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Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies

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Metoclopramide has been used for almost 40 yr to prevent postoperative nausea and vomiting (PONV). We have reviewed the efficacy and safety of metoclopramide for the prevention of PONV. A systematic search (MEDLINE, EMBASE, manufacturers' databases, hand searching, bibliographies, all languages, up to June 1998) was performed for full reports of randomized comparisons of metoclopramide with placebo in surgical patients. Relevant end-points were prevention of early PONV (within 6 h after operation), late PONV (48 h) and adverse effects. Combined data were analysed using relative benefit/risk and number-needed-to-treat/harm. In 66 studies, 3260 patients received 18 different regimens of metoclopramide, and 3006 controls received placebo or no treatment. There was no evidence of dose–responsiveness with oral, i.m., intranasal or i.v. metoclopramide in children and adults. In adults, the best documented regimen was 10 mg i.v. There was no significant anti-nausea effect. The numbers-needed-to-treat to prevent early and late vomiting were 9.1 (95% confidence intervals 5.5–27) and 10 (6–41), respectively. In children, the best documented regimen was 0.25 mg kg^{-1} i.v. The number-needed-to-treat to prevent early vomiting was 5.8 (3.9–11). There was no significant late anti-vomiting effect. Minor drug-related adverse effects (sedation, dizziness, drowsiness) were not significantly associated with metoclopramide. There was one adult who experienced extrapyramidal symptoms with metoclopramide.

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Nausea and vomiting occur frequently in patients undergoing general anaesthesia for surgery. The mean incidence of postoperative nausea and vomiting (PONV) is approximately 30%, although this varies widely depending on different clinical settings, patient characteristics and other poorly defined factors.[1–3]

Metoclopramide, a dopamine and serotonin receptor antagonist, was discovered almost 40 yr ago.[4] The first clinical studies on the efficacy of metoclopramide in the prevention of PONV were published in the 1960s. The appearance of metoclopramide triggered a new generation of gastrointestinal research.

Metoclopramide is still used widely in clinical practice. However, the dose–responsiveness of metoclopramide in the prevention of PONV has never been established. Textbooks suggested that 10 mg i.v. was the optimal dose in the surgical setting,[5 6] although much higher doses have been used for the prevention of chemotherapy-induced nausea and vomiting.[7 8]

This quantitative review of systematically searched, randomized, controlled studies had several goals: first, to define the antiemetic efficacy of metoclopramide compared with placebo or no treatment in the prevention of PONV; second, to establish dose–responsiveness; third, to compare anti-nausea with anti-vomiting efficacy; and fourth, to investigate the potential for toxic effects of metoclopramide in the surgical setting.

Methods

Systematic search

We performed a systematic search for full reports of randomized, controlled studies that tested the effect of prophylactic metoclopramide (experimental intervention) compared with placebo or 'no treatment' (control intervention) on PONV after general anaesthesia or combined spinal and general anaesthesia. Relevant studies had to report end-

points of interest in dichotomous form (i.e. presence or absence of the end-point with both metoclopramide and control). We searched MEDLINE (from 1966), Cochrane Library (issue 1, 1998), and EMBASE (from 1982) databases without restriction to the English language, and using different search strategies with the free text key words: 'metoclopramide' or 'paspertin' or 'primperan'; 'nausea' or 'vomiting' or 'emesis'; 'random'; 'surgery' or 'anaesthesia' or 'postoperative'. The date of the last electronic search was June 30, 1998. Additional studies were identified from reference lists of retrieved reports and review articles on PONV and metoclopramide, and by manually searching locally available anaesthesia journals. We contacted four manufacturers of metoclopramide (Heumann Pharma GmBH, Nuernberg, Germany; ASTA Medica AG, Wangen, Switzerland; Synthélabo-Pharma SA, Lausanne, Switzerland; Solvay Pharma AG, Bern, Switzerland) and asked for further studies, including unpublished data. Abstracts, letters, review articles and animal data were not considered. We did not analyse efficacy data of metoclopramide as a treatment of established PONV, or reports without a placebo or 'no treatment' arm.

Critical appraisal

All authors read independently each report that could possibly meet the inclusion criteria, and scored them for inclusion and methodological validity using the three-item, five-point Oxford scale.[9] We then met to reach a consensus by discussion. The minimum score of an included randomized, controlled study was 1, the maximum score was 5.

Data extraction

We obtained information from each included report on patients, surgery, dose and route of administration of metoclopramide, study end-points and adverse effects. We extracted cumulative incidences of PONV within 6 h after surgery and within 48 h. Incidences of PONV during the two times (0–6 h and 0–48 h) were used as indicators of early and late antiemetic efficacy, respectively. Events during recovery or 'postoperatively' were considered as early data. When several incidences of events were reported at different times, we analysed the cumulative values nearest to 6 and 48 h after operation. Three different PONV events, both early and late, were extracted in dichotomous form: nausea, vomiting (including retching) and any emetic event (nausea, vomiting, or nausea and vomiting). These events were treated separately. When multiple doses of metoclopramide were given (two doses of 10 mg i.v. in 24 h, for instance), we considered the first dose (in this case, 10 mg) for estimation of early efficacy and to test the evidence of dose–responsiveness for early outcomes. We used the cumulative 24-h dose (in this case, 20 mg) to estimate late efficacy and to establish dose–responsiveness for late outcomes. We did not take into account nausea scores, number of, or time to, first vomiting episode, number of patients needing antiemetic rescue medication, delay until discharge, *post hoc* analyses, stratified data analyses (by sex, for instance) or scores of patient satisfaction because these end-points were inconsistently reported.

