Single dose oral etodolac for acute postoperative pain in adults

Shravan Kumar Tirunagari[2], **Sheena Derry**[1], **R Andrew Moore**[1], and **Henry J McQuay**[1]

[1]Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK

[2]Anaesthesia and Critical Care, Oxford Deanery, Hemel Hempstead, UK

Abstract

Background—Etodolac is a selective cyclo-oxygenase-2 (COX-2) inhibitor, with evidence of efficacy in osteoarthritis and rheumatoid arthritis. Its analgesic efficacy in postoperative pain has not been clearly established. There are no systematic reviews on Etodolac's use in this condition.

Objectives—To assess the analgesic efficacy of etodolac in single oral doses for moderate and severe postoperative pain.

Search methods—We searched Cochrane CENTRAL, MEDLINE, EMBASE and the Oxford Pain Relief Database for studies to May 2009.

Selection criteria—Randomised, double blind, placebo-controlled trials of single dose orally administered etodolac (any formulation) in adults with moderate to severe acute postoperative pain.

Data collection and analysis—Two review authors independently assessed trial quality and extracted data. Pain relief or pain intensity data were extracted and converted into the dichotomous outcome of number of participants with at least 50% pain relief over 4 to 6 hours, from which relative risk (RR) and number needed to treat to benefit (NNT) were calculated. Numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, were sought as additional measures of efficacy. Information on adverse events and withdrawals were collected.

Main results—Nine studies (1459 participants) compared etodolac and placebo. Studies were of adequate reporting quality, and the majority of participants had pain following dental extractions.

The dose of etodolac used was 25 mg to 1200 mg, with most of the information for 100 mg and 200 mg. For at least 50% pain relief over 4 to 6 hours compared with placebo the NNT for etodolac 100 mg (498 participants) was 4.8 (3.5 to 7.8) and for etodolac 200 mg (670 participants) it was 3.3 (2.7 to 4.2). Very limited information with the extended release formulation did not suggest improved benefit for this outcome.

The proportion of participants with at least 50% pain relief was 41% with 100 mg and 44% with 200 mg. Remedication was needed by about 60% with etodolac 200 mg or 400 mg over 6 to 8 hours, compared with almost 80% with placebo.

Adverse events were uncommon, and not significantly different form placebo.

Authors' conclusions—Etodolac 200 mg may be a useful analgesic in postoperative pain, with efficacy similar to paracetamol 1000 mg and celecoxib 200 mg. Higher doses may provide analgesia equivalent to more commonly used drugs, such as ibuprofen 400 mg, naproxen 500 mg and diclofenac 50 mg.

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage; adverse effects]; Cyclooxygenase 2 Inhibitors [*administration & dosage; adverse effects]; Etodolac [*administration & dosage; adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Tooth Extraction [adverse effects]

MeSH check words

Adult; Humans

BACKGROUND

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care. This is one of a series of reviews whose aim is to increase awareness of the range of analgesics that are potentially available, and 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. Recently published reviews include paracetamol (Toms 2008), naproxen (Derry C 2009a), diclofenac (Derry P 2009), ibuprofen (Derry C 2009b), celecoxib (Derry 2008), parecoxib (Lloyd 2009) and etoricoxib (Clarke 2009).

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants is small, allowing no reliable conclusions to be drawn about safety. 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, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an

analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is hence important for all participants in the trials.

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 scales immediately before the intervention, and then using pain intensity and pain relief scales over the following 4 to 6 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. For patients given rescue medication 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 4 to 6 hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first 6 hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

NSAIDs have pain-relieving, antipyretic and anti-inflammatory properties, are proven to be effective following day surgery and minor surgery, and have an opiate-sparing effect after more major surgery (Grahame-Smith 2002). However, a major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site (because of the inhibition of platelet aggregation) (Forrest 2002) and from the upper gastrointestinal tract, (especially in patients stressed by surgery, the elderly, frail, or dehydrated). Drug treatments that combine the pain-relieving properties of NSAIDs without these adverse effects are likely to have a place in clinical practice.

Selective cyclo-oxygenase-2 (COX-2) inhibitors or 'coxibs' were developed to address the problem of upper gastrointestinal bleeding (Hawkey 2001). NSAIDs are thought to relieve pain by inhibiting cyclo-oxygenases and thus the production of prostaglandins (Hawkey 1999). Prostaglandins occur throughout body tissues and fluids and act to stimulate pain nerve endings and promote/inhibit the aggregation of blood platelets. Cyclooxygenase has at least two isoforms: COX-1 and COX-2. COX-1 is constitutive while COX-2 is induced at sites of inflammation and produces the prostaglandins involved in inflammatory responses and pain mediation (Grahame-Smith 2002). Unlike traditional NSAIDs such as ibuprofen and ketoprofen, the 'coxibs' are selective inhibitors, blocking primarily the action of COX-2 and causing fewer gastrointestinal effects (Moore 2005b). In common with other NSAIDS, COX-2 inhibitors can give rise to fluid retention and renal damage (Garner 2002), so particular caution is needed in the elderly (Hawkey 2001). They have also been associated with increased cardiovascular problems, mainly in trials in patients with pre-cancerous colorectal polyps, which led to the withdrawal of one coxib (Kearney 2006). Use of coxibs

and non-selective NSAIDs in patients with bowel problems such as ulcerative colitis and Crohn's Disease is complicated (Hawkey 2006).

COX-2 inhibitors, like non-selective NSAIDs, are also useful for the relief of acute pain, especially in patients with a high risk of upper gastrointestinal bleeding or those with a history of peptic ulcer. They should not precipitate bleeding events through inhibition of platelet aggregation (Straube 2005).

Etodolac, 2-(1,8-Diethyl-4,9-dihydro-3H-pyrano[3,4-b]indol-1-yl)acetic acid, is a selective COX-2 inhibitor. In vitro levels of COX-1 and COX-2 inhibition on whole blood are around 70% and 90% respectively (Garcia Rodriguez 2008). It is used primarily for the treatment of arthritic and musculoskeletal conditions. Etodolac is available in various oral dosage forms between 200 mg and 600 mg, but 300 mg and 600 mg tablets and capsules are available in the UK, for example. It is currently licensed in the UK for symptomatic relief in osteoarthritis and rheumatoid arthritis, and 345,000 primary care prescriptions were dispensed in England in 2007 (PACT 2007). It is rarely used for postoperative pain. Licensed indications and extent of prescribing vary between countries.

OBJECTIVES

To evaluate the analgesic efficacy and safety of oral etodolac in the treatment of acute postoperative pain, using criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005), and methods that will allow comparison with other analgesics evaluated in the same way.

METHODS

Criteria for considering studies for this review

Types of studies—Included studies were double blind trials of single dose etodolac compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Multiple dose studies were included if appropriate data from the first dose were available. Crossover studies were included provided data from the first arm was presented separately.

Studies were excluded if they were:

- posters or abstracts not followed up by full publication;

- reports of trials concerned with pain other than postoperative pain (including experimental pain);

- studies using healthy volunteers;

- studies where pain relief was assessed by clinicians, nurses or carers (i.e. not patient-reported);

- studies of less than four hours' duration or which failed to present data over four to six hours post-dose.

Types of participants—Studies of adult participants (> 15 yrs) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was equated to greater than 30 mm (Collins 1997). Studies of participants with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp). Studies investigating participants with pain due to uterine cramps alone were excluded.

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

Types of outcome measures—Data collected included the following:

- characteristics of participants;

- pain model;

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

- patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours;

- patient-reported global assessment of treatment (PGE), using a standard five-point scale;

- number of participants using rescue medication, and the time of assessment;

- time to use of rescue medication;

- withdrawals - all cause, adverse event;

- adverse events - participants experiencing one or more, and any serious adverse event, and the time of assessment.

Search methods for identification of studies

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

- Cochrane CENTRAL (issue 2, 2009);

- MEDLINE via Ovid (May 2009);

- EMBASE via Ovid (May 2009);

- Oxford Pain Relief Database (Jadad 1996a).

Please see Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the Cochrane CENTRAL search strategy.

Additional studies were sought from the reference lists of retrieved articles, textbooks and reviews.

Language—No language restriction was applied.

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

Data collection and analysis

Selection of studies—Two review authors independently assessed and agreed the search results for studies that might be included in the review. Disagreements were resolved by consensus or referral to a third review author.

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

The scale used is as follows.

- Is the study randomised? If yes give one point.

- Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.

- Is the study double blind? If yes then add one point.

- Is the double blind method reported and is it appropriate? If yes add one point, if no deduct one point.

- Are the reasons for patient withdrawals and dropouts described? If yes add one point.

Data management—Data was extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling was be entered into RevMan 5.0.

Data analysis—QUOROM guidelines were followed (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used number of participants who received study medication in each treatment group. Analyses were planned for different doses. Sensitivity analyses were planned for pain model (dental versus other postoperative pain), trial size (39 or fewer versus 40 or more per treatment arm), and quality score (two versus three or more), and formulation (standard tablet versus more soluble tablet or liquid preparations). A minimum of two studies and 200 participants were required for any analysis (Moore 1998).

Primary outcome

Number of participants achieving at least 50% pain relief: For each study, mean TOTPAR (total pain relief) or SPID (summed pain intensity difference) for active and placebo groups

were 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 was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then 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 treatment and placebo was then used to calculate relative benefit (RB) and number needed to treat to benefit (NNT).

Pain measures accepted for the calculation of TOTPAR or SPID were:

- 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.

If none of these measures were available, numbers of participants reporting "very good or excellent" on a five-point categorical global scale with the wording "poor, fair, good, very good, excellent" were taken as those achieving at least 50% pain relief (Collins 2001). Further details of the scales and derived outcomes are in the glossary (Appendix 4).

Secondary outcomes:

1. **Use of rescue medication**. Numbers of participants requiring rescue medication were used to calculate relative risk (RR) and numbers needed to treat to prevent (NNTp) use of rescue medication for treatment and placebo groups. Median (or mean) time to use of rescue medication was used to calculate the weighted mean of the median (or mean) for the outcome. Weighting was by number of participants.

2. **Adverse events**. Numbers of participants reporting adverse events for each treatment group were used to calculate RR and numbers needed to treat to harm (NNH) estimates for:

    i) any adverse event;

    ii) any serious adverse event (as reported in the study);

    iii) withdrawal due to an adverse event.

3. **Withdrawals**. Withdrawals for reasons other than lack of efficacy (participants using rescue medication - see above) and adverse events were noted, as were exclusions from analysis where data were presented.

RB or RR estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CI were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant

difference from control was assumed when the 95% CI of the RB did not include the number one.

Homogeneity of studies was assessed visually (L'Abbé 1987).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Searches identified 15 potentially relevant studies. Nine studies were included in the review (Fliedner 1984; Friedrich 1983; Gaston 1984; Gaston 1986; Giglio 1986; Hersh 1999; Hutton 1983; Nelson 1985; Versichelen 1982). Six studies were excluded (Apaydin 1994; Boni 1999; Koizuka 2004; Lin 2006; Mizraji 1990; Scott 1986). Details are in the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

In the nine included studies the total number of participants was 1764, of whom 1061 were treated with etodolac (dose range 25 mg to 1200 mg) and 398 placebo.

Dose—Etodolac 25 mg was used in two treatment arms (Friedrich 1983; Versichelen 1982), 50 mg in five treatment arms (Fliedner 1984; Gaston 1984; Gaston 1986; Nelson 1985; Versichelen 1982), 100 mg in six treatment arms (Fliedner 1984; Friedrich 1983; Gaston 1986; Hutton 1983; Nelson 1985; Versichelen 1982), 200 mg in eight treatment arms (Fliedner 1984; Gaston 1984; Gaston 1986;Giglio 1986; Hersh 1999; Hutton 1983; Nelson 1985; Versichelen 1982), and 400 mg in three treatment arms (Giglio 1986; Hersh 1999; Versichelen 1982). One study (Hersh 1999) also included two treatment arms using 400 mg and 1200 mg of the extended release (ER) formulation of etodolac.

Study duration—Study duration was 8 hours in three studies (Friedrich 1983; Gaston 1984; Versichelen 1982), 12 hours in five studies (Fliedner 1984; Gaston 1986; Giglio 1986; Hutton 1983; Nelson 1985), and 24 hours in one study (Hersh 1999).

