.
15. random allocation.sh.
16. double-blind method.sh.
17. clinical trial.pt.
18. exp clinical trials/
19. (clin$ adj25 trial$).ti,ab.
20. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
21. placebos.sh.
22. placebo$.ti,ab.
23. random$.ti,ab.
24. research design.sh.
25. OR/12-24
26. 3 AND 11 AND 25

Appendix 2. Glossary

Categorical rating scale

The commonest is the five category scale (none, slight, moderate, good or lots, and complete). For analysis numbers are given to the verbal categories (for pain intensity, none=0, mild=1, moderate=2 and severe=3, and for relief none=0, slight=1, moderate=2, good or lots=3 and complete=4). Data from different subjects is then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means). The validity of converting categories into numerical scores was checked by comparison with concurrent visual analogue scale measurements. Good correlation was found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

VAS

Visual analogue scale: lines with left end labelled “no relief of pain” and right end labelled “complete relief of pain”, seem to overcome this limitation. Patients mark the line at the point which corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the patient’s mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. More concentration and coordination are needed, which can be difficult post-operatively or with neurological disorders.

TOTPAR

Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule.

SPID

Summed pain intensity difference (SPID) is calculated as the sum of the differences between the pain scores over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the trapezoidal rule.

VAS TOTPAR and **VAS SPID** are visual analogue versions of TOTPAR and SPID.

See “Measuring pain” in Bandolier’s Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13.

HISTORY

Protocol first published: Issue 2, 2004

WHAT'S NEW

20 June 2008	New citation required and major changes	New authors have taken over this title and brought the protocol up to date
23 May 2008	Amended	Converted to new review format.

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* *Indicates the major publication for the study*