Qualitative analysis

We used the scatter of event rates (incidence of PONV) with metoclopramide (i.e. experimental event rate) against event rates with control (i.e. control event rate) as a graphical means to explore the consistency of the efficacy of metoclopramide and the homogeneity of the data.[10] On such plots, a scatter lying predominantly between the line of equality and the axis of the control intervention suggests consistent efficacy with metoclopramide and relative homogeneity.

Quantitative analysis

We defined antiemetic efficacy as prevention of a PONV event with metoclopramide or control. We made calculations for individual studies, and by combining metoclopramide and control arms of independent studies. We combined data only when they represented clinically homogenous subgroups (the same PONV event), the same observation period (early or late), the same dose and route of administration of metoclopramide, and only in adults or only in children.

Both relative benefit and number-needed-to-treat were calculated as estimates of antiemetic efficacy. We calculated relative benefit as relative risk with 95% confidence intervals (CI).[11] We used a fixed-effect model to calculate combined relative benefit.[12]

As an estimate of the clinical relevance of treatment effect, we calculated the number-needed-to-treat[13] for both individual studies and combined data using the weighted mean of the experimental and control event rates. A positive number-needed-to-treat indicated how many patients had to be exposed to metoclopramide to prevent one particular PONV event in one of them, who would have had this event had they all received placebo. We made a *pre hoc* decision that a number-needed-to-treat of 5 or less to prevent PONV compared with placebo would represent a clinically relevant degree of efficacy in this clinical setting.[14] A negative number-needed-to-treat suggested superiority of placebo over metoclopramide. The 95% CI around the number-needed-to-treat point estimate were obtained by taking the reciprocals of the values defining the 95% CI for the absolute risk reduction.[15] In text and tables, the actual upper and lower limits of 95% CI around the number-needed-to-treat, independent of whether or not they were positive or negative, are reported.[16] The 95% CI contain exclusively positive numbers if the difference between metoclopramide and control is statistically significant (i.e. $P<0.05$) in favour of metoclopramide. A 95% CI ranging from a positive limit to a negative limit indicates a result which is not statistically significant (i.e. the confidence interval includes zero, and thus infinity).

Dose–responsiveness

We attempted to test the evidence for dose–responsiveness using pre-set criteria.[17] Thus a statistically significant difference between at least two different doses of metoclopramide would be interpreted as strong evidence of a dose–response. A statistically significant difference between two doses would be assumed when the 95% CI of the corresponding numbers-needed-to-treat did not overlap. An increase in antiemetic efficacy of at least 20% (for example a decrease in the number-needed-to-treat from 5 to 4) would be considered a clinically relevant improvement and therefore justify an increase in dose. The optimal dose of metoclopramide would be defined as the dose that had, first, a number-needed-to-treat to prevent PONV of no more than 5, and second, for which a further increase in the dose would not lead to a further clinically relevant improvement.

Adverse drug reactions

To estimate the additional risk of drug-related adverse effects, relative risks and numbers-needed-to-harm[18] were calculated with 95% CI. There was an attempt to identify a relationship between dose of metoclopramide and the risk of adverse drug reactions. If there was no clear evidence of dose–responsiveness, we combined data from different doses (from studies with several metoclopramide arms). Data from control patients in the same study were counted only once.

Sensitivity analysis

We calculated relative benefit and number-needed-to-treat for the best documented regimens (i.e. 10 mg i.v. and orally for adults, 0.15 mg kg^{-1} and 0.25 mg kg^{-1} i.v. for children) within two pre-defined ranges of control event rates: early outcomes within 20–60% of control event rate, and late outcomes within 40–80% of control event rate.[19] Data outside these ranges were excluded from the sensitivity analyses. Thus estimated the relative efficacy of metoclopramide compared with other antiemetic interventions without the need for direct comparisons.

In studies with 4 to 1 randomization,[20] similar group sizes were achieved by dividing data of the larger group by 4. If any cell of a sample was zero, then 0.5 was added to all cells of that sample to calculate the relative risk.[21] Calculations were performed using Excel (version 5.0) on a Power Macintosh G3.

Results

Excluded and included studies

We considered 77 studies published in 74 reports for analysis. Twelve were subsequently excluded: three[22–24] could not be analysed because the number of patients per group was not mentioned; two[25 26] were not randomized; in two,[27 28] multiple doses of metoclopramide were given over several days; two[29 30] were duplicate reports (i.e. they contained patient data that had already been published in other full reports)[20 31]; one[32] was on both prophylaxis of PONV and treatment of established PONV; and in one,[33] droperidol treatment at induction was not correctly controlled.

We analysed data from 66 randomized, controlled studies that were published in 62 reports (Tables 1–4).[20 31 34–93] One manufacturer responded to our enquiry; no additional published or unpublished data were retrieved. In all analysed studies, 9656 patients were randomized but data from 414 patients (4.3% of all data) were subsequently excluded by the original authors. Thus we analysed data from 9242 patients of whom 3260 received metoclopramide and 3006 received placebo or 'no treatment'. A 'no treatment' control was used in one study[45]; all others used placebo. Data from no treatment controls were regarded as placebo. The median number of patients per study was 104 (range 38–1044). The median validity score was 3 (range 1–5). Eighteen different metoclopramide regimens were tested: oral, i.v., i.m. and intranasal routes; fixed doses (full mg) and variable doses (μg/kg per body weight); and single and double administrations in 24 h.