Type of surgery—Seven studies were carried out in participants with dental pain following surgical extraction of one or more impacted third molars (Fliedner 1984; Gaston 1984; Gaston 1986; Giglio 1986; Hersh 1999; Hutton 1983; Nelson 1985), one in participants with post episiotomy pain (Friedrich 1983), and one in participants with pain following orthopaedic and urological surgery (Versichelen 1982).

Risk of bias in included studies

Methodological quality of included studies—All included studies were both randomised and double blind. Two studies were given a score of five (Gaston 1986; Giglio 1986), four a score of four (Fliedner 1984; Hersh 1999; Nelson 1985; Versichelen 1982), and three a score of three (Friedrich 1983; Gaston 1984; Hutton 1983). Points were lost mainly due to inadequate descriptions of the methods of randomisation and double blinding. Details are in the 'Characteristics of included studies' table.

Effects of interventions

One study (Versichelen 1982) did not contribute data to the primary outcome. This study reported TOTPAR at 8 hours, using a non-standard scale, and did not provide sufficient data to allow recalculation over 4 to 6 hours. Non standard scales were used to assess pain intensity difference and patient global estimate.

Number of participants achieving at least 50% pain relief

Etodolac 50 mg versus placebo: Four studies with 360 participants provided data (Fliedner 1984; Gaston 1984; Gaston 1986; Nelson 1985) (Figure 1).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with etodolac 50 mg was 29% (44/154; range 27% to 32%).

- The proportion of participants experiencing at least 50% pain relief with placebo was 17% (34/206; range 14% to 21%).

- The relative benefit of treatment compared with placebo was 1.7 (1.1 to 2.6), giving an NNT for at least 50% pain relief over 4 to 6 hours of 8.3 (4.8 to 30).

Etodolac 100 mg versus placebo: Five studies with 498 participants provided data (Fliedner 1984; Friedrich 1983; Gaston 1986; Hutton 1983; Nelson 1985) (Figure 2).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with etodolac 100 mg was 41% (103/251; range 33% to 58%).

- The proportion of participants experiencing at least 50% pain relief with placebo was 20% (50/247; range 14% to 40%).

- The relative benefit of treatment compared with placebo was 2.0 (1.5 to 2.7), giving an NNT for at least 50% pain relief over 4 to 6 hours of 4.8 (3.5 to 7.8).

Etodolac 200 mg versus placebo: Seven studies with 670 participants provided data (Fliedner 1984; Gaston 1984; Gaston 1986; Giglio 1986; Hersh 1999; Hutton 1983; Nelson 1985) (Figure 3).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with etodolac 200 mg was 44% (145/333; range 36% to 56%).

- The proportion of participants experiencing at least 50% pain relief with placebo was 13% (44/337; range 4% to 21%).

- The relative benefit of treatment compared with placebo was 3.3 (2.5 to 4.5), giving an NNT for at least 50% pain relief over 4 to 6 hours of 3.3 (2.7 to 4.2).

There were insufficient data to give robust estimates for this outcome for etodolac 25 mg, 400 mg (standard preparation only), and 1200 mg ER. At 400 mg the extended release formulation appeared to perform less well than the standard preparation (Analysis 4.1). NNTs for both standard and combined formulations are given in the Summary of results table A, but should be interpreted with caution due to the small numbers of participants and the heterogeneity due to formulation. The results suggest a dose response, but the

differences are not significant since CIs are wide and overlap, possibly due to low numbers of participants.

Summary of results A: Number of participants with ≥ 50% pain relief over 4 to 6 hours					
Dose	Studies	Participants	Etodolac (%)	Placebo (%)	NNT (95%CI)
50 mg	4	360	27	17	8.3 (4.8 to 30)
100 mg	5	498	41	20	4.8 (3.5 to 7.8)
200 mg	7	670	44	13	3.3 (2.7 to 4.2)
400 mg (including ER)	3	222	39	5	2.9 (2.3 to 4.0)
400 mg (standard formulation)	2	149	51	5	2.2 (1.7 to 2.9)

Sensitivity analysis of primary outcome

Methodological quality: All studies had scores of three or more, so no sensitivity analysis could be carried out for this criterion.

Study size: All but one study (Fliedner 1984) used treatment groups with between 37 and 49 participants, so no sensitivity analysis could be carried out for this criterion.

Pain model: dental versus other surgery: Only two studies were not in participants with dental pain: one (Versichelen 1982) did not provide any data for the primary outcome, and the other (Friedrich 1983) was in post episiotomy pain. There were insufficient data to compare dental versus episiotomy models, but removing the episiotomy study from the efficacy analysis for etodolac 100 mg did not appreciably change the result (NNT 4.2 (3.1 to 6.9)).

Formulation: One study (Hersh 1999) included two treatment arms using the extended release formulation of etodolac at 400 mg and 1200 mg. There were insufficient data to compare this formulation with the standard one, but neither appeared to do well over 4 to 6 hours, and removing the ER treatment arm from the efficacy analysis for 400 mg etodolac did give an improved NNT, although the difference was not significant (see above).

Use of rescue medication

Proportion of participants using rescue medication: Four studies reported this outcome after 6 to 8 hours (Friedrich 1983; Giglio 1986; Hersh 1999; Versichelen 1982).

- Three studies using etodolac 200 mg reported this outcome after 6 to 8 hours (Giglio 1986; Hersh 1999; Versichelen 1982). The weighted mean proportion was 61% (67/110) with etodolac 200 mg and 77% (84/109) with placebo, giving an NNTp of 6.2 (3.5 to 24) (Analysis 3.2). In dental studies only (Giglio 1986; Hersh 1999) the weighted mean proportion was 64% (57/89) with etodolac 200 mg and 88% (77/88) with placebo, giving an NNTp of 4.3 (2.8 to 8.8).

- Three studies using etodolac 400 mg (standard formulation) reported this outcome after 6 to 8 hours (Giglio 1986; Hersh 1999; Versichelen 1982). The weighted

mean proportion was 63% (67/106) with etodolac 400 mg and 77% (84/109) with placebo, giving an NNTp of 7.2 (3.9 to 57) (Analysis 4.2). In dental studies only (Giglio 1986; Hersh 1999) the weighted mean proportion was 59% (51/86) with etodolac 400 mg and 88% (77/88) with placebo, giving an NNTp of 3.6 (2.5 to 6.4).

There were insufficient data for analysis of other doses. No significant difference was demonstrated between 200 mg and 400 mg for this outcome. It should be noted that the analyses in dental studies only have fewer than 200 participants.

Time to use of rescue medication: Only two studies (Friedrich 1983; Hersh 1999) reported this outcome. There were insufficient data for analysis.

Adverse events

Any adverse event: All studies, except Nelson 1985, provided data for this outcome. It was not always clear whether studies continued to collect data for adverse events after participants withdrew, for example due to lack of efficacy (took rescue medication). Most studies, including Nelson 1985, reported that the majority of adverse events were mild or moderate in severity.

Two studies (Friedrich 1983; Gaston 1984) collected data over 8 hours, four (Fliedner 1984; Gaston 1986; Giglio 1986) over 12 hours, and two (Hersh 1999; Versichelen 1982) over 24 hours. There was no obvious difference in rates of adverse events in studies conducted over the different time periods.

Adverse events were rare in the non dental studies (Friedrich 1983; Versichelen 1982), with only six events in active treatment arms (6/181, 3.3%), and no events in placebo arms (0/61). They were more common in the dental studies.

- Four studies using etodolac 50 mg reported on the number of participants with at least one adverse event (Fliedner 1984; Gaston 1984; Gaston 1986; Versichelen 1982): 8% (10/132) with etodolac, and 6% (12/188) with placebo (Analysis 1.2).

- Five studies using etodolac 100 mg reported on the number of participants with at least one adverse event (Fliedner 1984; Friedrich 1983; Gaston 1986; Hutton 1983; Versichelen 1982): 11% (26/230) with etodolac, and 7% (16/229) with placebo (Analysis 2.3).

- Seven studies using etodolac 200 mg reported on the number of participants with at least one adverse event (Fliedner 1984; Gaston 1984; Gaston 1986; Giglio 1986; Hersh 1999; Hutton 1983; Versichelen 1982): 22% (68/314) with etodolac, and 17% (55/319) with placebo (Analysis 3.3).

- Four studies using etodolac 400 mg reported on the number of participants with at least one adverse event (Giglio 1986; Hersh 1999; Versichelen 1982): 28% (43/154) with etodolac, and 34% (53/156) with placebo (Analysis 4.3).

No significant difference was demonstrated between etodolac at any of these doses and placebo.

Summary of results B: Participants with at least one adverse event					
Dose	Studies	Participants	Etodolac (%)	Placebo (%)	NNH (95%CI)
50 mg	4	320	8	6	not calculated
100 mg	5	459	11	7	not calculated
200 mg	7	633	22	17	not calculated
400 mg	4	310	28	34	not calculated

Serious adverse events: Only one serious adverse event was reported. This was a postoperative bleed in a patient who received etodolac 200 mg (Giglio 1986), and was more likely to be due to the surgical procedure than the analgesic medication.

Withdrawals—Participants who took rescue medication were classified as withdrawals due to lack of efficacy, and details are reported under "Use of rescue medication" above. A small number of participants were excluded from efficacy analyses, but these are unlikely to have affected results. The most common reason for exclusions due to protocol violations in single dose acute pain studies is that participants do not have moderate or severe pain (McQuay 1982).

The only withdrawal specifically reported was due to an adverse event (see above, Giglio 1986).

See Table 1 for details of results for measures of pain relief and use of rescue medication and Table 2 for details of results for adverse events and withdrawals.

DISCUSSION

This review included nine studies using etodolac to treat acute pain following dental, orthopaedic and urological surgery; 1061 participants were treated with etodolac (dose range 25 mg to 1200 mg) and 398 with placebo. The studies were of adequate quality to minimise bias, but analysis of some outcomes was limited by the small number of participants, and results should be interpreted with caution.

At a dose of 200 mg, etodolac provided a substantial level of pain relief to 44% of participants experiencing moderate or severe pain. The NNT for at least 50% pain relief over 4 to 6 hours was 3.3 (2.7 to 4.2) at this dose, meaning that for every seven individuals treated, two would experience this level of pain relief who would not have done so if treated with placebo. Results for other doses are compatible with a dose response over the range 50 mg to 400 mg, but there were insufficient data to determine whether differences seen were statistically significant. It is worth noting that the doses used in these studies were mostly lower than the recommended single dose of 300 mg (maximum 600 mg daily), and lower than those used in studies in osteoarthritis and rheumatoid arthritis where 150 mg to 300 mg twice daily was commonly given (Chen 2008).

Indirect comparisons of NNTs for at least 50% pain relief over 4 to 6 hours in reviews of other analgesics using identical methods indicate that etodolac 200 mg has equivalent efficacy to celecoxib 200 mg (3.2 (2.7 to 3.9)) (Derry 2008), naproxen 200 mg (3.4 (2.4 to 5.8)) (Derry C 2009a), and paracetamol 1000 mg (3.6 (3.2 to 4.1)) (Toms 2008). It is less effective than the commonly used higher doses of celecoxib (400 mg: 2.5 (2.2 to 2.9); Derry 2008) and naproxen (500 mg: 2.7 (2.3 to 3.2); Derry C 2009a), or ibuprofen 400 mg (2.5 (2.4 to 2.6) (Derry C 2009b), diclofenac 50 mg (2.7 (2.4 to 3.0) (Derry P 2009). The 400 mg dose of etodolac may be as effective as ibuprofen 400 mg, but further studies using this, and possibly higher doses are required to determine maximum analgesic benefit. A current listing of reviews of analgesics in the single dose postoperative pain model can be found at www.medicine.ox.ac.uk/bandolier/index.html.

There were sufficient data in these studies to allow direct comparison between etodolac and aspirin 650 mg. For etodolac 100 mg compared with aspirin 650 mg there was no significant difference for numbers of participants experiencing at least 50% pain relief over 4 to 6 hours, and for etodolac 200 mg the difference reached borderline significance in favour of etodolac (Analysis 6.1; Analysis 7.1).

