

Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials

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Abstract

Objective To assess the evidence from controlled trials on the efficacy and tolerability of parenteral metoclopramide for acute migraine in adults.

Data sources Cochrane Central Register of Controlled Trials, Medline, Embase, LILACS, CINAHL, conference proceedings, clinical practice guidelines, and other sources.

Selection criteria Randomised controlled trials of parenteral metoclopramide for acute migraine in adults.

Results We reviewed 596 potentially relevant abstracts and found 13 eligible trials totalling 655 adults. In studies comparing metoclopramide with placebo, metoclopramide was more likely to provide significant reduction in migraine pain (odds ratio 2.84, 95% confidence interval 1.05 to 7.68). Used as the only agent, metoclopramide showed mixed effectiveness when compared with other single agents. Heterogeneity of studies for combination treatment prevented statistical pooling. Treatments that did include metoclopramide were as, or more, effective than comparison treatments for pain, nausea, and relapse outcomes reported in all studies.

Conclusions Metoclopramide is an effective treatment for migraine headache and may be effective when combined with other treatments. Given its non-narcotic and antiemetic properties, metoclopramide should be considered a primary agent in the treatment of acute migraines in emergency departments.

Introduction

The pathophysiology of migraine is poorly understood, with no clear consensus on the best treatment for acute attacks. Current guidelines recommend agents such as sumatriptan, dihydroergotamine, ergotamine, chlorpromazine, and prochlorperazine.^{1,2} Metoclopramide has long been used for the treatment of nausea associated with acute migraine. It also relieves gastric stasis and has the potential to enhance the absorption of other analgesics.³ The dopamine antagonist properties of metoclopramide might make it effective as a single agent to treat acute migraine.⁴ Other dopamine antagonists such as prochlorperazine and chlorpromazine have also shown effectiveness in migraine.²

We assessed the evidence from controlled trials on the efficacy and tolerability of parenteral metoclopramide for acute migraine in adults.

Methods

Our a priori study protocol is described elsewhere.⁵ We searched the Cochrane Central Register of Controlled Trials, Medline, Embase, LILACS, and CINAHL using the search terms “headache” or “migraine” and “metoclopramide”, “Maxeran”, “Reglan”, or “Maxolon”.

To locate unpublished research, we reviewed proceedings from meetings on neurology, headache, and emergency medicine from 1998 to 2004, we assessed clinical practice guidelines, and we searched websites containing details of clinical trials, theses, or dissertations. We hand searched reference lists of all potentially relevant studies, and we contacted pharmaceutical companies, authors of previous studies, and experts in headache.

Studies were eligible for review if they were randomised controlled trials of parenteral metoclopramide given for acute migraine in adults, and described reasonable criteria to distinguish migraine from other headaches. We included trials conducted in a setting that indicated the headache was an acute episode—emergency department or headache clinic.

Study selection, data abstraction, and assessment of quality

Two independent reviewers (IC, EG) screened identified studies for eligibility. They reviewed the full manuscripts of potentially relevant papers for inclusion. Two independent reviewers (IC, MDB) abstracted information on to specially designed, pretested forms. Disagreements were resolved by consensus.

The internal validity of trials was assessed with the Jadad scale.⁶ This evaluates quality of randomisation, blinding, and withdrawals and assigns a score from 0 to 5, higher scores indicating higher quality in the conduct or reporting of trials.

