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Papers

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

Migraine headache is a common problem in adult populations, with 6% of men and 15-17% of women experiencing around 36 episodes each a year.[1 2] Migraine can be disabling; the average length of bed rest during an episode is 4.5 hours for men and 6.0 hours for women.[2] This impairs quality of life, limits daily activities, and strains personal and professional relationships.[3] Migraine headaches have important economic effects due to lost productivity and increased utilisation of healthcare services.[2]

The pathophysiology of migraine is poorly understood, and there is no clear consensus on the best treatment for acute attacks. Current clinical guidelines recommend agents such as sumatriptan, dihydroergotamine, ergotamine, chlorpromazine, and prochlorperazine.[4 5] Metoclopramide has long been used for the treatment of nausea associated with acute migraine. In addition to its antiemetic properties, metoclopramide relieves gastric stasis and has the potential to enhance the absorption of other analgesics.[6] In the late 1970s, anecdotal case reports suggested that patients with migraine who received metoclopramide for nausea experienced substantial pain relief before they had received an analgesic.[7] Subsequent studies concluded that the dopamine antagonist properties of metoclopramide might make it effective as a single agent to treat acute migraine.[8] Other dopamine antagonists such as prochlorperazine and chlorpromazine have also shown effectiveness in migraine.[5]

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

Methods

Search strategy for identification of studies

Our a priori study protocol is described in detail elsewhere.[9] 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". We identified randomised controlled trials using a previously described strategy.[10]

To locate unpublished research, we reviewed congress proceedings from major meetings on neurology, headache, and emergency medicine from 1998 to 2004, we assessed clinical practice guidelines for the management of acute migraine, and we searched websites containing details of clinical trials, theses, or dissertations. In addition, we handsearched the reference lists of all potentially relevant studies, and contacted experts in headache, pharmaceutical companies, and authors of previous studies to identify relevant articles.

Inclusion criteria

Studies were considered eligible for review if they were randomised controlled trials of parenteral metoclopramide given for acute migraine attacks in adults and if they described reasonable criteria to distinguish migraine from other types of headache. We included trials only if they were 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 the titles and abstracts of identified studies for eligibility. Papers deemed potentially relevant were obtained, and the full manuscripts were reviewed by IC and BHR for inclusion. Two independent reviewers (IC, MDB) abstracted information on patients, methods, interventions, outcomes, and adverse events from the original reports on to specially designed, pretested forms. Disagreements were resolved by consensus.

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

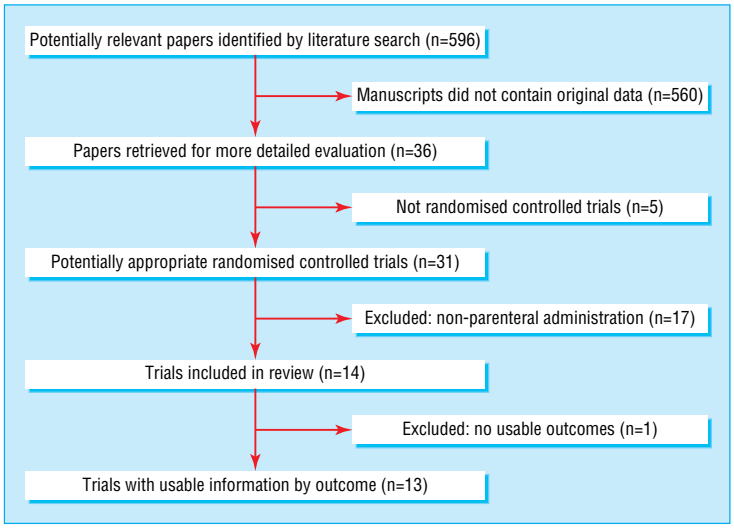

Fig 1 Identification of potentially relevant studies in review

The internal validity of trials was assessed with the Jadad scale.[11] This scale 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.

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 on the basis of a 10 cm 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 cointervention ("rescue") drugs required, and adverse events associated with treatment.

