Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis


Authors' objectives
To examine the postoperative analgesic efficacy and adverse effects of single doses, injected or oral, of pethidine and ketorolac compared with placebo.

Searching
The following electronic databases were searched: MEDLINE, (1966 to July 1998), EMBASE (1980 to 1998), the Cochrane Library (1998 issue 2) and the Oxford pain relief database (1950 to 1994). Broad free text searches with no language restrictions were undertaken using terms which are listed in the review. Reference lists of retrieved reports were searched for additional articles. Roche Products Ltd UK were contacted for ketorolac reports. Authors of articles were not contacted for unpublished work or for additional information relating to published reports.

Study selection
Study designs of evaluations included in the review
Placebo-controlled, double-blind, randomised trials of single-dose treatment. The study had to last for 4-6 hours. Abstracts and review articles were excluded.

Specific interventions included in the review
Single dose, oral, intravenous (i.v) or intramuscular (i.m) ketorolac or pethidine, administered for post-operative pain relief. The following drugs and doses were reported in the review: pethidine i.m. (50 or 100mg), ketorolac i.m. (10 mg, 30 mg or 60 mg) and ketorolac oral (5mg, 10mg and 20mg). Morphine i.m. (5 and 10mg) is also discussed in the review.

Participants included in the review
Patients aged more than 15 years, with moderate or severe post-operative pain, according to a verbal rating scale or a score of at least 30 mm on a 0-100 mm visual analogue scale (VAS).

Outcomes assessed in the review
Total pain relief (TOTPAR), summed pain intensity difference (SPID) or their visual analogue equivalents (VASTOPAR and VASSPID). Pain had to have been recorded using standard pain scales: four-point pain intensity scale (none, mild, moderate or severe); relief scale (none, slight, moderate, good, complete) or their VAS equivalents.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection. The citations of the studies excluded from the review and reasons for exclusion were available from the authors.

Assessment of study quality
All RCTs were scored for quality using a 1-5 score: two possible points for randomisation (one point if ‘randomised at all, two points if method of randomisation described); two possible points for blinding (one point if study described as double-blind, two points if the method by which the double-blinding was achieved was given; and one point if the number and reason for patient withdrawals was listed. Each paper was scored independently for quality by two of the authors who met to agree consensus.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The data extracted were: type of surgery; study treatment groups; number of patients treated; study duration; dose of pethidine or ketorolac and route of administration; and mean or derived 4 hour TOTPAR, SPID, VASTOTPAR.
or VASSPID scores. Where available, information on type incidence and severity of adverse effects, including study withdrawals, was also extracted.

**Methods of synthesis**

How were the studies combined?

Studies were combined using quantitative methods. The proportion of patients in individual studies to achieve at least 50% maximum pain relief over 4-6 hours for pethidine i.m, ketorolac i.m and ketorolac oral were calculated using verified equations (see Other Publications of Related Interest nos.1-3). These were used to calculate relative benefit and risk estimates with 95% CI using a fixed-effect model. Number Needed to Treat (NNT) and Number Needed to do Harm (NNH) with CI were calculated by the method of Cook and Sackett (see Other Publications of Related Interest no.4). The review emphasised results derived from at least three studies using identical doses and routes of administration.

How were differences between studies investigated?

A formal statistical test of heterogeneity was not performed.

**Results of the review**

Eight placebo-controlled studies of 100 mg i.m pethidine (n=203 pethidine and 161 placebo) and six placebo-controlled studies of i.m ketorolac (n=326 ketorolac and 291 placebo) and eight placebo-controlled studies of oral ketorolac (n=410 ketorolac and 380 placebo) were included in the review.

The relative benefit of pethidine i.m. 100mg compared with placebo was 3.2 (95% CI: 2.3, 4.6) with the NNT to produce at least 50% maximal pain relief of 2.9 (95% CI: 2.3, 3.9). The relative benefit of ketorolac 30mg i.m compared with placebo was 2.3 (95% CI: 1.8, 3.1) with an NNT of 3.4 (95% CI: 2.5, 4.9). The relative benefit of ketoroloc oral 10mg compared with placebo was 4.3 (95% CI: 3.2, 5.8) with an NNT of 2.6 (95% CI: 2.3, 3.1). The NNH for pethidine 100 mg i.m was 2.6 (95% CI: 2.1, 3.6) compared to 7.3 (95% CI: 4.7, 17) for oral ketorolac. The NNH for i.m. ketorolac versus placebo could not be calculated.

**Authors' conclusions**

There is clearly little difference in efficacy between i.m. morphine 10mg, pethidine 100 mg, and ketorolac 30 mg. Oral ketorolac was consistently at least as effective as ketorolac 30 mg i.m, but adverse events were more common with oral ketorolac than with placebo.

**CRD commentary**

The review addressed an appropriate and specific question regarding the relative efficacy of injectable and oral analgesics in the treatment of post-operative pain. The literature search conducted was adequate with reasonable efforts made to obtain unpublished data on the newer drug (ketorolac), although it is not clear how much extra information, if any was obtained. The quality of the studies included in the review was generally good with adequate checks made for validity made by more than one reviewer independently. The studies included in the review were all RCTs of a similar design with common outcome measures and the quantitative synthesis used to pool the data was appropriate, although a formal test for heterogeneity was lacking. The better quality data were highlighted. A good level of detail of all the studies was included in the review. The authors conclusions appear to be justified based on the pethidine and ketorolac data presented in this paper. Their broader conclusions, referring to conclusions from reviews of data on other analgesics may be weaker, given that those reviews may have been less systematic.

**Implications of the review for practice and research**

Practice: The authors state that 'The information suggests that, in patients who can swallow and in whom NSAIDs are not contraindicated, oral NSAIDs are as effective as injected NSAID, and provide analgesia equivalent to that from conventional doses of injected opioid'.

Research: The authors do not state any implications for further research.

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