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Additional forest plots and details of excluded trials are on bmj.com



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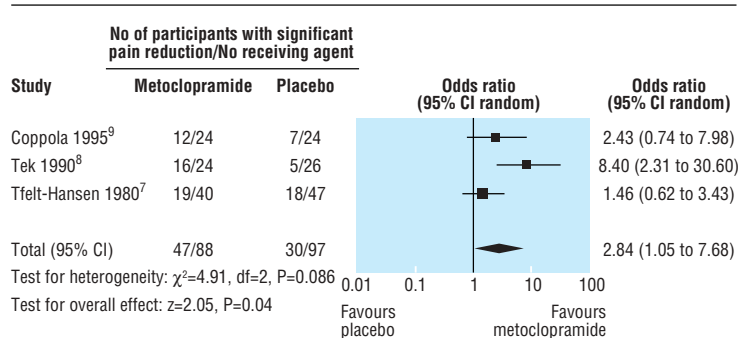


Fig 1 Metoclopramide compared with placebo for significant reduction in headache pain from acute migraine

We considered three outcomes describing relief of headache at the time closest to two hours after treatment. These were self reported as complete relief of headache, significant reduction in headache pain (from moderate or severe to mild or none), and reduction in headache pain using a visual analogue scale. Secondary outcomes included improvement in functional status or ability, relapse of migraine within 48 hours of treatment, reduction in nausea, number of co-intervention (“rescue”) drugs required, and adverse events associated with treatment.

Statistical analysis and sensitivity analyses

Using random effects models, we pooled the results of studies, if appropriate, after consideration of heterogeneity between the trials. We tested for heterogeneity using a χ^2 test, with P values of less than 0.10 representing significance. Trials were not pooled when heterogeneity was evident and could be explained by dissimilarities in clinical variables. See bmj.com for details.

We completed our a priori sensitivity analyses comparing studies of high quality to those of low quality, based on the Jadad scale. These sensitivity analyses were only performed for outcomes reported in at least three studies.

Results

We identified 596 abstracts, of which 36 were potentially relevant articles. Independent review led to the inclusion of 13 studies (see bmj.com). As three of these studies had multiple arms, we were able to make 17 total comparisons. Study methods varied significantly, particularly for comparators and outcomes, and study quality was generally poor.

Metoclopramide versus placebo

Five studies (263 patients) compared metoclopramide with placebo. Metoclopramide was superior to placebo for all outcomes related to pain and nausea, although differences were not always statistically significant. Pooled data from three studies showed that metoclopramide more often led to significant reductions in headache pain (odds ratio 2.84, 95% confidence interval 1.05 to 7.68; fig 1), and in these studies, patients who received metoclopramide were significantly less likely to require rescue drugs (0.21, 0.05 to 0.85).⁷⁻⁹ Three studies suggested that metoclopramide produced larger improvements in pain scores on a visual analogue scale, but no standard deviations were

reported, preventing statistical pooling. One study reported that metoclopramide was more likely than placebo to provide complete resolution of migraine; the difference, however, was not statistically significant (2.16, 0.36 to 12.84). Four studies found that metoclopramide was more effective than placebo in reducing nausea (4.20, 1.70 to 10.36), but only two studies reported relapse of migraine, and these found a statistically insignificant advantage favouring metoclopramide (0.30, 0.03 to 3.16).

Only two studies reported adverse events. One found a statistically insignificant increase in restlessness in the metoclopramide group (2.27, 0.19 to 26.81) whereas the other reported no restlessness, dystonic reactions, hypotension, or seizures in either treatment group.

Sensitivity analyses failed to identify differences between studies of high and low quality.

Metoclopramide versus other antiemetics

Three studies (194 patients) compared metoclopramide with other antiemetics (chlorpromazine and prochlorperazine). These suggested that metoclopramide was less effective in relieving pain and nausea, although differences were not always statistically significant. Two studies found no difference in the rate of complete resolution of migraine (0.64, 0.23 to 1.76) whereas two found that metoclopramide was less likely to provide significant relief of headache (0.39, 0.18 to 0.87); however, in one study, reduction in pain scores on a visual analogue scale was not different between groups (weighted mean difference -0.53 , 95% confidence interval -1.63 to 0.57). Pooled results from all three studies showed that patients who received metoclopramide were more likely to require rescue drugs (odds ratio 2.08, 1.04 to 4.17). Two studies found no significant differences in relapse of migraine (3.95, 0.88 to 17.66). Metoclopramide was less effective than other antiemetics in reducing nausea, but these differences were not statistically significant.