Statistical analysis

All data were entered into Review Manager (version 4.1, Update Software). Using random effects models, we pooled the results of studies, if appropriate, after consideration of heterogeneity between the trials. For dichotomous variables, we calculated individual and pooled statistics as odds ratios, with 95% confidence intervals. For continuous outcomes, we calculated individual and pooled statistics as weighted mean differences when data were on a uniform scale, or standardised mean differences when data were on different scales, with 95% confidence intervals. 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.

Sensitivity analyses

We completed our a priori sensitivity analyses comparing studies of high quality to those of low quality, based on the Jadad scale (assigning studies with a score of 3 or more as high quality and those with a score of 2 or less as low quality).[11] 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 of these 36 reports led to the inclusion of 13 studies (fig 1).[12–24] As three of these studies had multiple arms (table and table on bmj.com), we were able to make 17 total comparisons. Study methods varied significantly, particularly for comparators and outcomes, and study quality was generally poor. Comparisons included metoclopramide with placebo, metoclopramide with other antiemetics, metoclopramide with non-antiemetics, and metoclopramide combinations with other antimigraine regimens (see table).

Metoclopramide versus placebo

Five studies (263 patients) compared metoclopramide with placebo.[12–16] 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 2), and in these studies, patients who received metoclopramide were significantly less likely to require rescue drugs (0.21, 0.05 to 0.85).[12 13 15] 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.[14–16] 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).[16] Four studies found that metoclopramide was more effective than placebo in reducing nausea (4.20, 1.70 to 10.36),[12 14–16] but only two studies[15 16] 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.[13 16] 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.

Our 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).[15–17] These studies suggested that metoclopramide was less effective in relieving pain and nausea, although differences were not always statistically significant. Two studies[16 17] found no difference in the rate of complete resolution of migraine (0.64, 0.23 to 1.76) whereas two[15 17] found that metoclopramide was less likely to

Descriptive characteristics of studies included in systematic review

Trial	No of participants	Setting	Treatment	Comparison	Quality*
Belgrade 1989[19]	62	Emergency department	10 mg intravenous metoclopramide and 1 mg intravenous dihydroergotamine	50 mg intramuscular hydroxyzine plus 75 mg intramuscular meperidine or 2 mg intramuscular butorphanol	3
Cameron 1995[17]	91	Two emergency departments	0.1 mg/kg intravenous metoclopramide	0.1 mg/kg intravenous chlorpromazine	5
Coppola 1995[15]	70	Emergency department	10 mg intravenous metoclopramide	Control group 1 intervention, 10 mg intravenous prochlorperazine; control group 2 intervention, placebo	4
Edwards 2001[20]	40	Headache clinic	10 mg intramuscular metoclopramide plus 1 mg intramuscular dihydroergotamine	500 mg intravenous valproate	1
Ellis 1993[14]	40	Emergency department	Experimental group 1 intervention, 10 mg intravenous metoclopramide plus placebo by mouth; experimental group 2 intervention, 10 mg intravenous metoclopramide plus 600 mg ibuprofen by mouth	Control group 1 intervention, intravenous placebo plus 600 mg ibuprofen by mouth; control group 2 intervention, intravenous placebo plus placebo by mouth	2
Estaban-Morales 1999[18]	40	Emergency department	10 mg intravenous metoclopramide	6 mg subcutaneous sumatriptan	2
Haugh 1992[21]	16	Headache clinic	10 mg intramuscular metoclopramide plus 1 mg intramuscular dihydroergotamine	1 mg intramuscular dihydroergotamine	2
Jones 1996[16]	86	Emergency department	10 mg intramuscular metoclopramide	Control group 1 intervention, 10 mg intramuscular prochlorperazine; control group 2 intervention, placebo intramuscularly	5
Klapper 1991[22]	18	Private headache clinic	5 mg intravenous metoclopramide plus 1 mg intravenous dihydroergotamine	60 mg intramuscular ketorolac	1
Klapper 1993[23]	28	Private headache clinic	10 mg intravenous metoclopramide plus 1 mg intravenous dihydroergotamine	75 mg intramuscular hydroxyzine plus 75 mg intramuscular meperidine	3
Scherl 1995[24]	27	General medicine clinic	10 mg intravenous metoclopramide plus 0.5 mg intravenous dihydroergotamine	25 mg intramuscular promethazine plus 75 mg intramuscular meperidine	2
Tek 1990[13]	50	Emergency department	10 mg intravenous metoclopramide	Placebo intravenously	3
Tfelt-Hansen 1980[12]	87	Migraine clinic	10 mg intramuscular metoclopramide	Placebo intramuscularly	3