Etodolac versus Aspirin 650 mg: 50% pain relief over 4 to 6 hours

	Type of surgery	Studies	Participants	Relative risk (95% CI)
Etodolac 100 mg	Dental + episiotomy	5	491	1.00 (0.83 to 1.2)
Etodolac 100 mg	Dental	4	412	1.01 (0.82 to 1.3)
Etodolac 200 mg	Dental	5	485	1.3 (1.05 to 1.5)

The NNTp to use of rescue medication within 6 to 8 hours were six and seven for etodolac 200 mg or 400 mg respectively. For comparison, with diclofenac 50 mg and ibuprofen 400 mg, the corresponding number is less than three. There were insufficient data to determine the median or mean time to use of rescue medication but since over 60% of participants needed rescue medication within 6 to 8 hours, the median time will be less than this. Given the usual dosing schedule of twice daily, this may leave some patients with untreated pain in acute conditions.

Subgroup analyses to examine the effect of the pain model (dental versus other surgery) and formulation (standard versus extended release) on the primary outcome could not be performed because of insufficient data. Study size could not be examined because almost all treatment arms were of a very similar size.

The number of participants experiencing at least one adverse event was reported by most studies, although the methods used to collect the information were not always explicit. The time over which it was collected varied, from 6 to 12 hours, and may have included periods after the use of rescue medication, which may cause its own adverse events. Poor reporting of adverse events in acute pain trials has been noted before (Edwards 1999). The usefulness of single dose studies for assessing adverse events is questionable, but it is non-the-less reassuring that there was no difference between etodolac (at any dose) and placebo for

occurrence of any adverse event, and that the only serious adverse event and adverse event withdrawal was not thought to be related to the test drug. Although the proportion of participants with any adverse event increased with dose of etodolac, it also increased with corresponding placebo. The higher rates overall were due mainly to high rates in two studies (Giglio 1986; Hersh 1999) that collected data over 12 and 24 hours respectively, and may be the result of different methods of data collection. Direct comparison of etodolac 100 mg or 200 mg and aspirin 650 mg in these studies showed no significant difference in numbers of participants experiencing at least one adverse event (Analysis 6.2; Analysis 7.2).

Long-term, multiple dose studies should be used for meaningful analysis of adverse events since, even in acute pain settings, analgesics are likely to be used in multiple doses. Studies lasting up to one year in osteoarthritis and rheumatoid arthritis have shown rates of adverse events slightly higher than with placebo, but lower than non-selective NSAIDs and similar to that of other coxibs, and with fewer gastrointestinal or cardiovascular events than traditional NSAIDs (Chen 2008).

In single dose studies most exclusions occur for protocol violations such as failing to meet baseline pain requirements, or failing to return for post treatment visits after the acute pain results are concluded. These are unlikely to significantly affect the results. For missing data it has been shown that over the 4 to 6 hour period, there is no difference between baseline observation carried forward, which gives the more conservative estimate, and last observation carried forward (Moore 2005).

AUTHORS' CONCLUSIONS

Implications for practice

Etodolac is an effective analgesic in acute postoperative pain. At a dose of 200 mg it is comparable to paracetamol 1000 mg, and lower doses of commonly used analgesics, such as naproxen 200 mg and celecoxib 200 mg. It provides a clinically useful level of analgesia over 4 to 6 hours to about 40% of those treated with Etodolac. The higher dose of 400 mg may provide better levels of analgesia. In single dose, etodolac is well tolerated and is associated with a low rate of adverse events, similar to that with placebo.

Implications for research

Further information would be needed to confirm a dose response, and in particular to determine whether the higher dose of 400 mg can provide analgesia equivalent to other commonly used analgesics such as ibuprofen 400 mg, naproxen 500 mg, and diclofenac 50 mg. New studies should also report on time to use of rescue medication to provide information about duration of analgesia.

Acknowledgments

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.

- NIHR Biomedical Research Centre Programme, UK.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fliedner 1984

Methods	RCT, DB, single dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 30, 60 min, then hourly to 12 h
Participants	Moderate to severe pain following removal of impacted third molars Mean age 24 years N = 384 M = 160 F = 224
Interventions	Etodolac 50 mg, n = 37 Etodolac 100 mg, n = 87 Etodolac 200 mg, n = 86 Aspirin 650 mg, n = 83 Placebo, n = 87
Outcomes	PI: non standard (5 point scale) PR: standard 5 point scale PGE: non standard (4 point scale) Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 No analgesic or other potentially confounding medication within 4 h of surgery Rescue medication permitted - no further details

Friedrich 1983

Methods	RCT, DB, single dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 30, 60 mins, then hourly to 8 h
Participants	Elective gynaecological surgery Age range 18 to 34 years N = 159 All F
Interventions	Etodolac 25 mg, n = 40 Etodolac 100 mg, n = 40 Aspirin 650 mg, n = 39 Placebo, n = 40
Outcomes	PI: non standard scale (5 point) PR: 5 point scale - non standard wording, reverse order PGE: non standard scale (4 point) Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Rescue medication permitted - no further details

Gaston 1984

Methods	RCT, DB, single dose, 4 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed 30, 60 mins, then hourly to 8 h
Participants	Moderate to severe pain following removal of multiple impacted teeth
	Mean age 27 years
	N = 161
	M = 127
	F = 34
Interventions	Etodolac 50 mg, n = 39
	Etodolac 200 mg, n = 40
	Aspirin 650 mg, n = 40
	Placebo, n = 42
Outcomes	PI: non standard 5 point scale
	PR: standard 5 point scale (reverse order)
	PGE: non standard 4 point scale
	Adverse events: any, serious
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1
	No analgesic or psychotropic drugs within 4 h of surgery
	Rescue medication permitted - no further details

Gaston 1986

Methods	RCT, DB, single dose, 5 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed 30, 60 mins, then hourly to 12 h
Participants	Moderate to severe pain following reo mval of impacted third molar
	Mean age 24 years
	N = 189
	M = 90
	F = 98
Interventions	Etodolac 50 mg, n = 37
	Etodolac 100 mg, n = 38
	Etodolac 200 mg, n = 38
	Aspirin 650 mg, n = 38
	Placebo, n = 38
Outcomes	PI: non standard 5 point scale
	PR: standard 5 point scale
	PGE: standard 4 point scale
	Time use of rescue medication
	Numbers using rescue medication
	Adverse events: any
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication permitted after 1 h

Giglio 1986

Methods	RCT, DB, single dose, 3 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed at 30, 60 mins, then hourly to 12 h
Participants	Moderate to severe pain following reo mval of impacted third molar
	Mean age 24 years
	N = 122
	M = 48

	F = 74
Interventions	Etodolac 200 mg, n = 42 Etodolac 400 mg, n = 39 Placebo, n = 41
Outcomes	PI: non standard scale (5 point) PR: 5 point scale - standard wording, non standard numbers PGE: non standard scale (4 point) Numbers using rescue medication Adverse events: any, serious Withdrawals (combined with study A)
Notes	Oxford Quality Score: R2, DB2, W1 No analgesics or psychotropic drugs within 4 h of surgery Rescue medication permitted after 1 h

Hersh 1999

Methods	RCT, DB, single and two dose phases, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 15, 30, 45, 60, 75, 90, 105, 120 mins, then hourly to 12 h, then at 24 h
Participants	Moderate to severe pain following removal of impacted third molar Mean age 23 years N = 237 M = 104 F = 133
Interventions	Etodolac 200 mg, n = 47 Etodolac 400 mg, n = 46 Etodolac ER 400 mg, n = 49 Etodolac ER 1200 mg, n = 48 Placebo, n = 47
Outcomes	PI: standard 4 point scale PR: standard 5 point scale PGE: standard 5 point scale Time to use of rescue medication Numbers using rescue medication Adverse events: any Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 No analgesics, hypnotics, psychotropic agents, caffeine within 12 h of surgery Rescue medication permitted after 2 h (paracetamol + codeine)

Hutton 1983

Methods	RCT, DB, single dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 30, 60 min, then hourly to 12 h
Participants	Moderate to severe pain following removal of impacted third molar Mean age 24 years N = 169 (168 analysed for efficacy) M = 54 F = 114
Interventions	Etodolac 100 mg, n = 44 Etodolac 200 mg, n = 41 Aspirin 650 mg, n = 40 Placebo, n = 43
Outcomes	PI: non standard scale (5 point) PR: 5 point scale - standard wording, reverse order

PGE: non standard scale (4 point)
Adverse events: any, serious
Withdrawals

| Notes | Oxford Quality Score: R1, DB1, W1
Rescue medication permitted - no further details |

Nelson 1985

Methods	RCT, DB, single dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 30, 60 min, then hourly to 12 h
Participants	Moderate to severe pain following removal of impacted third molars Mean age 24 years N = 207 (201 analysed for efficacy) M = 116 F = 91
Interventions	Etodolac 50 mg, n = 41 Etodolac 100 mg, n = 42 Etodolac 200 mg, n = 39 Aspirin 650 mg, n = 40 Placebo, n = 39
Outcomes	PI: non standard scale (5 point) PR: 5 point scale - standard wording PGE: standard 5 point scale Withdrawals
Notes	Oxford Quality Scale: R1, DB2, W1 Rescue medication permitted after 1 h

Versichelen 1982

Methods	RCT, DB, single dose, 7 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 30, 60 mins, then hourly to 8 h
Participants	Moderate to severe pain following orthopedic or urologic surgery Mean age 36 years N = 142 M = 94 F = 48
Interventions	Etodolac 25 mg, n = 21 Etodolac 50 mg, n = 19 Etodolac 100 mg, n = 20 Etodolac 200 mg, n = 21 Etodolac 400 mg, n = 20 Aspirin 650 mg, n = 20 Placebo, n = 21
Outcomes	PI: no details about scale PR: no details about scale PGE: non standard scale (4 point) Number of patients using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 No analgesic, sedative or psychotropic drug within 4 h of surgery Rescue medication permitted after 1 h

DB - double blind; F - female; M - male; N - total number of participants in study; h - hour, n - number of participants in treatment arm; PGE - patient global evaluation of efficacy; PI - pain intensity; PR - pain relief; R - randomised; RCT - randomised controlled trial; std - standard; W - withdrawals

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Apaydin 1994	No placebo group.
Boni 1999	Pharmakokinetic and pharmacodynamic analysis on same participants as in Hersh 1999.
Koizuka 2004	Intervention was administered pre-operatively.
Lin 2006	Intervention was administered pre-operatively.
Mizraji 1990	Review. Includes some data that may not already be included, but insufficient to analyse
Scott 1986	No usable data.

DATA AND ANALYSES

Comparison 1

Etodolac 50 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	4	360	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.14, 2.56]
2 Participants with at least one adverse event	4	320	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.64, 3.19]

Comparison 2

Etodolac 100 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	5	498	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.53, 2.70]
2 Participants using rescue medication at 6 to 8 hours	2	121	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.96]
3 Participants with at least one adverse event	5	459	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.89, 2.84]

Comparison 3

Etodolac 200 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	7	670	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [2.47, 4.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Participants using rescue medication at 6 to 8 hours	3	219	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.94]
3 Participants with at least one adverse event	7	633	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.93, 1.66]

Comparison 4

Etodolac 400 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	2	222	Risk Ratio (M-H, Fixed, 95% CI)	9.03 [3.39, 24.06]
1.1 Standard preparation	2	149	Risk Ratio (M-H, Fixed, 95% CI)	10.91 [3.48, 34.21]
1.2 Extended release preparation	1	73	Risk Ratio (M-H, Fixed, 95% CI)	4.41 [0.59, 32.82]
2 Participants using rescue medication at 6 to 8 hours	3	235	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.89]
2.1 Standard preparation	3	191	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.04]
2.2 Extended release preparation	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.59]
3 Participants with at least one adverse event	3	263	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.12]
3.1 Standard preparation	3	190	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.51, 1.18]
3.2 Extended release preparation	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.66]

Comparison 5

Etodolac 1200 mg ER versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	1	95	Risk Ratio (M-H, Fixed, 95% CI)	9.79 [2.42, 39.58]
2 Participants using rescue medication 6 to 8 hours	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.65]
3 Participants with at least one adverse event	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.72, 2.14]

Comparison 6

Etodolac 100 mg versus aspirin 650 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	5	491	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.21]
2 Participants with at least one adverse event	5	452	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.45]

