

medicalisation, similar symptom control to immediate prescribing, and reduced reattendance for eye infections.

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Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial

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Abstract

Objectives To determine whether 10 mg, 25 mg, or 50 mg metoclopramide combined with 8 mg dexamethasone, given intraoperatively, is more effective in preventing postoperative nausea and vomiting than 8 mg dexamethasone alone, and to assess benefit in relation to adverse drug reactions.

Design Four-armed, parallel group, double blind, randomised controlled clinical trial.

Setting Four clinics of a university hospital and four district hospitals in Germany.

Participants 3140 patients who received balanced or regional anaesthesia during surgery.

Main outcome measures Postoperative nausea and vomiting within 24 hours of surgery (primary end point); occurrence of adverse reactions.

Results Cumulative incidences (95% confidence intervals) of postoperative nausea and vomiting were 23.1% (20.2% to 26.0%), 20.6% (17.8% to 23.4%), 17.2% (14.6% to 19.8%), and 14.5% (12.0% to 17.0%) for 0 mg, 10 mg, 25 mg, and 50 mg metoclopramide. In the secondary analysis, 25 mg and 50 mg metoclopramide were equally effective at preventing early nausea (0-12 hours), but only 50 mg reduced late nausea and vomiting (> 12 hours). The most frequent adverse drug reactions were hypotension and tachycardia, with cumulative incidences of 8.8% (6.8% to 10.8%), 11.2% (9.0% to 13.4%), 12.9% (10.5% to 15.3%), and 17.9% (15.2% to 20.6%) for 0 mg, 10 mg, 25 mg, and 50 mg metoclopramide.

Conclusion The addition of 50 mg metoclopramide to 8 mg dexamethasone (given intraoperatively) is an effective, safe, and cheap way to prevent postoperative nausea and vomiting. A reduced dose of 25 mg

metoclopramide intraoperatively, with additional postoperative prophylaxis in high risk patients, may be equally effective and cause fewer adverse drug reactions.

Trial registration Current Controlled Trials ISRCTN 31625370.

Introduction

A large clinical trial of postoperative nausea and vomiting showed that 4 mg ondansetron, 4 mg dexamethasone, or 1.25 mg droperidol were effective, and that combinations of these drugs had an additive effect.¹ Dexamethasone was recommended as the first line drug, as it is safe and cheap.

Data on metoclopramide as an antiemetic after surgery are contradictory. A meta-analysis found that an intravenous dose of 10 mg had only a marginal effect,² but because of its complex mode of action (it binds to dopamine, serotonin, and histamine receptors), metoclopramide remains an interesting drug.³ Studies have concluded that metoclopramide is ineffective in this context, but the timing of administration and use of larger doses were not investigated fully. We investigated the efficacy and safety of three doses of metoclopramide (10 mg, 25 mg, and 50 mg), on the assumption that each patient would receive basic antiemetic prophylaxis of 8 mg dexamethasone.

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Dose of metoclopramide and postoperative nausea and vomiting outcomes. Values are number (%) unless stated otherwise

Variable	Dose of metoclopramide (mg)				P value
	0 (n=788)	10 (n=783)	25 (n=781)	50 (n=788)	
All types of postoperative nausea and vomiting	182 (23.1)	161 (20.6)	134 (17.2)	114 (14.5)	<0.001
Nausea (regardless of vomiting)	147 (18.7)	129 (16.5)	110 (14.1)	84 (10.7)	<0.001
Vomiting (regardless of nausea)	134 (17.0)	106 (13.5)	94 (12.0)	80 (10.2)	0.001
Early form (0-12 hours after surgery)	138 (17.5)	116 (14.8)	84 (10.8)	85 (10.8)	<0.001
Late form (>12-24 hours after surgery), including repeat episodes	67 (8.5)	57 (7.3)	62 (7.9)	38 (4.8)	0.025
Multiple episodes of nausea and vomiting	77 (9.8)	54 (6.9)	46 (5.9)	46 (5.8)	0.007
Need for rescue drugs after nausea and vomiting	99 (12.6)	79 (10.1)	67 (8.6)	57 (7.2)	0.003

Methods

Protocol

We considered patients for inclusion if they were aged 18 years or more and having regional or balanced anaesthesia during hysterectomy, cholecystectomy, herniotomy, otolaryngological surgery, thyroidectomy, total knee or hip replacement, or arthroscopy of the shoulder or the knee. See bmj.com for exclusion criteria.