Forty-seven studies were in adults; 39 of those in women only. Eighteen studies were performed in children. One study[42] included adults and children (age range 12–69 yr). In this study, the metoclopramide regimen was 10 mg i.v. These data were analysed with the 10 mg data. In 44 studies (67% of all studies), metoclopramide was compared with both a placebo and another antiemetic intervention (mostly droperidol, ondansetron or granisetron).

Qualitative analyses

The event rate scatter for both early and late outcomes suggested improved efficacy with metoclopramide compared with placebo (Fig. 1). Late events were less frequently documented than early events. The average incidence of early nausea with metoclopramide and placebo was 13% (range 0–64%) and 18% (3–60%), respectively. The average incidence of early vomiting with metoclopramide and placebo was 21% (0–57%) and 31% (4–89%), respectively.

The average incidence of late nausea with metoclopramide and placebo was 30% (range 12–68%) and 38% (18–96%), respectively. The average incidence of late vomiting with metoclopramide and placebo was 34% (6–73%) and 44% (16–97%), respectively.

Efficacy data in adults

Five different fixed doses (5, 10, 15, 20 and 30 mg) and four different routes of administration (i.v., i.m., oral and intranasal) were tested. In two studies,[35 68] 0.25 mg kg^{-1} and 0.5 mg kg^{-1}, respectively, were given i.v. These doses were extrapolated to average fixed doses of 18 mg and 35 mg, respectively, using the average body weight reported in these studies.

Table 1 Prophylactic antiemetic efficacy of metoclopramide (Meto.) in placebo-controlled, randomized studies: efficacy date in adults. ∞=Infinity (zero, not statistically significant)

End-point (prevention of)	No. studies	Event rates (%)		No. with end-point/ total No.		Relative benefit (95% CI)	No. needed-to-treat (95% CI)	Ref.
		Meto.	Placebo	Meto.	Placebo			
Early outcomes (0–6 h)								
10 mg i.v.								
Nausea	10	18	25	221/270	206/273	1.07 (0.99 to 1.17)	16 (7.5 to –210)	39 40 51 54 70 75 89 90
Vomiting	9	20	31	214/266	189/272	1.16 (1.05 to 1.28)	9.1 (5.5 to 27)	39 40 48 51 54 61 70 77 90
Nausea and/or vomiting	14	32	42	293/429	264/452	1.13 (1.06 to 1.21)	10 (6.2 to 28)	43 45 51 54 61 66 70 71 74 75
0.2 mg kg^{-1} (14 mg) i.v.								
Vomiting	1	40	27	6/10	8/11	0.83 (0.44 to 1.54)	–8.0 (–2.0 to 3.6)	83
Nausea and/or vomiting	1	30	45	7/10	6/11	1.28 (0.56 to 2.52)	6.0 (1.8 to –4.0)	83
20 mg i.v.								
Nausea	3	16	19	128/153	116/144	1.04 (0.93 to 1.16)	32 (8.5 to –18)	46 75 90
Vomiting	3	19	23	125/154	115/149	1.04 (0.93 to 1.15)	25 (7.6 to –19)	46 48 90
Nausea and/or vomiting	3	14	20	182/212	167/210	1.08 (0.99 to 1.18)	16 (7.4 to –115)	46 60 75
0.5 mg kg^{-1} (35 mg) i.v.								
Vomiting	1	0	5	19/19	18/19	1.06 (0.95 to 1.17)	19 (6.5 to –21)	68
10 mg i.m.								
Nausea	2	8	20	157/171	123/153	1.14 (1.04 to 1.24)	8.8 (5.3 to 26)	57 88
Vomiting	3	12	23	186/212	149/194	1.14 (1.04 to 1.25)	9.1 (5.5 to 28)	57 85 88
Nausea and/or vomiting	3	20	34	170/194	128/194	1.21 (1.07 to 1.36)	7.0 (4.4 to 18)	57 85 88
20 mg i.m.								
Nausea	1	3	9	97/100	91/100	1.07 (0.99 to 1.14)	17 (8.0 to –189)	88
Vomiting	1	2	4	98/100	96/100	1.02 (0.97 to 1.07)	50 (14.9 to –37)	88
Nausea and/or vomiting	1	7	38	93/100	62/100	1.50 (1.27 to 1.76)	3.2 (2.4 to 4.9)	88
5 mg orally								
Nausea	1	30	25	14/20	15/20	0.93 (0.64 to 1.37)	–20 (–3.1 to 4.4)	76
Nausea and/or vomiting	1	55	65	9/20	7/20	1.29 (0.60 to 2.77)	10 (2.5 to –4.9)	76
10 mg orally								
Nausea	1	23	23	31/40	31/40	1.00 (0.79 to 1.27)	∞ (5.5 to –5.5)	76
Nausea and/or vomiting	1	25	35	30/40	26/40	1.15 (0.86 to 1.54)	10 (3.3 to –10)	76
20 mg orally								
Nausea	1	6	27	17/18	11/15	1.29 (0.93 to 1.78)	4.7 (2.2 to –27)	73
Vomiting	1	6	13	17/18	13/15	1.09 (0.87 to 1.37)	13 (3.6 to –8.1)	73
Nausea and/or vomiting	1	11	25	93/104	77/102	1.18 (1.04 to 1.35)	7.2 (4.1 to 27)	44
30 mg orally								
Nausea	2	8	14	55/60	51/59	1.06 (0.93 to 1.20)	19 (6.1 to –17)	47 59
Vomiting	1	11	5	17/19	19/20	0.94 (0.78 to 1.13)	–18 (–4.5 to 8.9)	47
20 mg intranasally								
Nausea and/or vomiting	1	36	38	38/50	31/50	1.04 (0.78 to 1.39)	41.5 (4.9 to –6.3)	91
Late outcomes (0–48 h)								
10 mg i.v.								
Nausea	5	48	57	132/256	125/289	1.19 (1.00 to 1.42)	12 (6.0 to –1587)	20 36 53 54 77
Vomiting	8	39	48	218/356	192/372	1.24 (1.10 to 1.40)	10 (6.0 to 41)	20 32 36 40 42 53 54 77
Nausea and/or vomiting	6	49	62	75/146	57/151	1.35 (1.05 to 1.73)	7.3 (4.0 to 41)	37 53 54 74 79 92
20 mg i.v.								
Nausea	1	16	18	81/96	77/94	1.03 (0.91 to 1.17)	41 (7.6 to –12)	46
Vomiting	2	23	33	101/132	87/130	1.14 (0.99 to 1.31)	10 (4.9 to –80)	46 63
Nausea and/or vomiting	3	29	37	162/229	144/227	1.11 (0.99 to 1.26)	14 (6.3 to –77)	46 60 63
10 mg orally								
Nausea	3	36	43	104/162	91/160	1.12 (0.95 to 1.33)	14 (5.6 to –30)	34 62 80
Vomiting	2	30	39	57/82	49/80	1.14 (0.92 to 1.42)	12 (4.4 to –16)	34 80
Nausea and/or vomiting	4	38	50	128/208	103/207	1.24 (1.05 to 1.47)	8.5 (4.7 to 44)	34 62 72 80
20 mg orally								
Nausea and/or vomiting	1	50	80	9/18	3/15	2.50 (0.82 to 7.61)	3.3 (1.6 to –140)	73
30 mg orally								
Nausea	1	68	65	6/19	7/20	0.90 (0.37 to 2.20)	–29 (3.0 to –3.8)	47
Vomiting	1	63	65	7/19	7/20	1.05 (0.46 to 2.43)	54 (3.1 to –3.5)	47
0.25 mg kg^{-1} i.v.								
Nausea	1	35	53	26/40	19/40	1.37 (0.92 to 2.04)	5.7 (2.6 to –26)	35
Vomiting	1	15	30	34/40	28/40	1.21 (0.95 to 1.55)	6.7 (3.0 to –33)	35

