Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review

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Authors' objectives

To assess the evidence for a difference in analgesic efficacy and adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) given by different routes.

Searching

MEDLINE from 1966 to 1996, EMBASE from 1986 to 1996, and the Oxford Pain Relief Database from 1950 to 1993, were searched using the keywords 'NSAID' and 'non-steroidal anti-inflammatory'. Searches were also conducted with the individual drug names in combination with 'post-operative pain', 'renal colic', '*colic', 'intravenous', 'intramuscular', 'rectal' and combinations of these words. Publications in any language were considered. Additional reports were identified from the reference lists of retrieved reports, review articles and textbooks; from manual searches of locally available anaesthetic journals; and by contacting pharmaceutical companies with licenced parenteral or rectal NSAID preparations. Letters, abstracts and review articles were excluded, and there was no attempt to find unpublished studies.

Study selection

Study designs of evaluations included in the review

Published randomised controlled trials (RCTs) of direct comparisons of NSAIDs, given by different routes of administration, and tested in acute or chronic pain with assessment of pain outcomes, were eligible for inclusion. Comparisons of different drugs across different routes were not analysed. The included trials were those with an internal sensitivity index in the form of a placebo control, a no-treatment control, or two dose levels of the same drug administered by the same route.

Specific interventions included in the review

Different doses of 8 different NSAIDs, given by intravenous, intramuscular, intrawound, rectal and oral routes, were tested in 58 single-dose or multiple-dose comparisons. The NSAIDs studied were diclofenac (50 to 100 mg), ibuprofen (600 to 800 mg), indomethacin (50 to 150 mg), ketoprofen (100 to 200 mg), ketorolac (10 to 60 mg), naproxen (500 mg), piroxicam (40 mg) and tenoxicam (20 mg). Paracetamol (650 mg or 35 microg/kg), fentanyl (100 mg or 1 microg/kg), dipyrone (1-2g) and avafortan (dose not stated) were also described but not evaluated. Saline, placebo and no treatment were used as comparisons. Topical formulations or intra-articular uses of NSAIDs were excluded.

Participants included in the review

Patients with acute or chronic pain, including pain associated with orthopaedic, gynaecological, renal colic, rheumatoid arthritis, third molar extraction, tonsillectomy and hernia repair settings.

Outcomes assessed in the review

The outcomes assessed were pain intensity at rest or on movement, additional analgesic consumption, and adverse effects.

How were decisions on the relevance of primary studies made?

At least two of the authors read each of the eligible papers and scored them for inclusion. The readers met to agree scores.

Assessment of study quality

The authors used the 3-item, 5-point scale of Jadad et al. (see Other Publications of Related Interest) to judge the validity of the included studies. At least two of the authors scored each of the papers for methodological quality. The authors met to agree scores.

Data extraction

The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. However, the authors listed the information that was extracted from the individual studies.

Methods of synthesis

How were the studies combined?

A quantitative analysis was not possible because of the variety of clinical settings, drugs, doses, routes and pain outcomes reported. The trials were combined narratively and valid direct comparisons, grouped by type of pain, were reported in the results. The overall adverse effects were also discussed.

How were differences between studies investigated?

The authors do not state how differences between the studies were investigated.

Results of the review

Twenty-six RCTs (2,225 participants) were considered eligible: 14 trials of post-operative pain (1,268 participants), 4 of renal colic (647 participants), 1 of acute musculoskeletal pain (77 participants), 1 of dysmenorrhoea (32 participants), and 6 of rheumatoid arthritis (201 participants).

The median quality score of all trials was 3 (range: 1 to 5).

Only 10 of the included trials reported a significant difference between the administration routes, or reported an equivalence, but had an internal sensitivity index. These trials reported on postoperative pain (5 trials), renal colic (3 trials), dysmenorrhoea (1 trial) and chronic pain (1 trial).

In the 5 direct comparisons in post-operative pain, results were inconsistent. In all 3 direct comparisons in renal colic, intravenous NSAID had a faster onset of action than intramuscular or rectal. In one direct comparison in dysmenorrhoea, oral NSAID was better than rectal. In the one direct comparison in rheumatoid arthritis, intramuscular NSAID was better than oral.

The commonly reported adverse effects were nausea, vomiting, dizziness, drowsiness, sedation, anxiety, dyspepsia, indigestion and dry mouth. Adverse effects related to the route of administration were most often reported for intramuscular and rectal regimes.

Authors' conclusions

In renal colic there was evidence that NSAIDs act quickest when given intravenously. In all other pain conditions there was a lack of evidence of any difference between administration routes. In pain conditions other than renal colic, there is, therefore, a strong argument to give oral NSAIDs when patients can swallow.

CRD commentary

The authors made a very thorough search of the literature for pertinent articles. Hhowever, they may have missed relevant material by excluding unpublished data, reviews, abstracts and letters, and by not contacting the original authors.

The inclusion criteria, and the judgements on inclusion and exclusion were all reported. The authors also made a quality review of the included trials. The process by which the data were extracted was not reported, although the details of the individual articles were tabulated. There were no data reported for age, gender, or the numbers of participants in the individual trials, although the numbers of participants were summed and reported in the text.

The authors presented the data in a narrative format, which allowed only 10 direct comparisons for four acute or chronic pain conditions. The results of the measurement instruments used for the outcome measures were summarised, without detail, in the table of individual trials.

The results showed a lack of evidence for any difference between the administration routes studied. However, this is due to the poor quality of the available trials, rather than conclusive evidence favouring the oral route for administering NSAIDs. Further research is evidently needed.

Implications of the review for practice and research

The authors state that the lack of evidence requires a research agenda to be set, in order to determine whether or not there is any clinical advantage of one route over another. Further research should design simple comparisons of the same drug at the same dose across routes, with validity, and ideally with standardised outcome measures so that a combined quantitative analysis is possible.

The authors also state that in practice, in pain conditions other than renal colic, there is a strong argument to give oral NSAIDs when patients can swallow.

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Bibliographic details

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Other publications of related interest

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12. McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. Health Technol Assess 1998;2(12):1-236.

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