Comparison 7

Etodolac 200 mg versus aspirin 650 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	5	485	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.05, 1.54]
2 Participants with at least one adverse event	5	450	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.60, 1.60]

Analysis 1.1. Comparison 1 Etodolac 50 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 1 Etodolac 50 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	10/37	14/87		29.6 %	1.68 [0.82, 3.43]
Gaston 1984	11/39	6/42		20.5 %	1.97 [0.81, 4.83]
Gaston 1986	10/37	6/38		21.0 %	1.71 [0.69, 4.23]
Nelson 1985	13/41	8/39		29.0 %	1.55 [0.72, 3.32]
Total (95% CI)	**154**	**206**		**100.0 %**	**1.71 [1.14, 2.56]**

Total events: 44 (Etodolac), 34 (Placebo)
Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² =0.0%
Test for overall effect: Z = 2.60 (P = 0.0094)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Favours placebo   Favours etodolac 50 mg
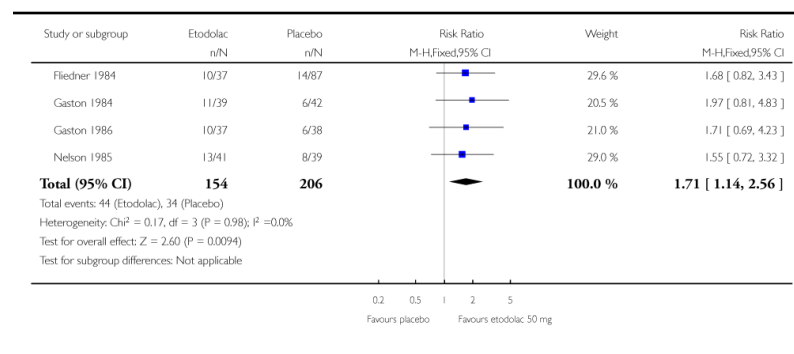
Analysis 1.2. Comparison 1 Etodolac 50 mg versus placebo, Outcome 2 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 1 Etodolac 50 mg versus placebo

Outcome: 2 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	5/37	9/87		61.0 %	1.31 [0.47, 3.63]
Gaston 1984	0/39	0/42			Not estimable
Gaston 1986	4/37	3/38		33.6 %	1.37 [0.33, 5.70]
Verschelen 1982	1/19	0/21		5.4 %	3.30 [0.14, 76.46]
Total (95% CI)	**132**	**188**		**100.0 %**	**1.44 [0.64, 3.19]**
Total events: 10 (Etodolac), 12 (Placebo)					
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² =0.0%					
Test for overall effect: Z = 0.89 (P = 0.38)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10
Favours etodolac   Favours placebo

Analysis 2.1. Comparison 2 Etodolac 100 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 2 Etodolac 100 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	36/87	14/87		27.8 %	2.57 [1.50, 4.42]
Friedrich 1983	23/40	16/40		31.8 %	1.44 [0.90, 2.29]
Gaston 1986	15/38	6/38		11.9 %	2.50 [1.09, 5.75]
Hutton 1983	15/44	6/43		12.0 %	2.44 [1.05, 5.71]
Nelson 1985	14/42	8/39		16.5 %	1.63 [0.77, 3.44]
Total (95% CI)	**251**	**247**		**100.0 %**	**2.03 [1.53, 2.70]**
Total events: 103 (Etodolac), 50 (Placebo)					
Heterogeneity: Chi² = 3.62, df = 4 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 4.88 (P < 0.00001)					
Test for subgroup differences: Not applicable					

0.2 0.5 1 2 5
Favours placebo   Favours etodolac 100 mg

Analysis 2.2. Comparison 2 Etodolac 100 mg versus placebo, Outcome 2 Participants using rescue medication at 6 to 8 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 2 Etodolac 100 mg versus placebo

Outcome: 2 Participants using rescue medication at 6 to 8 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Friedrich 1983	6/40	10/40		42.3 %	0.60 [0.24, 1.49]
Versichelen 1982	7/20	14/21		57.7 %	0.53 [0.27, 1.03]
Total (95% CI)	**60**	**61**		**100.0 %**	**0.56 [0.32, 0.96]**

Total events: 13 (Etodolac), 24 (Placebo)
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%
Test for overall effect: Z = 2.09 (P = 0.036)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Favours etodolac 100 mg   Favours placebo

Analysis 2.3. Comparison 2 Etodolac 100 mg versus placebo, Outcome 3 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 2 Etodolac 100 mg versus placebo

Outcome: 3 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	14/88	9/87		54.5 %	1.54 [0.70, 3.37]
Friedrich 1983	2/40	0/40		3.0 %	5.00 [0.25, 100.97]
Gaston 1986	4/38	3/38		18.1 %	1.33 [0.32, 5.56]
Hutton 1983	6/44	4/43		24.4 %	1.47 [0.44, 4.83]
Versichelen 1982	0/20	0/21			Not estimable
Total (95% CI)	**230**	**229**		**100.0 %**	**1.59 [0.89, 2.84]**

Total events: 26 (Etodolac), 16 (Placebo)
Heterogeneity: Chi² = 0.64, df = 3 (P = 0.89); I² =0.0%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours etodolac   Favours placebo

Analysis 3.1. Comparison 3 Etodolac 200 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 3 Etodolac 200 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	42/86	14/87		31.9 %	3.03 [1.79, 5.14]
Gaston 1984	13/40	6/42		13.4 %	2.28 [0.96, 5.40]
Gaston 1986	18/38	6/38		13.7 %	3.00 [1.34, 6.72]
Giglio 1986	16/42	2/41		4.6 %	7.81 [1.92, 31.85]
Hersh 1999	17/47	2/47		4.6 %	8.50 [2.08, 34.76]
Hutton 1983	17/41	6/43		13.4 %	2.97 [1.30, 6.79]
Nelson 1985	22/39	8/39		18.3 %	2.75 [1.40, 5.41]
Total (95% CI)	**333**	**337**		**100.0 %**	**3.34 [2.47, 4.51]**
Total events: 145 (Etodolac), 44 (Placebo)					
Heterogeneity: Chi² = 4.44, df = 6 (P = 0.62); I² =0.0%					
Test for overall effect: Z = 7.88 (P < 0.00001)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours placebo   Favours etodolac 200 mg

Analysis 3.2. Comparison 3 Etodolac 200 mg versus placebo, Outcome 2 Participants using rescue medication at 6 to 8 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 3 Etodolac 200 mg versus placebo

Outcome: 2 Participants using rescue medication at 6 to 8 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Giglio 1986	32/42	37/41		44.3 %	0.84 [0.69, 1.03]
Hersh 1999	25/47	40/47		47.4 %	0.63 [0.47, 0.84]
Versichelen 1982	10/21	7/21		8.3 %	1.43 [0.67, 3.03]
Total (95% CI)	**110**	**109**		**100.0 %**	**0.79 [0.66, 0.94]**
Total events: 67 (Etodolac), 84 (Placebo)					
Heterogeneity: Chi² = 5.26, df = 2 (P = 0.07); I² =62%					
Test for overall effect: Z = 2.66 (P = 0.0078)					
Test for subgroup differences: Not applicable					

0.2   0.5   1   2   5

Favours etodolac 200 mg   Favours placebo

Analysis 3.3. Comparison 3 Etodolac 200 mg versus placebo, Outcome 3 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 3 Etodolac 200 mg versus placebo

Outcome: 3 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	13/85	9/87		16.3 %	1.48 [0.67, 3.28]
Gaston 1984	0/40	0/42			Not estimable
Gaston 1986	2/38	3/38		5.5 %	0.67 [0.12, 3.77]
Giglio 1986	21/42	23/41		42.6 %	0.89 [0.59, 1.34]
Hersh 1999	20/47	15/47		27.5 %	1.33 [0.78, 2.27]
Hutton 1983	9/41	4/43		7.2 %	2.36 [0.79, 7.07]
Versichelen 1982	2/21	0/21		0.9 %	5.00 [0.25, 98.27]
Total (95% CI)	**314**	**319**		**100.0 %**	**1.24 [0.93, 1.66]**

Total events: 67 (Etodolac), 54 (Placebo)
Heterogeneity: Chi^2 = 5.45, df = 5 (P = 0.36); I^2 =8%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours etodolac 200 mg   Favours placebo

Analysis 4.1. Comparison 4 Etodolac 400 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 4 Etodolac 400 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours
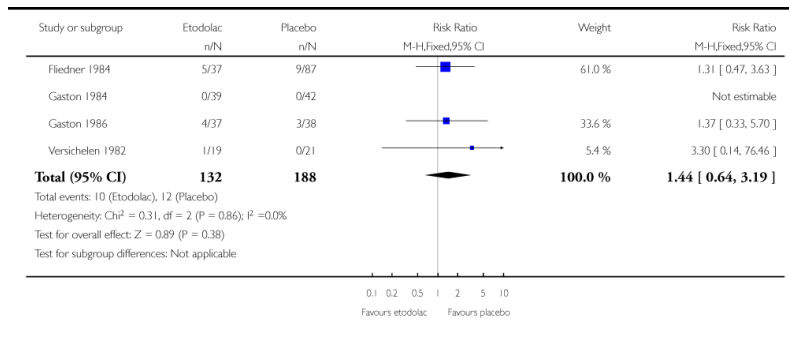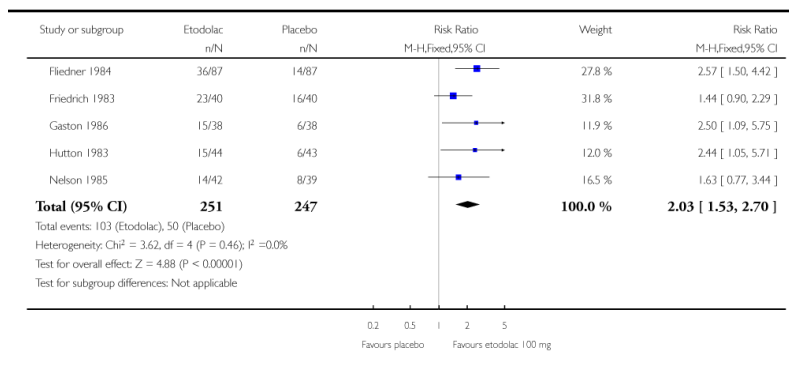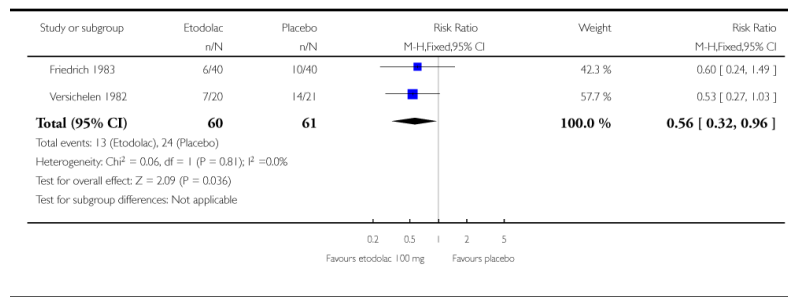
Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard preparation					
Giglio 1986	20/39	2/41		42.2 %	10.51 [2.63, 42.03]
Hersh 1999	23/46	1/23		28.8 %	11.50 [1.66, 79.91]
Subtotal (95% CI)	**85**	**64**		**71.0 %**	**10.91 [3.48, 34.21]**
Total events: 43 (Etodolac), 3 (Placebo)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 4.10 (P = 0.000041)					
2 Extended release preparation					
Hersh 1999	9/49	1/24		29.0 %	4.41 [0.59, 32.82]
Subtotal (95% CI)	**49**	**24**		**29.0 %**	**4.41 [0.59, 32.82]**
Total events: 9 (Etodolac), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Total (95% CI)	**134**	**88**		**100.0 %**	**9.03 [3.39, 24.06]**

Total events: 52 (Etodolac), 4 (Placebo)
Heterogeneity: Chi^2 = 0.60, df = 2 (P = 0.74); I^2 =0.0%
Test for overall effect: Z = 4.40 (P = 0.000011)
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%

0.01 0.1 1 10 100
Favours etodolac   Favours placebo

Analysis 4.2. Comparison 4 Etodolac 400 mg versus placebo, Outcome 2 Participants using rescue medication at 6 to 8 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 4 Etodolac 400 mg versus placebo