*Jadad scale: scores of ≥3 represent high quality, those of ≤2 represent low quality.

provide significant relief of headache (0.39, 0.18 to 0.87); however, in one study,[17] reduction in pain scores on a visual analogue scale were 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).[15 17] Metoclopramide was less effective than other antiemetics in reducing nausea, but these differences were not statistically significant.

Two studies looked at adverse events.[16 17] One reported no restlessness, dystonic reactions, hypotension, or seizures in either treatment group, whereas the other described several subgroups of adverse events (restlessness, drowsiness, nasal congestion, nausea, dizziness, dry mouth, significant falls in diastolic or systolic blood pressure) but found no statistically significant differences between groups.

No sensitivity analyses on study quality were possible because the studies were of high quality.

Metoclopramide versus non-antiemetics

Two studies (60 patients) compared metoclopramide with non-antiemetics.[14 18] 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).[18] 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, making analysis difficult. 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

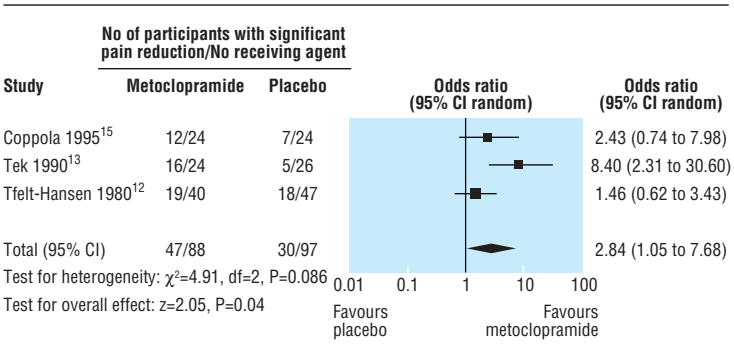

Fig 2 Metoclopramide compared with placebo in reducing pain from acute migraine

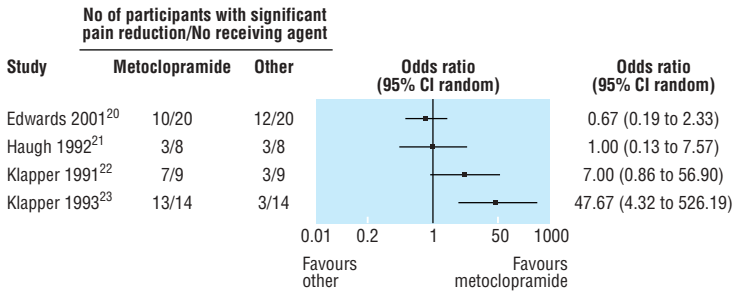

Fig 3 Metoclopramide combined with other agents compared with other agents in reducing pain from acute migraine

pooling was possible. We did not perform sensitivity analyses because there were too few studies and no common outcomes.

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).[14 19–24] Owing to significant heterogeneity in study methods (see table), particularly for comparison treatments, studies were not pooled statistically.