We randomised patients to receive 0 mg, 10 mg, 25 mg, or 50 mg metoclopramide and the standard 8 mg dexamethasone. Both drugs were given intravenously 30-60 minutes before the anticipated end of surgery or immediately after the start of anaesthesia if surgery was expected to take less than one hour. If postoperative nausea and vomiting occurred, 62 mg dimenhydrinate or 12.5 mg dolasetron was given as the rescue drug.

Assignment and masking

We generated blocked randomisation lists stratified by centre, sex, and type of surgery. Study nurses randomised patients immediately before the trial drug was administered. Anaesthesiologists and patients were blinded to the assignment.

Documentation and follow-up

We recorded eligibility criteria and history on the day before surgery. During surgery, details of anaesthesia, relevant drug, and adverse reactions were recorded. Twenty four hours after the end of surgery the anaesthesiologists visited the patients to record any nausea and vomiting, other adverse events, and relevant drugs.

Statistical analysis

The primary end point was occurrence of nausea and vomiting within 24 hours of the end of surgery. Secondary end points were nausea and vomiting separately, occurrence of early (≤ 12 hours) and late (> 12 hours after surgery, including repeat events) postoperative nausea and vomiting, occurrence of multiple episodes of nausea and vomiting, and need for rescue drug. We compared the frequency of nausea and vomiting in the four treatment groups. Safety end points were the occurrence of adverse reactions after the study drug was given and postoperative adverse events. We performed trend tests for each end point. We performed stepwise multiple logistic regression analyses of early and late postoperative nausea and vomiting and adverse drug reactions to identify predictors. It was estimated that we needed a sample size of 3000. See bmj.com.

Results

Study sample

We screened 4078 patients from January to November 2004; we included 3149 in the study and analysed 3140. See bmj.com for demographic data and putative risk factors and flow of participants through the trial.

End points

The addition of 10 mg, 25 mg, and 50 mg metoclopramide reduced the cumulative incidence of postoperative nausea and vomiting from 23.1% (95% confidence interval 20.2% to 26.0%) to 20.6% (17.8% to 23.4%), 17.2% (14.6% to 19.8%), and 14.5% (12.0% to 17.0%), respectively. The corresponding numbers needed to treat are 40.0 (not significant), 16.9 (10.1 to 52.6), and 11.6 (8.0 to 20.8). Whereas overall rates (irrespective of the time of postoperative nausea and vomiting) suggest "the more, the better," 25 mg metoclopramide was as effective in preventing early events as 50 mg, but only the 50 mg dose reduced nausea and vomiting in the late phase. Metoclopramide also reduced the number of multiple episodes of nausea and vomiting and the need for rescue drugs (table).

The incidence of postoperative nausea and vomiting decreased continuously up to 12 hours after surgery, but increased after that point (fig 1). The curves for the 25 mg and 50 mg groups diverged in the later phase. These findings justify setting the cut-off point at 12 hours to distinguish between early and late events.

Adverse events

Only intraoperative hypotension and tachycardia were clearly related to metoclopramide, and these events correlated with each other ($P < 0.001$). The incidence

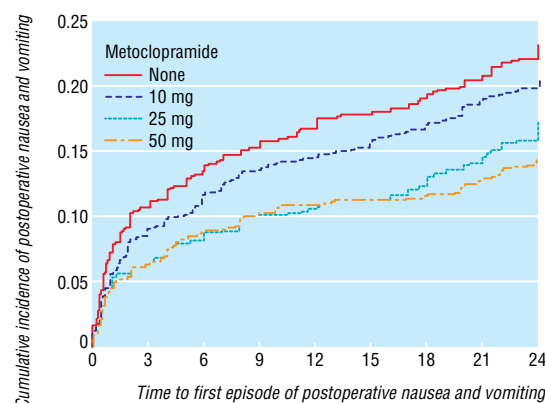


Fig 1 Cumulative incidence of postoperative nausea and vomiting in four treatment groups

