The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that meperidine is less effective for migraine headache than dihydroergotamine regimens and may be more likely to cause adverse events. Meperidine may also be less effective than antiemetics. A degree of caution may be necessary in interpreting these conclusions because the primary trials were small, their quality was mixed and there were marked differences between them.

Authors' objectives
To compare the efficacy and safety of injectable opioids versus other treatments for acute migraine headache.

Searching
The following databases were searched from inception: MEDLINE (to April 2008), the Cochrane Central Register of Controlled Trials, EMBASE, LILACS and CINAHL (to April 2007). Search terms were reported. Electronically published abstracts from national meetings of emergency medicine, neurology and headache medicine societies were searched from 1985 to 2007. The reference lists of articles retrieved and relevant guidelines and reviews were hand searched. The PubMed 'Related articles' feature was used for all trials identified in previous systematic reviews and experts in the field were consulted. No language restriction was applied.

Study selection
Randomised controlled trials (RCTs) of the treatment of acute migraine were eligible for inclusion, provided they compared an injectable (intravenous, intramuscular or subcutaneous) opioid with an active comparator and reported on headache intensity within two hours of treatment. Trials were required to have define acute migraine by International Headache Society criteria or, failing this, to have taken reasonable steps to restrict the study to participants with migraine headaches rather than benign headaches. The primary review outcome was headache relief (as defined in the primary study), measured within an hour of treatment. Other outcomes of interest were functional disability, headache recurrence and adverse effects.

The trials in the review included participants with migraine diagnosed by International Headache Society criteria, migraine scores or physician assessment. Most were set in emergency departments. Intramuscular meperidine/pethidine (usually in conjunction with an antihistamine) or butorphanol were compared with intramuscular or intravenous dihydroergotamine (with or without antiemetics), antiemetics alone or ketorolac. The dose of meperidine was usually 75 milligrams (mgs) but ranged from 50 mgs to 1.5 mgs per kilogram (kg). Four different antiemetics were compared with the opioids (chlorpromazine, methotrimeprazine, droperidol and metoclopramide. Only half the trials reported rate of headache relief as an outcome; the others reported use of rescue medication or measured pain using a Likert or visual analogue scale (VAS).

One reviewer screened articles retrieved by the search and two other reviewers selected studies for inclusion from those potentially eligible. Disagreements were resolved by consensus or by the third reviewer.

Assessment of study quality
Study validity was assessed using the Jadad scale, which measures adequacy of randomisation, blinding, and management of withdrawals and dropouts. Each study was awarded a score out of a maximum of five points.

Two authors independently conducted the assessment, with disagreements resolved by consensus.

Data extraction
Where studies did not report headache relief, use of rescue medication was used instead or (failing either of these),
mean change in visual analogue scale. Odds ratios with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences for continuous outcomes. Where standard deviations were not reported, they were requested from study authors or, if necessary, imputed using established methods (Higgins 2006).

Two reviewers extracted the data. Disagreements were resolved by consensus or by a third reviewer.

**Methods of synthesis**
The trials were grouped by comparator and were combined using a random-effects model to calculate pooled odds ratios and standardised mean differences, with 95% confidence intervals (CIs). The standard error of the standardised mean difference was calculated and transformed to an odds ratio and 95% CI, using established methods (Higgins 2006) to enable dichotomous and continuous data to be pooled for the primary outcome. A pooled relative risk was also calculated for each comparison, using a random-effects model; for continuous data this was approximated from the odds ratio using published methods (Zhang 1998). Heterogeneity was assessed using the $I^2$ statistic and a fixed-effect model was applied as a sensitivity analysis. Trends in the data were examined to assess the impact of methodological and clinical differences between the trials.

**Results of the review**
Eleven RCTs were included (n=625). Four trials had Jadad scores of five points (the maximum); two scored 4 points, two scored 3, and three scored 2.

Meperidine versus active controls

Headache relief: A dihydroergotamine regimen was significantly more effective than meperidine (odds ratio 0.30, 95% CI: 0.09, 0.97, four RCTs, n=254), but statistical heterogeneity was high ($I^2=73\%$). There was no statistically significant difference in effectiveness between meperidine and anti-emetics, though there was a trend in favour of antiemetics (odds ratio 0.46, 95% CI: 0.19, 1.11, four RCTs, n=248); with considerable statistical heterogeneity ($I^2=51\%$). There was no statistically significant difference in effectiveness between meperidine and ketorolac (three RCTs, n=123). There was a trend in the data for larger and better quality studies to have less extreme odds ratios.

Adverse effects: Meperidine caused significantly more dizziness than dihydroergotamine regimens (odds ratio 8.67, 95% CI 2.66, 28.23, three RCTs). Meperidine caused less akathisia than antiemetics (odds ratio 0.10, 95% CI: 0.02, 0.57, three RCTs). There were no statistically significant differences between the groups for other side effects, but there was a trend for meperidine to cause more sedation than dihydroergotamine regimens (odds ratio 3.52, 95% CI: 0.87, 14.19, three RCTs).

Butorphanol versus dihydroergotamine regimen

No statistically significant differences were found for any outcome (one RCT).

Other results were reported in the review.

**Authors' conclusions**
Meperidine is less effective for migraine headache than dihydroergotamine regimens and may be more likely to cause adverse events. Meperidine may also be less effective than antiemetics.

**CRD commentary**
The objectives and inclusion criteria of the review were clear and a wide range of relevant sources were searched for published and unpublished studies, without language restriction. The processes of validity assessment and data extraction were conducted by more than one independent reviewer, but the preliminary screening of studies for selection was conducted by a single reviewer, which increased the potential bias and error in this process. The Jadad scale was used to evaluate study quality but this scale has limited scope. No details were reported on relevant methodological characteristics of the included trials such as allocation concealment and follow-up rates. Relevant statistical methods appear to have been used to combine the trials and assess heterogeneity. Potential reasons for the heterogeneity detected were well addressed in the text, along with other potential biases such as small trial size and...
possible publication bias. The review was mostly well conducted but a degree of caution may be necessary in interpreting the authors’ conclusions because the primary trials were small, their quality was mixed and there was marked heterogeneity between them.

Implications of the review for practice and research
Practice: The authors stated that clinicians using injectable agents to treat acute migraine should consider alternatives to meperidine.

Research: The authors stated that several questions remain unanswered in this area. These included: the risk of overuse headache or addiction associated with opioids; the role of drugs such as morphine, hydromorphone and sumatriptan; the relative efficacy of dihydroergotamine, metoclopramide and/or both combined; and whether the efficacy of meperidine is enhanced by co-administration of antihistamines. Future research should also investigate provider choice of drugs for acute migraine in different clinical scenarios and the role of patient preference.

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