Early events (within 6 h) in adults

Metoclopramide 10 mg and 20 mg i.v. and 10 mg i.m. were tested in at least three studies (Table 1). The best documented dose was 10 mg i.v.; nausea was reported in 10 studies and vomiting in nine. The anti-nausea effect with 10 mg i.v. was not significantly different from placebo. The number-needed-to-treat to prevent early vomiting with metoclopramide 10 mg i.v. was 9.1, with 95% CI including 27. With

Table 2 Prophylactic antiemetic efficacy of metoclopramide (Meto.) in placebo-controlled, randomized studies: efficacy date in children. ∞=Infinity (zero, not statistically significant)

End-point (prevention of)	No. studies	Event rates (%)		No. with end-point/ total No.		Relative benefit (95% CI)	No. needed-to-treat (95% CI)	Ref.
		Meto.	Placebo	Meto.	Placebo			
Early outcomes (0–6 h)								
0.10 mg kg^{-1} i.v.								
Vomiting	1	4	18	24/25	23/28	1.17 (0.97 to 1.41)	7.2 (3.3 to –44)	78
0.12 mg kg^{-1} i.v.								
Nausea	1	10	10	18/20	18/20	1.00 (0.81 to 1.23)	∞ (5.4 to –5.4)	31
Vomiting	1	25	10	15/20	18/20	0.83 (0.62 to 1.12)	–6.8 (–3 to 12)	31
0.15 mg kg^{-1} i.v.								
Vomiting	3	43	68	69/120	40/124	1.71 (1.33 to 2.19)	4 (2.7 to 7.6)	38 64 67
0.20 mg kg^{-1} i.v.								
Nausea	1	50	60	25/50	20/50	1.25 (0.81 to 1.94)	10 (3.4 to –11)	41
Vomiting	1	38	44	31/50	28/50	1.11 (0.80 to 1.54)	17 (4.0 to –8)	41
0.25 mg kg^{-1} i.v.								
Vomiting	7	31	48	176/254	133/256	1.44 (1.11 to 1.87)	5.8 (3.9 to 11)	52 67 81 82 84 86 87
0.50 mg kg^{-1} i.v.								
Vomiting	2	20	38	79/99	63/101	1.32 (0.89 to 1.96)	5.7 (3.4 to 20)	56 81
Late outcomes (0–48 h)								
0.10 mg kg^{-1} i.v.								
Nausea and/or vomiting	1	44	48	14/25	13/25	1.08 (0.65 to 1.80)	25 (3.2 to –4)	49
0.15 mg kg^{-1} i.v.								
Vomiting	2	57	82	36/84	16/85	2.28 (1.37 to 3.78)	4.2 (2.7 to 9.5)	50 64
0.25 mg kg^{-1} i.v.								
Nausea	1	35	53	26/40	19/40	1.37 (0.92 to 2.04)	5.7 (2.6 to –26)	35
0.15 mg kg orally								
Vomiting	1	62	56	16/42	15/34	0.86 (0.50 to 1.48)	–17 (–4 to 6.2)	65