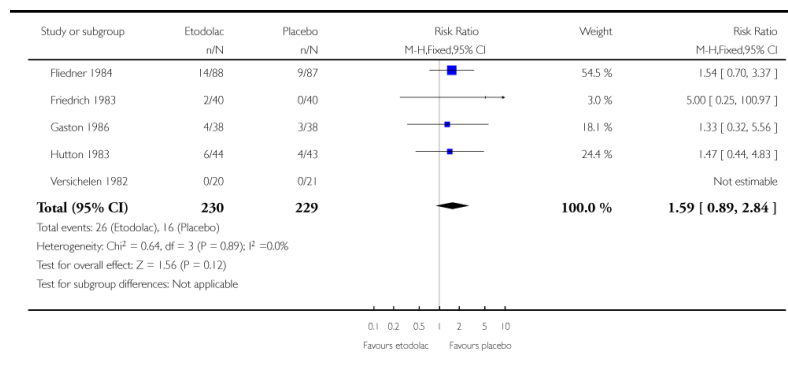Outcome: 2 Participants using rescue medication at 6 to 8 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard preparation					
Giglio 1986	28/39	37/41		41.0 %	0.80 [0.64, 0.99]
Hersh 1999	23/47	20/23		30.5 %	0.56 [0.40, 0.78]
Versichelen 1982	16/20	7/21		7.8 %	2.40 [1.26, 4.57]
Subtotal (95% CI)	**106**	**85**		**79.3 %**	**0.86 [0.72, 1.04]**
Total events: 67 (Etodolac), 64 (Placebo)					
Heterogeneity: Chi² = 16.60, df = 2 (P = 0.00025); I² =88%					
Test for overall effect: Z = 1.57 (P = 0.12)					
2 Extended release preparation					
Hersh 1999	4/20	20/24		20.7 %	0.24 [0.10, 0.59]
Subtotal (95% CI)	**20**	**24**		**20.7 %**	**0.24 [0.10, 0.59]**
Total events: 4 (Etodolac), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.13 (P = 0.0018)					
Total (95% CI)	**126**	**109**		**100.0 %**	**0.73 [0.61, 0.89]**
Total events: 71 (Etodolac), 84 (Placebo)					
Heterogeneity: Chi² = 21.99, df = 3 (P = 0.00007); I² =86%					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Test for subgroup differences: Chi² = 0.0, df = 1 (P = 0.0), I² =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours etodolac — Favours placebo

Analysis 4.3. Comparison 4 Etodolac 400 mg versus placebo, Outcome 3 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 4 Etodolac 400 mg versus placebo

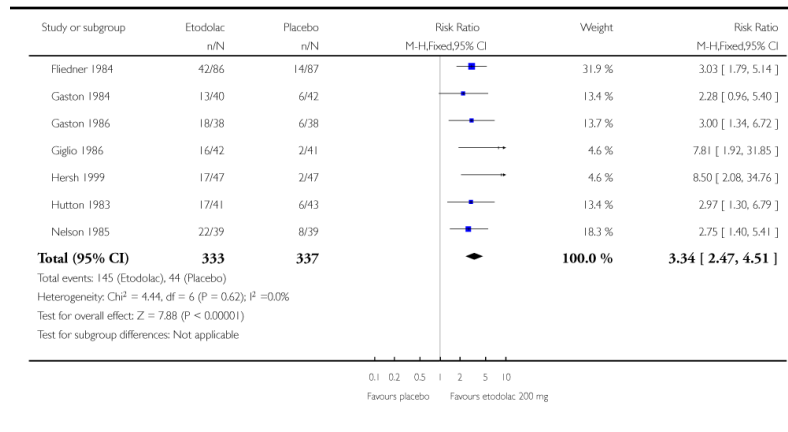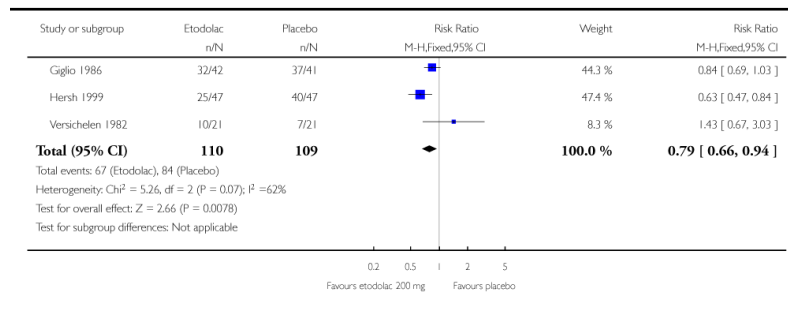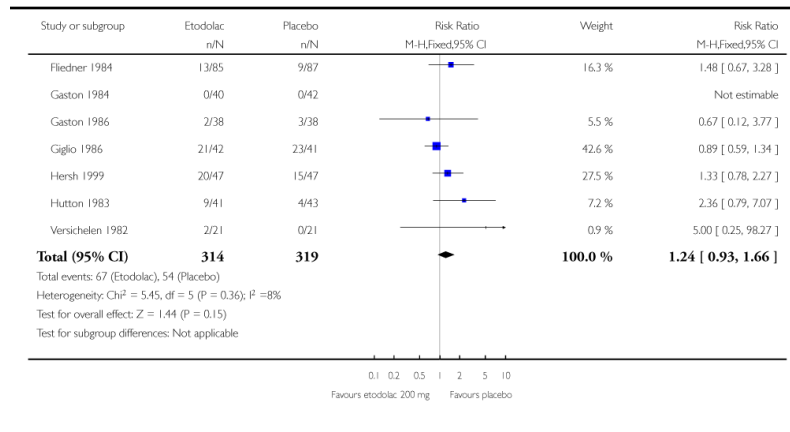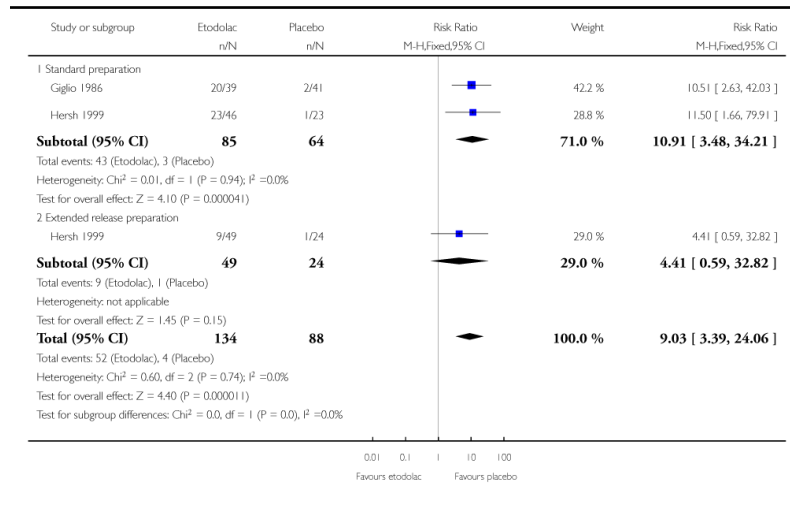Outcome: 3 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard preparation					
Giglio 1986	13/39	23/41		52.8 %	0.59 [0.35, 1.00]
Hersh 1999	17/46	7/23		22.0 %	1.21 [0.59, 2.50]
Versichelen 1982	0/20	0/21			Not estimable
Subtotal (95% CI)	**105**	**85**		**74.7 %**	**0.78 [0.51, 1.18]**
Total events: 30 (Etodolac), 30 (Placebo)					
Heterogeneity: Chi² = 2.48, df = 1 (P = 0.12); I² =60%					
Test for overall effect: Z = 1.19 (P = 0.23)					
2 Extended release preparation					
Hersh 1999	13/49	8/24		25.3 %	0.80 [0.38, 1.66]
Subtotal (95% CI)	**49**	**24**		**25.3 %**	**0.80 [0.38, 1.66]**
Total events: 13 (Etodolac), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**154**	**109**		**100.0 %**	**0.78 [0.54, 1.12]**
Total events: 43 (Etodolac), 38 (Placebo)					
Heterogeneity: Chi² = 2.49, df = 2 (P = 0.29); I² =20%					
Test for overall effect: Z = 1.33 (P = 0.18)					
Test for subgroup differences: Chi² = 0.0, df = 1 (P = 0.0), I² =0.0%					

0.2 0.5 1 2 5

Favours etodolac — Favours placebo

Analysis 5.1. Comparison 5 Etodolac 1200 mg ER versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 5 Etodolac 1200 mg ER versus placebo

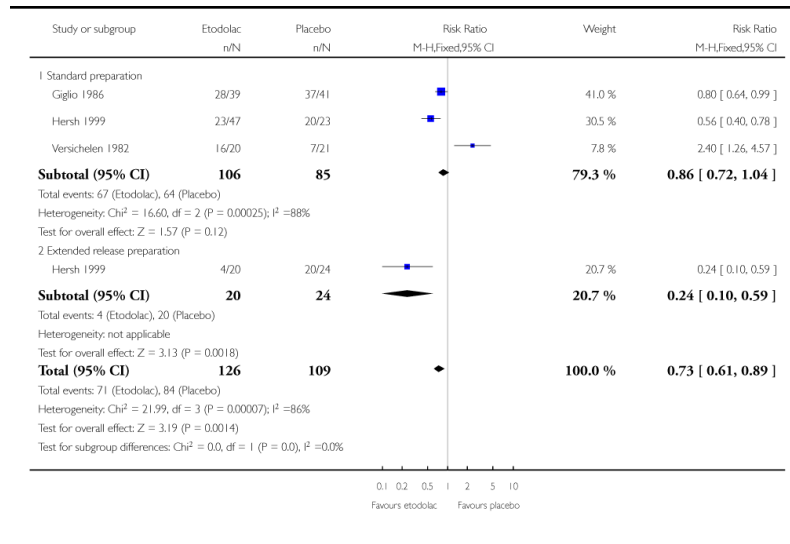Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hersh 1999	20/48	2/47		100.0 %	9.79 [2.42, 39.58]
Total (95% CI)	**48**	**47**		**100.0 %**	**9.79 [2.42, 39.58]**
Total events: 20 (Etodolac), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.20 (P = 0.0014)					
Test for subgroup differences: Not applicable					

0.02 0.1 1 10 50
Favours placebo   Favours etodolac 1200mg

Analysis 5.2. Comparison 5 Etodolac 1200 mg ER versus placebo, Outcome 2 Participants using rescue medication 6 to 8 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 5 Etodolac 1200 mg ER versus placebo

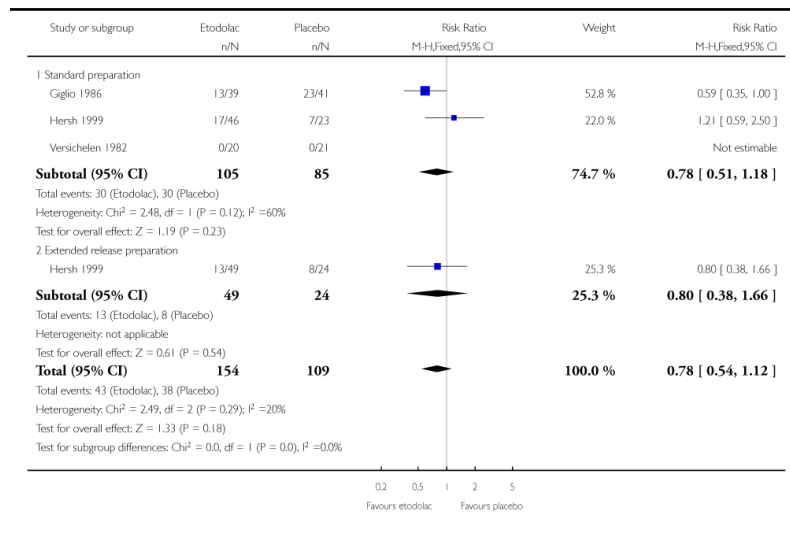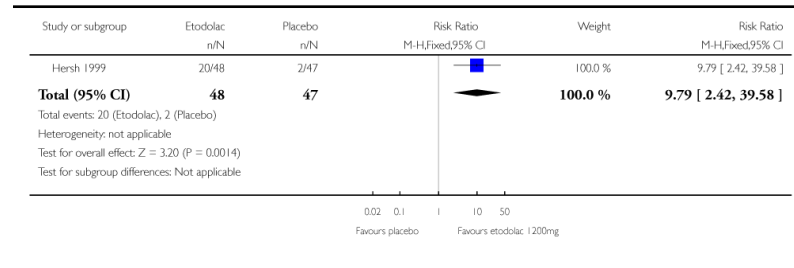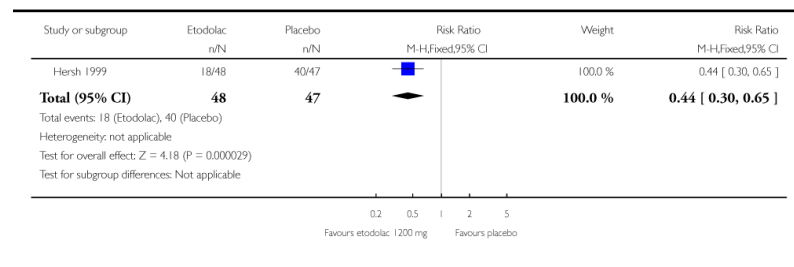Outcome: 2 Participants using rescue medication 6 to 8 hours