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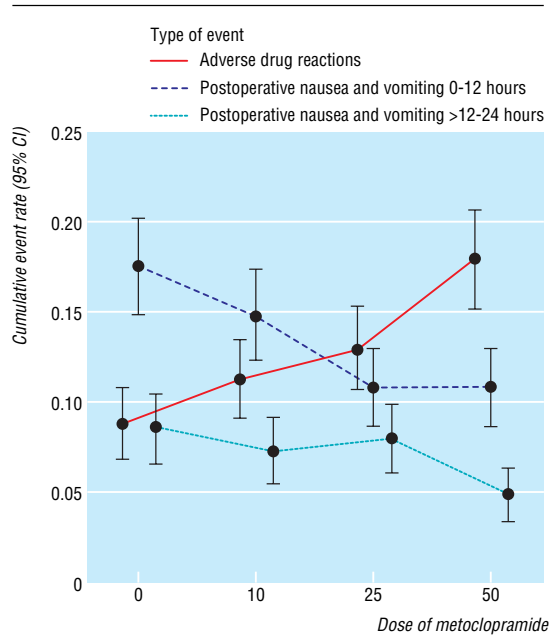


Fig 2 Rates of early and late postoperative nausea and vomiting and intraoperative adverse drug reactions (hypotension and tachycardia) in four treatment groups

of either of these events was 8.8% (6.8% to 10.8%), 11.2% (9.0% to 13.4%), 12.9% (10.5% to 15.3%), and 17.9% (15.2% to 20.6%) for 0 mg, 10 mg, 25 mg, and 50 mg metoclopramide; this corresponded to numbers needed to harm of 41.7 (not significant), 24.4 (13.9 to 100.0), and 11.0 (8.1 to 17.2). Metoclopramide was also associated with dyskinesia or extrapyramidal symptoms (number needed to harm: 156, 81 to 3333 for doses of 25 or 50 mg), impaired taste and smell (167, 93 to 5000 for any dose), and hot flushes (182, 106 to 345 for any dose), but the results were only marginally significant. See bmj.com.

Serious adverse events were bleeding (four), myocardial infarction (one), tachycardia and hypotension (one), aspiration (one), and inspiratoric stridor with cyanosis (one); these events were classified as definitely (five) or probably (three) not related to metoclopramide.

Predictors of nausea and vomiting and adverse reactions

The results of multiple regression for predictors of early and late postoperative nausea and vomiting and adverse reactions (hypotension or tachycardia after the study drug was given) are on bmj.com. Only the 25 mg and 50 mg doses significantly reduced nausea and vomiting. The frequency of adverse reactions increased with the dose of metoclopramide (fig 2).

Female sex, history of nausea and vomiting after surgery or motion sickness, non-smoking, low alcohol consumption and postoperative opioids were associated with increased rates of postoperative nausea and vomiting. Late application of opioids increased postoperative nausea and vomiting much more than early application. Frequency depended on the type of surgery.

Discussion

No single antiemetic drug has proved to be a universal solution to postoperative nausea and vomiting. It is not feasible to give very high doses of such drugs because of saturation effects and safety, so combinations of antiemetic drugs are a possibility. We found that 25 mg or 50 mg metoclopramide added to the basic intervention of 8 mg dexamethasone is effective, safe, and cheap.

Strengths and limitations

We investigated the dose-response relation between metoclopramide and postoperative nausea and vomiting. Although we had insufficient power to obtain precise information on rare events, we carried out a large prospective assessment of metoclopramide related adverse reactions. Thus, we can derive recommendations from our data, by weighing efficacy against safety. Because of the size of our study, our data on extrapyramidal symptoms are probably more reliable than those from a meta-analysis of 537 patients from 13 trials.^{3 4}

Our study design allowed us to investigate only the effect of adding metoclopramide to dexamethasone, and not the separate effects of each drug. The numbers needed to treat reflect the effectiveness of metoclopramide only as a secondary, not primary, intervention.