Table 3 Prophylactic antiemetic efficacy of metoclopramide (Meto.) in placebo-controlled, randomized studies: subgroup analyses (control event rate banding)

End-point (prevention of)	No. studies	Event rates (%)		No. with end-point/ total No.		Relative benefit (95% CI)	No. needed-to-treat (95% CI)	Ref.
		Meto.	Placebo	Meto.	Placebo			
Early outcomes: studies with control event rate 20–60%								
Adults, 10 mg i.v.								
Nausea	5	28	36	106/147	97/151	1.12 (0.96 to 1.29)	13 (5.4 to –38)	39 70 75 89 90
Vomiting	7	21	30	157/198	138/157	1.13 (1.01 to 1.26)	11 (5.6 to 140)	39 40 51 54 61 77 90
Children, 0.25 mg kg^{-1} i.v.								
Vomiting	5	29	41	145/203	121/206	1.32 (1.12 to 1.57)	7.9 (4.6 to 28)	81 82 84 86 87
Late outcomes: studies with control event rate 40–80%								
Adults, 10 mg i.v.								
Vomiting	5	53	65	127/245	86/228	1.36 (1.12 to 1.69)	7.1 (4.4 to 19.1)	20 32 42 77
Adults, 10 mg orally								
Nausea	2	43	52	68/120	58/120	1.17 (0.92 to 1.49)	12 (4.8 to –23)	34 62
Vomiting	1	43	55	24/42	18/40	1.27 (0.83 to 1.95)	8.2 (3.0 to –11)	34

metoclopramide 20 mg i.v. and 10 mg i.m., numbers-needed-to-treat point estimate to prevent vomiting were 25 and 9.1, respectively. Metoclopramide 10 mg i.m. was significantly more efficacious than placebo, but the numbers-needed-to-treat to prevent nausea and vomiting were approximately 9. Metoclopramide 20 mg i.v. was not significantly different from placebo.

Late events (within 48 h) in adults

Metoclopramide 10 mg i.v. and 10 mg orally were tested in at least three studies (Table 1). The best documented dose was 10 mg i.v.; nausea was reported in five studies and vomiting in eight. The late anti-nausea effect with 10 mg i.v. was not significantly different from placebo. The number-needed-to-treat to prevent late vomiting was 10, with a 95% CI including 41. Metoclopramide 10 mg orally was not significantly different from placebo.

Most regimens were tested in one study only; no definite conclusions could be drawn. For both early and late outcomes in adults, there was no evidence of dose–responsiveness with any route of administration.

Data in children

Six different variable doses (0.10, 0.12, 0.15, 0.20, 0.25 and 0.50 mg kg^{-1}) and two different routes of administration (i.v. and oral) were tested. Two regimens, 0.15 and 0.25 mg kg^{-1}, were tested in at least three studies (Table 2). Most studies analysed prevention of vomiting only.

Table 4 Adverse reactions with metoclopramide (Meto.) in adults and children. ∞=infinity (zero, no difference between active and control). Numbers of studies do not add up because some studies reported more than one adverse reaction and also in some studies more than one dose of metoclopramide was investigated