Two studies looked at adverse events. One reported no restlessness, dystonic reactions, hypotension, or seizures in either treatment group, whereas the other described several subgroups of adverse events but found no statistically significant differences between groups.

Metoclopramide versus non-antiemetics

Two studies (60 patients) compared metoclopramide with non-antiemetics. The first found no significant differences between metoclopramide and sumatriptan in the rate of complete resolution of migraine (2.27, 0.64 to 8.11), the likelihood of significant reduction of pain (18.38 to 0.96, 352.59), or the likelihood of significant reduction of nausea (19.74, 1.00 to 390.32). In the second study, metoclopramide was compared with ibuprofen on the basis of scores to measure pain and nausea on a visual analogue scale. Metoclopramide produced larger decreases in scores for both outcomes, but standard deviations were not reported. Patients in the metoclopramide group were significantly less likely to require rescue drugs (0.05, 0.00 to 0.56). Neither study reported adverse events, no common outcomes were reported, and no statistical pooling was possible.

Metoclopramide combinations versus other agents

Seven studies (211 patients) compared metoclopramide combinations (usually metoclopramide with dihydroergotamine) with other antimigraine regimens (hydroxyzine-meperidine, dihydroergotamine alone, valproate, ibuprofen, ketorolac, promethazine-meperidine). Owing to significant heterogeneity in study methods, studies were not pooled statistically.

One study showed that complete resolution of migraine was significantly more likely in patients who received metoclopramide (7.79, 1.79 to 33.86), and results from four studies suggested that patients who received metoclopramide were equally, or more, likely to have "significant reductions" in headache (fig 2).¹⁰⁻¹³ Two studies showed that patients who received metoclopramide had equivalent, or larger, reductions in pain scores on the basis of a visual analogue scale (see fig A on bmj.com). We found no significant differences between groups for functional ability in two studies (see fig B on bmj.com) or nausea in two studies (see fig C on bmj.com). One study found no significant differences between groups in requirement for rescue drugs (0.22, 0.04 to 1.12). Three studies reported that patients who received metoclopramide were equally, or less, likely to have relapse of migraine (see fig D on bmj.com).

Reporting for adverse events was inconsistent. Four studies found no significant differences for nausea between groups. One study found restlessness, dysphoria, and flushing more common among patients treated with metoclopramide and dihydroergotamine than those treated with hydroxyzine and meperidine or butorphanol, and no significant differences for dizziness. Another study found that drowsiness, dizziness, and an orthostatic blood pressure response were less common among patients treated with metoclopramide and dihydroergotamine than those treated with promethazine and meperidine.

What is already known on this topic

Migraine headache is a common and disabling phenomenon that is not well understood

Parenteral metoclopramide is often given to relieve nausea associated with migraine headache

Metoclopramide may reduce pain associated with migraine headache

What this study adds

Parenteral metoclopramide is effective in reducing headache pain from acute migraine

As few as four patients need to be treated with metoclopramide to enable one additional patient to achieve significant reduction in pain

Parenteral metoclopramide may also be effective when combined with other treatments to enhance antimigraine effects

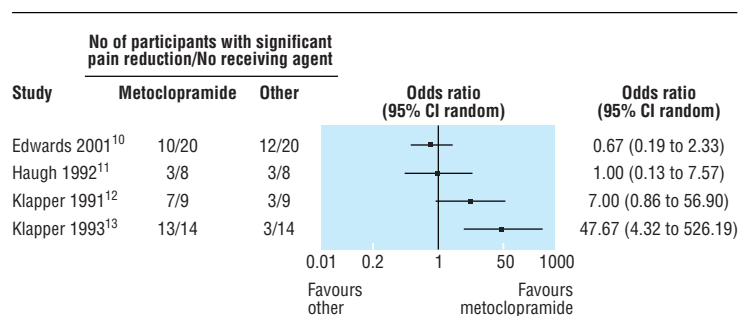


Fig 2 Metoclopramide combined with other agents compared with other agents for significant reduction in headache pain from acute migraine in adults

Discussion

Metoclopramide is an effective treatment for migraine headache in adults. Our systematic review suggests that as few as four patients need to be treated with metoclopramide to enable one patient to achieve a significant reduction in pain. Given its non-narcotic and antiemetic properties, metoclopramide should be considered as a primary agent in the treatment of acute migraine in emergency departments. Metoclopramide may, however, have less beneficial effects on nausea than other antiemetics.