Comparison with other studies

A meta-analysis reported that 10 mg metoclopramide was clinically ineffective and did not improve when combined with 8 mg dexamethasone.³ Larger dosages, however, were as effective as ondansetron or droperidol when added to dexamethasone (odds ratios around 0.5).¹

A randomised double blind trial with 240 children and adults per treatment arm found that 50 mg metoclopramide was not effective for postoperative vomiting (odds ratio 0.83, 0.45 to 1.52) but significantly reduced postoperative nausea and vomiting (odds ratio 0.47, 0.27 to 0.84).⁵ That study reported a higher rate of restlessness and extrapyramidal symptoms than was seen in our study.

Other studies also found that 20 mg metoclopramide was ineffective, possibly because of the small sample sizes.⁶⁻⁸ The timing of antiemetic prophylaxis seems to influence efficacy. In most of the studies, metoclopramide was given immediately after induction of anaesthesia, irrespective of its time of maximum effect and short half life.

Despite the neuroleptic properties of metoclopramide, its addition to dexamethasone did not increase rates of headache, dizziness, sedation, or dry mouth. The incidences seen in our trial are similar to those of low dose droperidol.

Clinical implications and future research

The addition of 10 mg metoclopramide to dexamethasone is a standard prophylaxis for postoperative nausea and vomiting in Germany. We recommend a combination of 8 mg dexamethasone and 50 mg metoclopramide, given 30-60 minutes before the end of surgery. If house policy allows postoperative antiemetic prophylaxis, 8 mg dexamethasone and 25 mg metoclopramide should be given intraoperatively.

What is already known on this topic

The results of trials on the use of metoclopramide to prevent postoperative nausea and vomiting have been contradictory

What this study adds

This large randomised trial showed that the addition of 25 mg or 50 mg metoclopramide to dexamethasone (given intraoperatively) reduces postoperative nausea and vomiting

The optimal dose will depend on the hospital's policy on prophylaxis for postoperative nausea and vomiting

Additional drugs can then be given after surgery, but the patient's risk profile should be taken into account. Rescue drugs should be given after postoperative nausea and vomiting to prevent repeat episodes.

The role of different types of surgery and of alcohol consumption should be investigated further. Timing of administration should also be investigated, and a suitable dose of metoclopramide should be compared with a 5-hydroxytryptamine receptor antagonist (both combined with dexamethasone).

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Case finding for patients at risk of readmission to hospital: development of algorithm to identify high risk patients

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Abstract

Objective To develop a method of identifying patients at high risk of readmission to hospital in the next 12 months for practical use by primary care trusts and general practices in the NHS in England.

Data sources Data from hospital episode statistics showing all admissions in NHS trusts in England over five years, 1999-2000 to 2003-4; data from the 2001 census for England.

Population All residents in England admitted to hospital in the previous four years with a subset of "reference" conditions for which improved management may help to prevent future admissions.

Design Multivariate statistical analysis of routinely collected data to develop an algorithm to predict patients at highest risk of readmission in the next 12 months. The algorithm was developed by using a 10% sample of hospital episode statistics data for all of England for the period indicated. The coefficients for 21 most powerful (and statistically significant) variables were then applied against a second 10% test

sample to validate the findings of the algorithm from the first sample.

Results The key factors predicting subsequent admission included age, sex, ethnicity, number of previous admissions, and clinical condition. The algorithm produces a risk score (from 0 to 100) for each patient admitted with a reference condition. At a risk score threshold of 50, the algorithm identified 54.3% of patients admitted with a reference condition who would have an admission in the next 12 months; 34.7% of patients were "flagged" incorrectly (they would not have a subsequent admission). At risk score threshold levels of 70 and 80, the rate of incorrectly "flagged" patients dropped to 22.6% and 15.7%, but the algorithm found a lower percentage of patients

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