End-point	No. studies	Event rates (%)		No. with end-point/total No.		Relative risk (95% CI)	No. needed-to-harm (95% CI)	Ref.
		Meto.	Placebo	Meto.	Placebo			
Extrapyramidal symptoms (including abnormal movements)								
Adults								
Extrapyramidal symptoms								
10 mg i.v.	4	0.0	0.0	0/164	0/201	1.20 (0.17 to 8.29)	n/a	36 43 75
20 mg i.v.	1	5.3	0.0	1/19	0/19	3.00 (0.13 to 69.2)	20 (5.3 to –12)	75
0.50 mg kg^{-1}	1	0.0	0.0	0/19	0/19	1.00 (0.02 to 47.9)	n/a	68
Abnormal movements								
10 mg i.v.	3	4.2	4.1	5/118	5/121	1.03 (0.32 to 3.25)	952 (19 to –20)	37 70 71
Combined	8	1.9	1.5	6/320	5/341	1.11 (0.43 to 2.48)	245 (42 to –65)	36 37 43 75 68 70 71
Children								
Extrapyramidal symptoms								
0.15 mg kg^{-1} i.v.	2	0.0	0.0	0/58	0/60	1.03 (0.07 to 16.2)	n/a	64 67
0.20 mg kg^{-1} i.v.	1	0.0	0.0	0/50	0/50	1.00 (0.02 to 49.4)	n/a	41
0.25 mg kg^{-1} i.v.	2	0.0	0.0	0/53	0/51	0.96 (0.06 to 15.0)	n/a	55 67
0.50 mg kg^{-1} i.m.	1	0.0	0.0	0/59	0/61	1.03 (0.02 to 51.2)	n/a	56
Combined	5	0.0	0.0	0/220	0/222	1.00 (0.21 to 4.92)	n/a	41 55 56 64 67
Adults and children	13	1.0	1.0	6/537	5/640	1.13 (0.52 to 2.45)	556 (72 to –98)	36 37 41 43 55 56 64 67 68 70 71 75
Sedation and drowsiness								
Adults								
10 mg i.v.	10	32.2	27.2	123/382	103/378	1.18 (0.95 to 1.47)	20 (8.7 to –65)	37 40 42 43 53 54 61 66 70 71
10 mg i.m.	1	9.8	9.8	4/41	4/41	1.00 (0.27 to 3.73)	∞ (8 to –8)	85
0.2 mg kg^{-1} (14 mg) i.v.	1	80.0	54.5	8/10	6/11	1.47 (0.79 to 2.73)	3.9 (1.6 to –7.7)	83
20 mg i.m.	1	0.0	0.0	0/100	0/100	1.00 (0.02 to 49.9)	n/a	88
20 mg intranasally	1	8.5	4.0	5/59	2/50	2.12 (0.43 to 10.5)	22 (7.5 to –22)	91
Combined	14	21.2	19.5	138/651	113/580	1.17 (0.97 to 1.41)	58 (16 to –36)	37 40 42 43 53 54 61 66 70 71 85 88
Children								
0.25 mg kg^{-1} i.v.	2	2.3	2.3	2/87	2/86	1.03 (0.19 to 5.58)	–3741 (–22 to 23)	38 52
0.20 mg kg^{-1} i.v.	1	0.0	0.0	0/50	0/50	1.00 (0.02 to 49.4)	n/a	41
Combined	3	1.5	1.5	2/137	2/136	1.02 (0.22 to 4.83)	–9316 (–35 to 35)	38 52
Adults and children	17	17.8	16.1	140/788	115/716	1.17 (0.97 to 1.41)	60 (18 to –47)	37 38 40–43 52–54 61 66 70
Dizziness and vertigo								
Adults								
10 mg i.v.	5	5.1	8.1	11/216	15/201	0.66 (0.34 to 1.27)	–42 (–14 to 44)	40 42 75 20 79
10 mg i.m.	1	4.9	2.4	2/41	1/41	2.00 (0.19 to 21.2)	41 (9.5 to –18)	85
20 mg i.v.	1	5.3	0.0	1/19	0/19	13.0 (0.78 to 215)	3.3 (1.9 to 12)	75
20 mg intranasally	1	8.0	4.0	5/59	2/50	2.12 (0.43 to 10.5)	22 (7.5 to –22)	91
30 mg orally	1	2.0	3.0	1/41	1/39	0.95 (0.06 to 14.7)	–800 (–14 to 15)	59
Combined	8	6.5	6.0	26/455	19/331	0.93 (0.54 to 1.63)	–3862 (–30 to 31)	40 42 59 75 20 79 85
Headache								
Adults								
10 mg i.v.	4	3.5	6.1	7/201	11/189	0.61 (0.25 to 1.48)	–43 (–15 to 54)	20 42 53 54
20 mg i.v.	1	3.0	5.0	3/100	5/100	0.60 (0.15 to 2.44)	–50 (–14 to 29)	88
Combined	5	3.8	6.4	10/301	16/289	0.62 (0.20 to 1.90)	–45 (–18 to 90)	20 42 53 54 88
Children								
0.20 mg kg^{-1} i.v.	1	2.0	4.0	1/50	2/50	0.50 (0.05 to 5.34)	–50 (–12 to 21)	41
0.25 mg kg^{-1} i.v.	1	9.0	8.0	2/23	2/24	1.04 (0.16 to 6.80)	276 (6.1 to –6.4)	52
Combined	2	4.1	5.4	3/73	4/74	0.77 (0.18 to 3.27)	–77 (–12 to 18)	41 52
Adults and children	7	3.5	5.5	13/374	20/363	0.64 (0.33 to 1.24)	–49 (–20 to 104)	20 41 42 52–54 88

Early events (within 6 h) in children

The best documented regimen was 0.25 mg kg^{-1} i.v. (Table 2). This dose was tested in seven studies. The combined data suggested a statistically significant antiemetic effect with metoclopramide compared with placebo; the number needed-to-treat to prevent vomiting was 5.8, with 95% CI including 11. The other regimens were tested in one study only, and no further conclusions could be drawn. No dose–responsiveness could be established.

Late events (within 48 h) in children

Only a minority of studies in children reported late outcomes (Table 2). No definite conclusions could be drawn.

Sensitivity analysis

Some studies reported early incidences of nausea or vomiting with placebo of less than 20% or greater than the 60% boundary of the comparator control event rate ranges, respectively.[31 40 45–48 51 52 54 57 59 60 64 67 70 73 75 76 78 88 89]