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hersh 1999	18/48	40/47		100.0 %	0.44 [0.30, 0.65]
Total (95% CI)	**48**	**47**		**100.0 %**	**0.44 [0.30, 0.65]**
Total events: 18 (Etodolac), 40 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.18 (P = 0.000029)					
Test for subgroup differences: Not applicable					

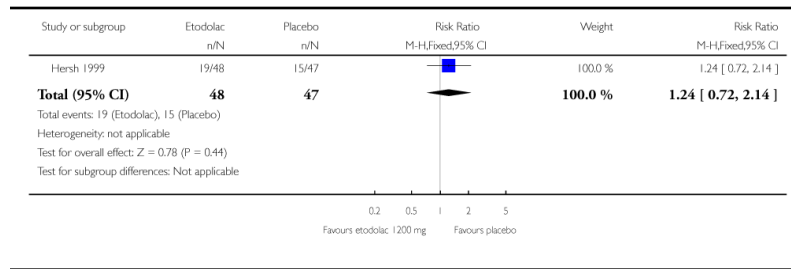0.2 0.5 1 2 5
Favours etodolac 1200 mg   Favours placebo

Analysis 5.3. Comparison 5 Etodolac 1200 mg ER versus placebo, Outcome 3 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 5 Etodolac 1200 mg ER versus placebo

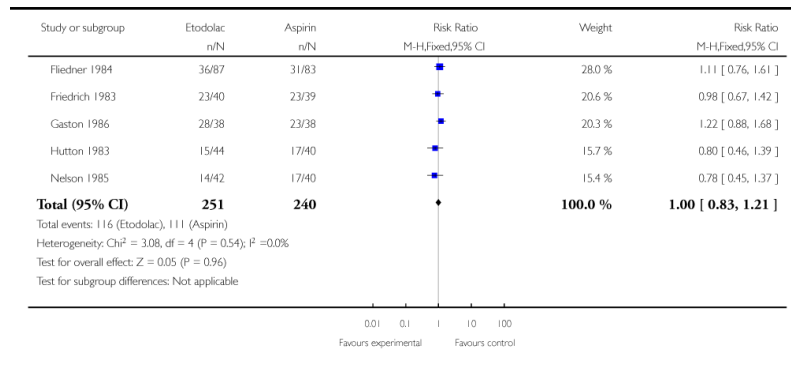Outcome: 3 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hersh 1999	19/48	15/47		100.0 %	1.24 [0.72, 2.14]
Total (95% CI)	**48**	**47**		**100.0 %**	**1.24 [0.72, 2.14]**
Total events: 19 (Etodolac), 15 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					
Test for subgroup differences: Not applicable					

0.2   0.5   1   2   5
Favours etodolac 1200 mg   Favours placebo

Analysis 6.1. Comparison 6 Etodolac 100 mg versus aspirin 650 mg, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 6 Etodolac 100 mg versus aspirin 650 mg

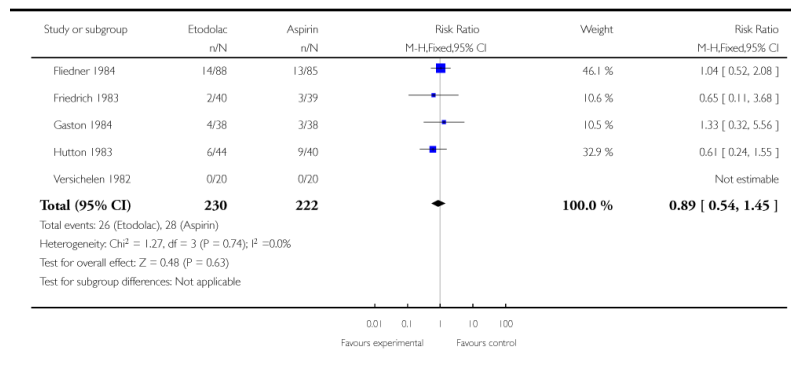Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	36/87	31/83		28.0 %	1.11 [0.76, 1.61]
Friedrich 1983	23/40	23/39		20.6 %	0.98 [0.67, 1.42]
Gaston 1986	28/38	23/38		20.3 %	1.22 [0.88, 1.68]
Hutton 1983	15/44	17/40		15.7 %	0.80 [0.46, 1.39]
Nelson 1985	14/42	17/40		15.4 %	0.78 [0.45, 1.37]
Total (95% CI)	**251**	**240**		**100.0 %**	**1.00 [0.83, 1.21]**
Total events: 116 (Etodolac), 111 (Aspirin)					
Heterogeneity: Chi² = 3.08, df = 4 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100
Favours experimental   Favours control

Analysis 6.2. Comparison 6 Etodolac 100 mg versus aspirin 650 mg, Outcome 2 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 6 Etodolac 100 mg versus aspirin 650 mg

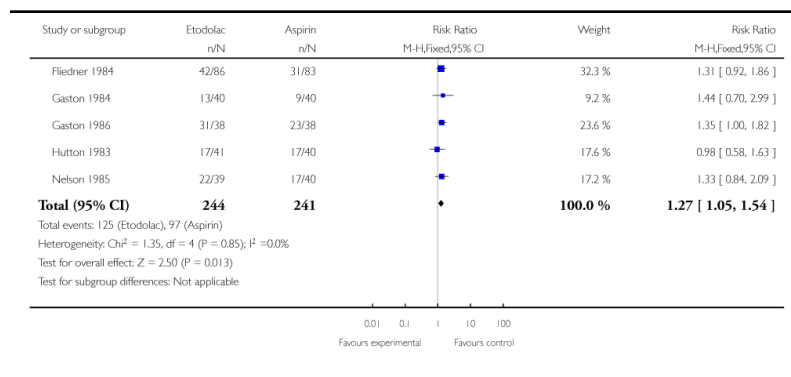Outcome: 2 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	14/88	13/85		46.1 %	1.04 [0.52, 2.08]
Friedrich 1983	2/40	3/39		10.6 %	0.65 [0.11, 3.68]
Gaston 1984	4/38	3/38		10.5 %	1.33 [0.32, 5.56]
Hutton 1983	6/44	9/40		32.9 %	0.61 [0.24, 1.55]
Verschelen 1982	0/20	0/20			Not estimable
Total (95% CI)	**230**	**222**		**100.0 %**	**0.89 [0.54, 1.45]**
Total events: 26 (Etodolac), 28 (Aspirin)					
Heterogeneity: Chi² = 1.27, df = 3 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1    10   100
     Favours experimental   Favours control
```

Analysis 7.1. Comparison 7 Etodolac 200 mg versus aspirin 650 mg, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 7 Etodolac 200 mg versus aspirin 650 mg

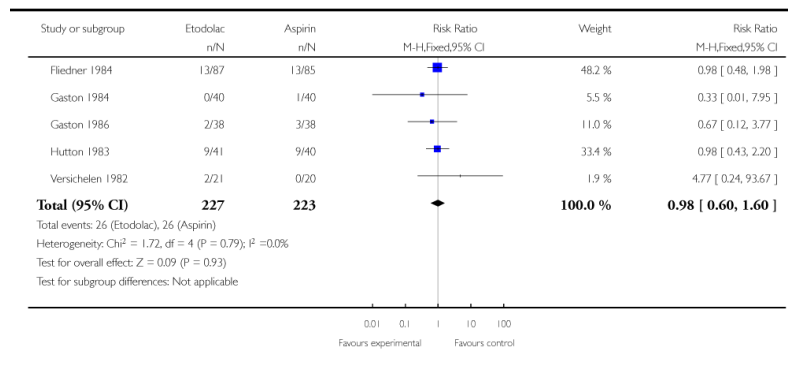Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours

Study or subgroup	Etodolac n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	42/86	31/83		32.3 %	1.31 [0.92, 1.86]
Gaston 1984	13/40	9/40		9.2 %	1.44 [0.70, 2.99]
Gaston 1986	31/38	23/38		23.6 %	1.35 [1.00, 1.82]
Hutton 1983	17/41	17/40		17.6 %	0.98 [0.58, 1.63]
Nelson 1985	22/39	17/40		17.2 %	1.33 [0.84, 2.09]
Total (95% CI)	**244**	**241**		**100.0 %**	**1.27 [1.05, 1.54]**
Total events: 125 (Etodolac), 97 (Aspirin)					
Heterogeneity: Chi² = 1.35, df = 4 (P = 0.85); I² =0.0%					
Test for overall effect: Z = 2.50 (P = 0.013)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1    10   100
     Favours experimental   Favours control
```

Analysis 7.2. Comparison 7 Etodolac 200 mg versus aspirin 650 mg, Outcome 2 Participants with at least one adverse event

Review: Single dose oral etodolac for acute postoperative pain in adults

Comparison: 7 Etodolac 200 mg versus aspirin 650 mg

Outcome: 2 Participants with at least one adverse event

Study or subgroup	Etodolac n/N	Aspirin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fliedner 1984	13/87	13/85		48.2 %	0.98 [0.48, 1.98]
Gaston 1984	0/40	1/40		5.5 %	0.33 [0.01, 7.95]
Gaston 1986	2/38	3/38		11.0 %	0.67 [0.12, 3.77]
Hutton 1983	9/41	9/40		33.4 %	0.98 [0.43, 2.20]
Versichelen 1982	2/21	0/20		1.9 %	4.77 [0.24, 93.67]
Total (95% CI)	**227**	**223**		**100.0 %**	**0.98 [0.60, 1.60]**

Total events: 26 (Etodolac), 26 (Aspirin)
Heterogeneity: Chi² = 1.72, df = 4 (P = 0.79); I² =0.0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours experimental   Favours control

Appendix 1. MEDLINE search strategy (via OVID)

1. Etodolac.sh

2. (etodolac OR Lodine, OR Ramodar, OR Ultradol).ti,ab,kw.

3. OR/1-2

4. Pain, postoperative.sh

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$) or ("post-operative analgesi$")).ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")).ti,ab,kw.

11. OR/4-10

12. randomized controlled trial.pt.

13. controlled clinical trial.pt.

14. randomized.ab.

15. placebo.ab.

16. drug therapy.fs.

17. randomly.ab.

18. trial.ab.

19. groups.ab.

20. OR/12-19

21. humans.sh.

22. 20 AND 21

23. 3 AND 11 AND 22

Appendix 2. EMBASE search strategy (via OVID)

1. Etodolac.sh

2. (etodolac OR Lodine, OR Ramodar, OR Ultradol).ti,ab,kw.

3. OR/1-2

4. Postoperative pain.sh

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$) or ("post-operative analgesi$")).ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")).ti,ab,kw.

11. OR/4-10

12. clinical trials.sh

13. controlled clinical trials.sh

14. randomized controlled trial.sh

15. double-blind procedure.sh

16. (clin$ adj25 trial$).ab

17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab

18. placebo$.ab

19. random$.ab

20. OR/12-19

21. 3 AND 11 AND 20

Appendix 3. CENTRAL search strategy

1. MESH descriptor Etodolac

2. (etodolac OR Lodine, OR Ramodar, OR Ultradol).ti,ab,kw.