Several studies scored less than 3 on the Jadad scale, undermining confidence in any conclusions drawn. It was difficult to combine the studies because of the many different comparators used and the many different outcomes reported.

Future trials should include multiple arms to compare various treatments under similar conditions, and there should be improvement in the quality of research. The International Headache Society's guidelines for controlled trials of drugs in migraine are a step in the right direction.¹⁴

Some of the trials did not report on inclusion and exclusion criteria in sufficient detail; consequently, we may have included studies of non-migraine headaches. Some failed to describe their study population, and most did not report initial severity and duration of headache. It is therefore possible we pooled studies with differing patient characteristics, so it is difficult to determine whether our results are generalisable.

Poor reporting of adverse events in most of the studies limits any conclusions about the relative safety of different agents, and the relatively small sample sizes provided insufficient power to detect meaningful differences in rates of uncommon adverse events.

Our study may have been affected by publication bias. However, we employed comprehensive search strategies to identify all relevant research. To avoid any selection bias, we used two independent reviewers and developed standardised criteria to identify and select studies for review.

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Contributors: See bmj.com

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Competing interests: BHR has received fees on two occasions from Aventis for speaking on venous thromboembolism. He has not been sponsored to speak on Maxeran or migraine headaches.

Ethical approval: Not required.

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Randomised controlled trial of an occupational therapy intervention to increase outdoor mobility after stroke

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Abstract

Objective To evaluate an occupational therapy intervention to improve outdoor mobility after stroke.

Design Randomised controlled trial.

Setting General practice registers, social services departments, a primary care rehabilitation service, and a geriatric day hospital.

Participants 168 community dwelling people with a clinical diagnosis of stroke in previous 36 months: 86 were allocated to the intervention group and 82 to the control group.

Interventions Leaflets describing local transport services for disabled people (control group) and leaflets with assessment and up to seven intervention sessions by an occupational therapist (intervention group).

Main outcome measures Responses to postal questionnaires at four and 10 months: primary outcome measure was response to whether participant got out of the house as much as he or she would like, and secondary outcome measures were response to how many journeys outdoors had been made in the past month and scores on the Nottingham extended activities of daily living scale, Nottingham leisure questionnaire, and general health questionnaire.

Results Participants in the treatment group were more likely to get out of the house as often as they wanted at both four months (relative risk 1.72, 95% confidence interval 1.25 to 2.37) and 10 months (1.74, 1.24 to 2.44). The treatment group reported more journeys outdoors in the month before assessment at both four months (median 37 in intervention group,

14 in control group; $P < 0.01$) and 10 months (median 42 in intervention group, 14 in control group; $P < 0.01$). At four months the mobility scores on the Nottingham extended activities of daily living scale were significantly higher in the intervention group, but there were no significant differences in the other secondary outcomes. No significant differences were observed in these measures at 10 months.

Conclusion A targeted occupational therapy intervention at home increases outdoor mobility in people after stroke.

Introduction

Many people after stroke do not get out of the house as much as they would like, and this has deleterious effects on quality of life.^{1,2} Some reasons for poor outdoor mobility are potentially remediable, including lack of confidence and inadequate information on transport options, aids, appliances, or adaptations to the home.³ On the basis of findings of a qualitative interview study, we developed an occupational therapy intervention programme to overcome these barriers.³

Methods

We identified patients with a clinical diagnosis of stroke in the previous 36 months from general practice registers and other sources in the community. We included people in care homes.

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