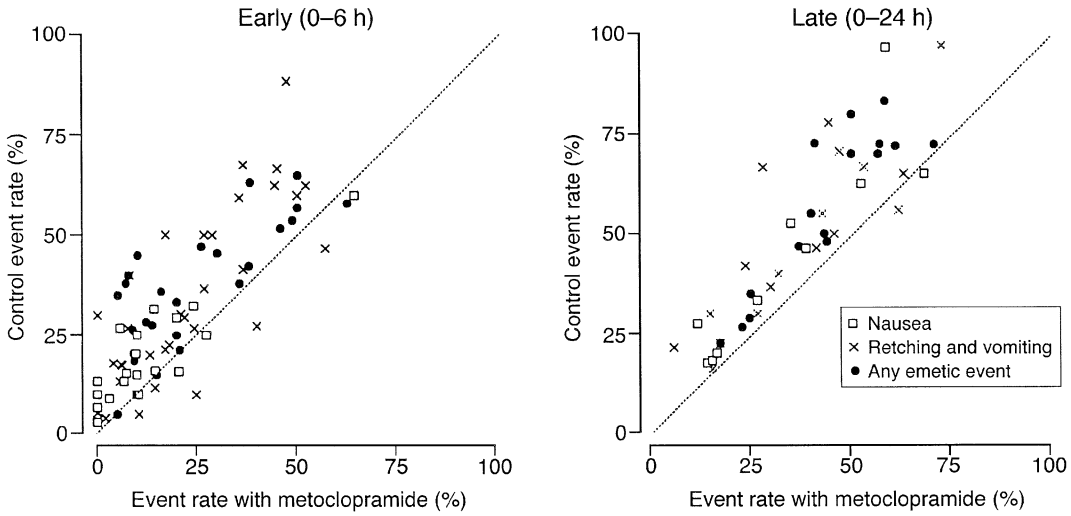

Fig 1 Early (0–6 h) and late (0–48 h) emetic event rates (incidence of nausea, vomiting or any emetic event) with metoclopramide (any dose and any route of administration, in children and adults) compared with control (placebo or no treatment). Symbols are comparisons of metoclopramide groups with control groups. Symbols do not take into account study size. One study may report 1–3 different emetic events (see key), both early and late. Broken lines indicate equality. A scatter lying predominantly between the line of equality and the control axis indicates consistent efficacy of metoclopramide compared with placebo or no treatment, and relative homogeneity of the data.

These studies were excluded from the sensitivity analysis for early outcomes.

Some studies reported late incidences of nausea or vomiting with placebo of less than the 40% or greater than the 80% boundary, respectively.[34–36 46 53 54 60 63 64 74 80 92] These studies were excluded from the sensitivity analysis for late outcomes.

Early events (within 6 h)

In adults, the 10 mg i.v. dose could be analysed within the restricted range of control event rates (Table 3). Numbers-needed-to-treat to prevent nausea or vomiting were 13 and 11, respectively. The anti-nausea effect was not significantly different from placebo. In children, the 0.25 mg kg^{-1} i.v. dose could be analysed. This dose was significantly more efficacious than placebo; the number-needed-to-treat to prevent vomiting was 7.9.

Late events (within 48 h)

There were enough relevant data for a sensitivity analysis with both the i.v. and oral 10 mg doses in adults (Table 3). The number-needed-to-treat to prevent vomiting was 7.1 with 10 mg i.v. Metoclopramide 10 mg orally was not significantly different from placebo. No relevant paediatric data were available.

Adverse effects

Extrapyramidal symptoms

The presence or absence of extrapyramidal symptoms (including abnormal movements) was described in eight studies in adults and in five studies in children (Table 4). In adults, one patient who had received metoclopramide 20 mg i.v. developed extrapyramidal symptoms.[75] In children, no extrapyramidal symptoms were reported. The number-needed-to-harm point estimate for extrapyramidal symptoms, including abnormal movements, with metoclopramide compared with placebo in 1177 adults or children was 556.

Sedation and drowsiness

Sedation or drowsiness was described in 14 studies in adults and in three studies in children (Table 4). In adults, 138 of 651 patients (21.2%) felt sedated or drowsy with metoclopramide 10–20 mg. With placebo, 113 of 580 patients (19.5%) felt drowsy or sedated. Of 273 children treated with metoclopramide 0.20 or 0.25 mg kg^{-1} or placebo, four (two with metoclopramide and placebo, respectively) were reported to feel sedated or drowsy. The number-needed-to-harm point estimate for sedation or drowsiness with metoclopramide compared with placebo in 1504 adults or children was 60.

Dizziness and vertigo

Dizziness or vertigo was described in adults only (Table 4). In eight studies, 26 of 455 adults treated with metoclopramide 10–30 mg reported dizziness or vertigo compared with 19 of 331 patients receiving placebo. The number-needed-to-harm point estimate for dizziness or vertigo with metoclopramide compared with placebo in 786 adults was –3862.

Headache

Postoperative headache was reported in 10 of 301 adults receiving metoclopramide 10 or 20 mg, and in three of 73 children receiving metoclopramide 0.20 or 0.25 mg kg^{-1} (Table 4). The respective values for placebo were 16 of 289 adults and four of 74 children. The number-needed-to-harm point estimate for postoperative headache with metoclopramide compared with placebo in 737 adults or children was –49.

There was no significant difference between metoclopramide and placebo for any of these adverse drug reactions (i.e. extrapyramidal symptoms, sedation and drowsiness, dizziness and vertigo, headaches). No dose–responsiveness was established.

Other adverse reactions

Other adverse reactions were described in one study only. Tachycardia,[88] weakness,[91] subcutaneous emphysema[79] and epistaxis[91] were more often reported in patients treated with metoclopramide compared with patients receiving placebo. In no study was there a statistically significant difference. Hypotension,[43] eye disturbances,[37] pruritus and itching,[37] delirium emergens,[88] dry mouth,[91] and taste or smell disturbances[91] were less often reported in patients treated with metoclopramide compared with those receiving placebo. Again, there were no significant differences.