One study[19] 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 pain (fig 3).[20–23] 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).[14 19] We found no significant differences between groups for functional ability in two studies (see fig B on bmj.com)[21 22] or nausea in two studies (see fig C on bmj.com).[20 21] One study found no significant differences between groups in requirement for rescue drugs (0.22, 0.04 to 1.12).[14] Three studies reported that patients who received metoclopramide were equally, or less, likely to have relapse of migraine (see fig D on bmj.com).[20 22]

Reporting for adverse events was inconsistent. Four studies found no significant differences for nausea between groups.[19–21 24] One study found restlessness, dysphoria, and flushing more common among patients treated with metoclopramide and dihydroergotamine compared with those treated with hydroxyzine and meperidine or butorphanol, and no significant differences for dizziness.[19] Another study found that drowsiness, dizziness, and an orthostatic blood pressure response were less common among patients treated with metoclopramide and dihydroergotamine compared with those treated with promethazine and meperidine.[24]

Because the study results were not pooled, we did not carry out sensitivity analyses.

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.

Five studies confirmed that metoclopramide is more effective than placebo for multiple outcomes related to migraine, including relief of pain and nausea and relapse of headache. In these studies, side effects, such as akathisia, were described but poorly quantified.[12–16] Although metoclopramide was better than placebo, three studies suggested that it may provide less relief from pain and nausea than other phenothiazine antiemetics (prochlorperazine and chlorpromazine).[15–17] Again, adverse events were poorly reported and sample sizes were insufficient to rule out rare events. Only two studies compared metoclopramide with non-antiemetics (ibuprofen and sumatriptan).[14 18] Although metoclopramide compared favourably with these agents, there were insufficient data on which to base firm conclusions on relative effectiveness.

These data suggest that metoclopramide may also be effective as an adjunctive treatment. Several studies showed that metoclopramide combinations were similarly, or more, effective for pain related outcomes than comparison regimens (for example, hydroxyzine-meperidine, dihydroergotamine alone, valproate, ibuprofen, ketorolac, promethazine-meperidine), although no significant differences were noted for relief of nausea.[14 19–24] Adverse events were, however, inconsistently reported. Other treatments may be more effective; many common anti-migraine treatments have not been compared with metoclopramide combination treatments in randomised controlled trials and consequently could not be included in this review.

Trial quality

The studies were of variable quality, with several scoring less than 3 on the Jadad scale, and this undermines confidence in any of the conclusions drawn. A noteworthy feature was the wide variability in execution of the studies. Many different comparators were used and many different outcomes reported. The variety of comparators is not surprising given the lack of consensus about a standard of care for acute migraine headache. The variety of study outcomes, however, made it difficult to combine the studies and to come to an overall conclusion on the relative effectiveness of different treatments.

Future trials should include multiple arms to compare various treatments under similar conditions, and researchers should focus on adequate randomisation, concealment of allocation, appropriate controls, and blinding of all researchers. New research standards such as the International Headache Society's guidelines for controlled trials of drugs in migraine[25] are a step in the right direction; however, further progress must be made to improve the quality of research.

Limitations

Some of the trials did not report their inclusion and exclusion criteria in sufficient detail; consequently, we may have included

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 the 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

studies that enrolled patients with non-migraine headaches. Similarly, some authors failed to describe their study population, and most did not report initial severity and duration of headache. It is therefore possible that we pooled studies with differing patient characteristics, and it is therefore difficult to determine whether our results are generalisable to other settings.

Poor adverse event reporting 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. For example, although restlessness is an important side effect of metoclopramide, and hypotension and dystonic reactions important side effects of phenothiazines, we found no significant differences between groups receiving these treatments.

As with any review, our study may have been affected by publication bias. If there are unpublished trials showing no benefits from metoclopramide, the real treatment efficacy of this agent may be less than suggested here; however, we employed comprehensive search strategies to identify all relevant research, including a search of conference proceedings, and we contacted authors and experts in the specialty and pharmaceutical companies to identify unpublished work. Although several obscure and negative studies were identified and included in our review, we acknowledge that publication bias may still be an important limitation of our work. Finally, 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: IC conceived the project, conducted searches, coordinated the reviewers, data collection, and extraction, and prepared the manuscript. MDB contributed to the protocol, data collection and extraction, and review of the manuscript. GDI, EG, and TER contributed to the protocol, selection of articles, and review of the manuscript. BHR conceived the project, contributed to the protocol, coordinated the review, and prepared the manuscript; he is guarantor.

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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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