3. OR/1-2

4. MESH descriptor Pain, Postoperative

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$) or ("post-operative analgesi$")):ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)):ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")): ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")):ti,ab,kw.

11. OR/4-10

12. 3 and 11

Appendix 4. 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 composite trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

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 (Moore 2003).

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 3, 2009

Date	Event	Description
24 September 2010	Amended	Contact details updated.

WHAT'S NEW

Last assessed as up-to-date: 9 November 2010.

Date	Event	Description
10 November 2010	Review declared as stable	The authors declare that there is unlikely to be any further studies to be included in this review and so it should be published as a 'stable review'

References to studies included in this review

Fliedner 1984   {published data only}   . Fliedner L, Levsky M, Kechejian H. Analgesia with etodolac in oral postsurgical pain. Current Therapeutic Research. 1984; 36(1):33–45.

Friedrich 1983   {published data only}   . Friedrich E. A comparison of etodolac (Ultradol) with aspirin and placebo in patients with episiotomy pain. Current Therapeutic Research - Clinical and Experimental. 1983; 33(1):100–7.

Gaston 1984   {published data only}   . Gaston GW, Mallow RD, Frank JE. The efficacy of etodolac for patients with pain following oral surgery. Journal of Oral and Maxillofacial Surgery. 1984; 42(6):362–6. [PubMed: 6232359]

Gaston 1986   {published data only}   . Gaston GW, Mallow RD, Frank JE. Comparison of etodolac, aspirin and placebo for pain after oral surgery. Pharmacotherapy. 1986; 6(5):199–205. [PubMed: 2948162]

Giglio 1986   {published data only}   . Giglio JA, Campbell RL. Comparison of etodolac, zomepirac, and placebo for relief of pain after oral surgery. Journal of Oral & Maxillofacial Surgery. 1986; 44(10):765–70. [PubMed: 2944997]

Hersh 1999   {published data only}   . Hersh EV, Levin LM, Cooper SA, Reynolds D, Gallegos LT, McGoldrick K, et al. Conventional and extended-release etodolac for postsurgical dental pain. Clinical therapeutics. 1999; 21(8):1333–42. [PUBMED: 10485505]. [PubMed: 10485505]

Hutton 1983   {published data only}   . Hutton CE. The effectiveness of 100 and 200 mg etodolac (Ultradol), aspirin, and placebo in patients with pain following oral surgery. Oral Surgery, Oral Medicine, and Oral Pathology. 1983; 56(6):575–80.

Nelson 1985   {published data only}   . Nelson SL, Bergman SA. Relief of dental surgery pain: a controlled 12-hour comparison of etodolac, aspirin, and placebo. Anesthesia Progress. 1985; 32(4):151–6. [PubMed: 2934008]

Versichelen 1982   {published data only}   . Versichelen L, Bilsback P, Rolly G, Merlo M, Joubert L. Etodolac in postsurgical pain: a double-blind dose-ranging efficacy study with aspirin and placebo. International Journal of Clinical Pharmacology, Therapy, and Toxicology. 1982; 20(5): 236–9.

References to studies excluded from this review

Apaydin 1994   {published data only}   . Apaydin A, Ozyuvaci H, Ordulu M, Disci R. Postoperative pain relief by single dose Diclofenac Kalium and Etodolac. A comparative clinical study. Agri Dergisi: The Journal of The Turkish Society of Algology. 1994; 6(4):28–34.

Boni 1999   {published data only}   . Boni J, Korth-Bradley J, McGoldrick K, Appel A, Cooper S. Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. Journal of Clinical Pharmacology. 1999; 39(7):729–37. [PUBMED: 10392328]. [PubMed: 10392328]

Koizuka 2004   {published data only}   . Koizuka S, Saito S, Obata H, Sasaki M, Nishikawa K, Takahashi K, et al. Oral etodolac, a COX-2 inhibitor, reduces postoperative pain immediately after fast-track cardiac surgery. Journal of Anesthesia. 2004; 18(1):9–13. [PubMed: 14991469]

Lin 2006   {published data only}   . Lin S, Levin L, Emodi O, Abu El-Naaj I, Peled M. Etodolac versus dexamethasone effect in reduction of postoperative symptoms following surgical endodontic treatment: a double-blind study. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2006; 101(6):814–7. [PUBMED: 16731406].

Mizraji 1990 {published data only} . Mizraji M. Clinical response to etodolac in the management of pain. European Journal of Rheumatology and Inflammation. 1990; 10(1):35–43. [PUBMED: 1699764]. [PubMed: 1699764]

Scott 1986 {published data only} . Scott R, Ellis E 3rd, Upton LG. Double-blind evaluation of etodolac (200 mg, 400 mg) compared with zomepirac (100 mg) and placebo on third molar extraction pain. Oral Surgery, Oral Medicine, Oral Pathology. 1986; 62(6):638–42.

Additional references

Chen 2008 . Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technology Assessment. 2008; Vol. 12:11.

Clarke 2009 . Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009; (Issue 2) [DOI: 10.1002/14651858.CD004309.pub2].

Collins 1997 . Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997; 72:95–7. [PubMed: 9272792]

Collins 2001 . Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough? Pain. 2001; 91:189–94. [PubMed: 11240091]

Cook 1995 . Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ. 1995; 310:452–4. [PubMed: 7873954]

Cooper 1991 . Cooper, SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max, MB.; Portenoy, RK.; Laska, EM., editors. The Design of Analgesic Clinical Trials (Advances in Pain Research and Therapy Vol. 18). Raven Press; New York: 1991. p. 117-24.

Derry 2008 . Derry S, Moore RA, McQuay HJ. Single dose oral celecoxib for acute postoperative pain. Cochrane Database of Systematic Reviews. 2008; (Issue 3) [DOI: 10.1002/14651858.CD004233].

Derry C 2009a . Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009; (Issue 1) [DOI: 10.1002/14651858.CD004234.pub2].

Derry C 2009b . Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009; (Issue 3) [DOI: 10.1002/14651858.CD001548.pub2].

Derry P 2009 . Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009; (Issue 2) [DOI: 10.1002/14651858.CD004768.pub2].

Edwards 1999 . Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. Journal of Pain and Symptom Management. 1999; 18(6):427–37. [PubMed: 10641469]

Forrest 2002 . Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. British Journal of Anaesthesia. 2002; 88(2):227–33. [PubMed: 11883386]

Garcia Rodriguez 2008 . García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. Journal of the American College of Cardiology. 2008; 52(20): 1628–36. [DOI: 10.1016/j.jacc.2008.08.041]. [PubMed: 18992652]

Garner 2002 . Garner S, Fidan D, Frankish R, Judd M, Towheed T, Wells G. Rofecoxib for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2002; (Issue 2) [DOI: 10.1002/14651858.CD003685.pub2].
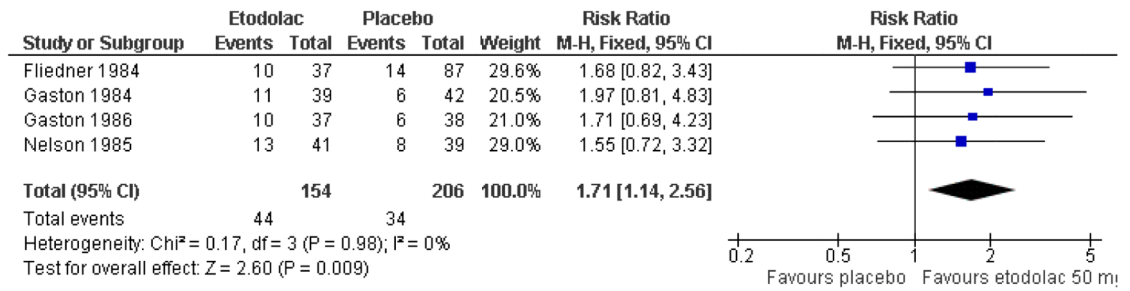
Grahame-Smith 2002 . Grahame-Smith, DG.; Aronson, JK. Oxford Textbook of Clinical Pharmacology and Drug Therapy. Vol. 3. Oxford University Press; Oxford: 2002. [ISBN: 13: 978–0–19–263234–0]

Hawkey 1999 . Hawkey CJ. Cox-2 inhibitors. Lancet. 1999; 353(9149):307–14. [PubMed: 9929039]

Hawkey 2001 . Hawkey CJ, Jones JI. Gastrointestinal safety of COX-2 specific inhibitors. Gastroenterology Clinics of North America. 2001; 30(4):921–36. [PubMed: 11764535]

Hawkey 2006 . Hawkey CJ. NSAIDs, coxibs, and the intestine. Journal of Cardiovascular Pharmacology. 2006; 47(Suppl 1):S72–5. [PubMed: 16785834]

Jadad 1996a . Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. Pain. 1996; 66(2-3):239–46. [PubMed: 8880846]

Jadad 1996b . Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials. 1996; 17:1–12. [PubMed: 8721797]

Kearney 2006 . Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ (Clinical research ed.). 2006; 3(332):1302–8. [DOI: 10.1136/bmj.332.7553.1302].

L'Abbé 1987 . L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Annals of Internal Medicine. 1987; 107:224–33. [PubMed: 3300460]

Lloyd 2009 . Lloyd R, Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009; (Issue 2) [DOI: 10.1002/14651858.CD004771.pub4].

McQuay 1982 . McQuay HJ, Bullingham RE, Moore RA, Evans PJ, Lloyd JW. Some patients don't need analgesics after surgery. Journal of the Royal Society of Medicine. 1982; 75(9):705–8. [PubMed: 7120254]

McQuay 2005 . McQuay HJ, Moore RA. Placebo. Postgraduate Medical Journal. 2005; 81:155–60. [PubMed: 15749790]

Moher 1999 . Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet. 1999; 354:1896–900. [PubMed: 10584742]

Moore 1996 . Moore RA, McQuay HJ, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. Pain. 1996; 66(2-3):229–37. [DOI: 10.1016/0304-3959(96)03032-1]. [PubMed: 8880845]

Moore 1997a . Moore RA, Moore O, McQuay HJ, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Use of pain intensity and visual analogue scales. Pain. 1997; 69(3):311–5. [DOI: 10.1016/S0304-3959(96)03306-4]. [PubMed: 9085306]

Moore 1997b . Moore RA, McQuay HJ, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Verification from independent data. Pain. 1997; 69(1-2):127–30. [DOI: 10.1016/S0304-3959(96)03251-4]. [PubMed: 9060022]

Moore 1998 . Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything-large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain. 1998; 78(3):209–16. [DOI: 10.1016/S0304-3959(98)00140-7]. [PubMed: 9870574]

Moore 2003 . Moore, RA.; Edwards, J.; Barden, J.; McQuay, HJ. Bandolier's Little Book of Pain. Oxford University Press; Oxford: 2003. [ISBN: 0–19–263247–7]

Moore 2005 . Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. Pain. 2005; 116(3):322–31. [DOI: 10.1016/j.pain.2005.05.001]. [PubMed: 15979792]

Moore 2005b . Moore RA, Derry S, Makinson GT, McQuay HJ. Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-

analysis of information from company clinical trial reports. Arthritis Research & Therapy. 2005; 7(3):R644–65. [DOI: 10.1186/ar1704]. [PubMed: 15899051]

Moore 2006   . Moore, A.; McQuay, H. Bandolier's Little Book of Making Sense of the Medical Evidence. Oxford University Press; Oxford: 2006. [ISBN: 0–19–856604–2]

Morris 1995   . Morris, JA.; Gardner, MJ. Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. In: Gardner, MJ.; Altman, DG., editors. Statistics with Confidence - Confidence Intervals and Statistical Guidelines. British Medical Journal; London: 1995. p. 50-63.

PACT 2007   . Prescription cost analysis, England 2007. NHS Information Centre; 2007. Anonymous. [: ISBN:978–1–84636–210–1]

Straube 2005   . Straube S, Derry S, McQuay HJ, Moore RA. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. Acta Anaesthesiologica Scandinavica. 2005; 49(5):601–13. [DOI: 10.1111/j. 1399-6576.2005.00666.x]. [PubMed: 15836672]

Toms 2008   . Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database of Systematic Reviews. 2008; (Issue 4) [DOI: 10.1002/14651858.CD004602.pub2].

* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Single dose oral etodolac for acute postoperative pain in adults

Etodolac 200 mg provides a high level of pain relief in about 40% of those with moderate or severe acute postoperative pain. This is fewer than one would expect to see of the same level of pain relief with standard doses of ibuprofen, naproxen and diclofenac. Higher doses of etodolac may be more effective There were no more adverse events than with placebo in these single dose studies.

Study or Subgroup	Etodolac Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fliedner 1984	10	37	14	87	29.6%	1.68 [0.82, 3.43]
Gaston 1984	11	39	6	42	20.5%	1.97 [0.81, 4.83]
Gaston 1986	10	37	6	38	21.0%	1.71 [0.69, 4.23]
Nelson 1985	13	41	8	39	29.0%	1.55 [0.72, 3.32]
Total (95% CI)		**154**		**206**	**100.0%**	**1.71 [1.14, 2.56]**
Total events	44		34			

Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

Figure 1.

Forest plot of comparison: 1 Etodolac 50 mg versus placebo, outcome: 1.1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or Subgroup	Etodolac Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fliedner 1984	36	87	14	87	27.8%	2.57 [1.50, 4.42]
Friedrich 1983	23	40	16	40	31.8%	1.44 [0.90, 2.29]
Gaston 1986	15	38	6	38	11.9%	2.50 [1.09, 5.75]
Hutton 1983	15	44	6	43	12.0%	2.44 [1.05, 5.71]
Nelson 1985	14	42	8	39	16.5%	1.63 [0.77, 3.44]
Total (95% CI)		251		247	100.0%	2.03 [1.53, 2.70]
Total events	103		50			

Heterogeneity: Chi² = 3.62, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.88 (P < 0.00001)

Figure 2.

Forest plot of comparison: 2 Etodolac 100 mg versus placebo, outcome: 2.1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or Subgroup	Etodolac Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fliedner 1984	42	86	14	87	31.9%	3.03 [1.79, 5.14]
Gaston 1984	13	40	6	42	13.4%	2.27 [0.96, 5.40]
Gaston 1986	18	38	6	38	13.7%	3.00 [1.34, 6.72]
Giglio 1986	16	42	2	41	4.6%	7.81 [1.92, 31.85]
Hersh 1999	17	47	2	47	4.6%	8.50 [2.08, 34.76]
Hutton 1983	17	41	6	43	13.4%	2.97 [1.30, 6.79]
Nelson 1985	22	39	8	39	18.3%	2.75 [1.40, 5.41]
Total (95% CI)		333		337	100.0%	3.34 [2.47, 4.51]
Total events	145		44			

Heterogeneity: Chi² = 4.44, df = 6 (P = 0.62); I² = 0%
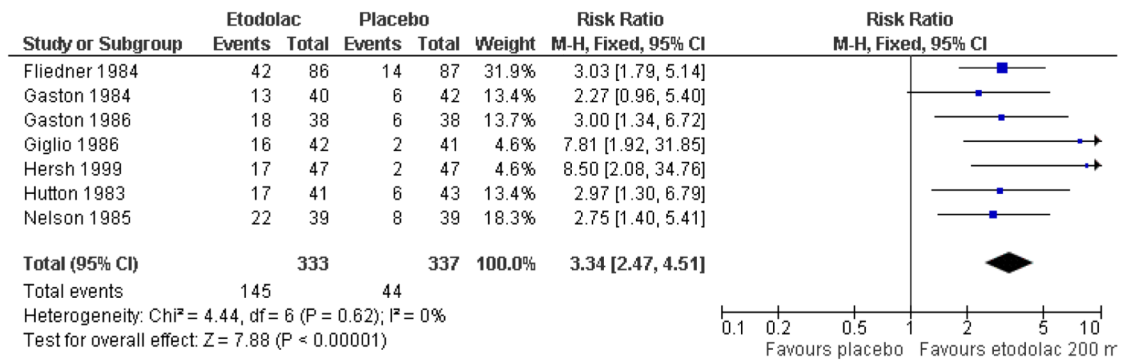Test for overall effect: Z = 7.88 (P < 0.00001)

Figure 3.
Forest plot of comparison: 3 Etodolac 200 mg versus placebo, outcome: 3.1 Participants with at least 50% pain relief over 4 to 6 hours.

Table 1

Summary of outcomes: analgesia and rescue medication

| Study ID | Treatment | Analgesia | | | Rescue medication | |
		PI or PR	Number with 50% PR	PGE: v good or excellent	Median time to use (hr)	% using
Fliedner 1984	(1) Etodolac 50 mg, n = 37 (2) Etodolac 100 mg, n = 87 (3) Etodolac 200 mg, n = 86 (4) Aspirin 650 mg, n = 83 (5) Placebo, n = 87	TOTPAR 0.5 to 6: (1) 6.2 (2) 8.8 (3) 10.0 (4) 8.0 (5) 4.5	(1) 10/37 (2) 36/87 (3) 42/86 (4) 31/83 (5) 14/87	No usable data	No usable data	No usable data
Friedrich 1983	(1) Etodolac 25 mg, n = 40 (2) Etodolac 100 mg, n = 40 (3) Aspirin 650 mg, n = 39 (4) Placebo, n = 40	TOTPAR 6: (1) 9.3 (2) 12.5 (3) 12.9 (4) 9.3	(1) 16/40 (2) 23/40 (3) 23/39 (4) 16/40	No usable data	No usable data	At 6 h: (1) 30 (2) 15 (3) 15 (4) 25
Gaston 1984	(1) Etodolac 50 mg, n = 39 (2) Etodolac 200 mg, n = 40 (3) Aspirin 650 mg, n = 40 (4) Placebo, n = 42	TOTPAR 6: (1) 7.3 (2) 7.9 (3) 6.0 (4) 4.8	(1) 11/39 (2) 13/40 (3) 9/40 (4) 6/42	No usable data	No data	No data
Gaston 1986	(1) Etodolac 50 mg, n = 37 (2) Etodolac 100 mg, n = 38 (3) Etodolac 200 mg, n = 38 (4) Aspirin 650 mg, n = 38 (5) Placebo, n = 38	TOTPAR 0.5 to 6: (1) 6.2 (2) 8.5 (3) 9.8 (4) 6.3 (5) 4.4	(1) 10/37 (2) 15/38 (3) 18/38 (4) 10/38 (5) 6/38	No usable data	No usable data	No usable data
Giglio 1986	(1) Etodolac 200 mg, n = 42 (2) Etodolac 400 mg, n = 39 (3) Placebo, n = 41	TOTPAR 0.5 to 6: (1) 8.3 (2) 10.2 (3) 2.7	(1) 14/42 (2) 18/39 (3) 1/41	No usable data	No usable data	At 6 h: (1) 76 (2) 72 (3) 90
Hersh 1999	(1) Etodolac 200 mg, n = 47 (2) Etodolac 400 mg, n = 46 (3) Etodolac ER 400 mg, n = 49 (4) Etodolac ER 1200 mg, n = 48 (5) Placebo n = 47	TOTPAR 6: (1) 8.6 (2) 11.1 (3) 5.4 (4) 9.7 (5) 2.8	(1) 17/47 (2) 23/46 (3) 9/49 (4) 20/48 (5) 2/47	No usable data	(1) 5.1 (2) 6.0 (3) 2.9 (4) 10.1 (5) 2.6	at 6 h: (1) 53 (2) 50 (3) 74 (4) 37 (5) 85
Hutton 1983	(1) Etodolac 100 mg, n = 44 (2) Etodolac 200 mg, n = 41 (3) Aspirin 650 mg, n = 40 (4) Placebo, n = 43	TOTPAR 0.5 to 6: (1) 7.6 (2) 8.6 (3) 8.9 (4) 4.2	(1) 15/44 (2) 17/41 (3) 17/40 (4) 6/43	No usable data	No data	No data
Nelson 1985	(1) Etodolac 50 mg, n = 41 (2) Etodolac 100 mg, n = 42 (3) Etodolac 200 mg, n = 39	TOTPAR 0.5 to 6: (1) 7.0 (2) 7.4 (3) 1.3 (4) 8.9 (5) 5.4	(1) 13/41 (2) 14/42 (3) 22/39 (4) 17/40 (5) 8/39	No usable data	No data	No data

		Analgesia			Rescue medication	
Study ID	**Treatment**	**PI or PR**	**Number with 50% PR**	**PGE: v good or excellent**	**Median time to use (hr)**	**% using**
	(4) Aspirin 650 mg, n = 40 (5) Placebo, n = 39					
Versichelen 1982	(1) Etodolac 25 mg, n = 21 (2) Etodolac 50 mg, n = 19 (3) Etodolac 100 mg, n = 20 (4) Etodolac 200 mg, n = 21 (5) Etodolac 400 mg, n = 20 (6) Aspirin 650 mg, n = 20 (7) Placebo, n = 21	No usable data	No usable data	No usable data	No usable data	At 8 h: (1) 67 (2) 63 (3) 65 (4) 52 (5) 20 (6) 60 (7) 67

Table 2

Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Adverse events		Withdrawals	
		Any	Serious	Adverse event	Other
Fliedner 1984	(1) Etodolac 50 mg, n = 37 (2) Etodolac 100 mg, n = 87 (3) Etodolac 200 mg, n = 86 (4) Aspirin 650 mg, n = 83 (5) Placebo, n = 87	At 12 h: (1) 5/37 (2) 14/88 (3) 13/85 (4) 13/85 (5) 9/87	None	None	4 participants took medication but were excluded from analysis due to protocol violations (2) 1, (3) 1, (4) 2
Friedrich 1983	(1) Etodolac 25 mg, n = 40 (2) Etodolac 100 mg, n = 40 (3) Aspirin 650 mg, n = 39 (4) Placebo, n = 40	At 8 h: (1) 0/40 (2) 2/40 (3) 3/39 (4) 0/40	None reported	None reported	None reported
Gaston 1984	(1) Etodolac 50 mg, n = 39 (2) Etodolac 200 mg, n = 40 (3) Aspirin 650 mg, n = 40 (4) Placebo, n = 42	At 8 h: (1) 0/39 (2) 0/40 (3) 1/40 (4) 0/42	None	None	None
Gaston 1986	(1) Etodolac 50 mg, n = 37 (2) Etodolac 100 mg n = 38 (3) Etodolac 200 mg n = 38 (4) Aspirin 650 mg n = 38 (5) Placebo n = 38	At 12 h: (1) 4/37 (2) 4/38 (3) 2/38 (4) 3/38 (5) 3/38	None reported	None	None
Giglio 1986	(1) Etodolac 200 mg, n = 42 (2) Etodolac 400 mg, n = 39 (3) Placebo n = 41	At 12 h: (1) 21/42 (2) 13/39 (3) 23/41	(1) 1/55 (postop bleeding)	(1) 1/55 (postop bleeding)	None
Hersh 1999	(1) Etodolac 200 mg, n = 47 (2) Etodolac 400 mg n = 46 (3) Etodolac ER 400 mg n = 49 (4) Etodolac ER 1200 mg n = 48 (5) Placebo n = 47	At 24 h: (1) 20/47 (2) 17/46 (3) 13/49 (4) 19/48 (5) 15/47	None reported	None	None
Hutton 1983	(1) Etodolac 100 mg, n = 44 (2) Etodolac 200 mg, n = 41 (3) Aspirin 650 mg, n = 40 (4) Placebo, n = 43	at 12 h: (1) 6/44 (2) 9/41 (3) 9/40 (4) 4/43	None reported	None	I participant excluded from analysis due to protocol violation (confounding medication)
Nelson 1985	(1) Etodolac 50 mg, n = 41 (2) Etodolac 100 mg, n = 42 (3) Etodolac 200 mg, n = 39 (4) Aspirin 650 mg, n = 40 (5) Placebo, n = 39	No data	None reported	None	3 participants excluded because withdrew consent within 1 h, 3 participants lost to follow up (did not return diaries)
Versichelen 1982	(1) Etodolac 25 mg, n = 21 (2) Etodolac 50 mg, n = 19 (3) Etodolac 100 mg, n = 20 (4) Etodolac 200 mg, n = 21 (5) Etodolac 400 mg, n = 20 (6) Aspirin 650 mg, n = 20 (7) Placebo, n = 21	(1) 1/21 (2) 1/19 (3) 0/20 (4) 2/21 (5) 0/20 (6) 0/20 (7) 0/21	None reported	None reported	4 participants excluded from analyses for protocol violations