Discussion

We searched the literature systematically for relevant and valid randomized, controlled studies, and analysed data on more than 6000 adults and children who were treated with metoclopramide or placebo in the surgical setting. In most studies, observation periods did not last longer than 6 h. In adults, best numbers-needed-to-treat to prevent PONV up to 6 h after surgery (i.e. short-term effect) were approximately 9, and to prevent PONV up to 48 h after surgery (i.e. long-term effect) approximately 10 (Table 1). In children, efficacy was slightly better; the number-needed-to-treat to prevent early vomiting was approximately 6 (Table 2). However, only five studies[35 49 50 64 65] investigated the long-term effect of metoclopramide in children. Because of the lack of valid data, no conclusions could be drawn on late efficacy in children. There was no evidence of dose–responsiveness for efficacy or harm with metoclopramide in adults or children. Thus these data provide strong evidence that metoclopramide in the doses described in these studies had no clinically relevant antiemetic effect in the prevention of PONV.

In adults, metoclopramide doses of 5–30 mg were used. In children, doses were 0.10–0.50 mg kg^{-1}. We have to assume that these doses represent daily clinical practice. Knowing that the doses of metoclopramide used in anaesthesia are not really antiemetic begs the question as to whether these doses are too low. There are two arguments in favour of this hypothesis. First, high-dose metoclopramide has been used successfully as an antiemetic in highly emetogenic chemotherapy (treatment with cisplatin, for instance).[7 8] However, doses of metoclopramide which are used commonly in chemotherapy are approximately 50 times higher compared with the PONV setting (2 mg kg^{-1} i.v. five times a day, corresponding to approximately 700 mg day^{-1} for a 70-kg patient).[7] Second, in these systematically searched studies, there was no evidence of an increased risk of adverse drug reactions with metoclopramide compared with placebo (Table 4). For example, extrapyramidal symptoms, the most serious adverse reaction of drugs acting at the dopamine receptor, are not likely to occur more often than in one in 550 patients treated with metoclopramide who would not have had any symptoms had they all received placebo. Sedation and drowsiness were more often reported in patients receiving metoclopramide, but the number-needed-to-harm point estimate (approximately 60) did not indicate that this would be clinically important. Other possible adverse effects occurred even less often with metoclopramide (headache, for instance), thus the drug could theoretically provide some protection. Interestingly, in the chemotherapy setting, there was no evidence of an increased risk of serious adverse reactions with increasing doses of high-dose metoclopramide.[8]

The question now is, is it worthwhile establishing a dose–response relationship for metoclopramide and identifying its optimal dose in the surgical setting? The optimal dose would be the minimal effective dose which has an acceptable level of adverse effects. Several arguments speak in favour of such a research agenda. For example, metoclopramide is a potentially interesting molecule for the control of PONV because of its triple antiemetic action. Metoclopramide acts on central dopaminergic receptors, on both central and peripheral 5-HT_3 receptors and on peripheral 5-HT_4 receptors. The affinity for the dopaminergic D_2 receptor explains partly the antiemetic effect of metoclopramide.[94] However, blocking this receptor type may provoke undesirable effects such as extrapyramidal symptoms. The effect of metoclopramide on the 5-HT_3 receptor seems to be dose-dependent.[8] The minimal dose of metoclopramide required to block this receptor in humans is unknown. The effect on the 5-HT_4 receptor may explain the prokinetic effect of metoclopramide on the motility of the gastrointestinal tract.[95] Thus theoretically metoclopramide provides three additive antiemetic actions.

Second, metoclopramide has been well known for almost 40 yr and is cheap. Newer antiemetics may be more efficacious[96] but they are also more expensive.

Third, recently, two new metoclopramide hydrochloride formulations, suitable for high dose (e.g. 1–2 mg kg^{-1}) i.v. or i.m. administration have been tested.[97–99] These formulations differ mainly in their pH, the acid form having a pH of 2.5–3.5, and the neutral form 6.5–7.0. Data from human[97 98] and animal[99] studies suggested that i.m., pH neutral metoclopramide may be 100% bioavailable, and that it may have less side effects compared with acidic metoclopramide, within the dose range 3.5–14 mg kg^{-1}. It seems that the pH neutral metoclopramide has a significantly decreased affinity for the D_2 receptor and an increased affinity for the 5-HT_3 receptor. Thus this new pH neutral metoclopramide may be useful for the control of PONV.

A final issue relates to the direct comparison of metoclopramide with newer antiemetics. In several studies, metoclopramide 10 mg was compared with ondansetron 4 mg or 8 mg. Often it was not clear if these studies were designed to show equivalence. Meta-analysis showed superiority of

ondansetron; the number-needed-to-treat to prevent PONV with ondansetron compared with metoclopramide was approximately 6.[96] Ondansetron 4 mg and 8 mg, however, have been shown to be antiemetic,[17] while this systematic review clearly shows that metoclopramide 10 mg is not. To use metoclopramide 10 mg as an active comparator to test the efficacy of newer antiemetics is inappropriate as metoclopramide at this dose cannot be regarded as a valid active comparator. Before a sensible comparison between two antiemetics can be made, the optimal doses of both drugs need to be established.

In summary, metoclopramide, although used as an antiemetic for almost 40 yr in the prevention of PONV, has no clinically relevant antiemetic effect and does not show an increased risk of adverse effects in the doses currently used in anaesthesia. It is very likely that the doses used in daily clinical practice are too low. The continued use of metoclopramide in the dose ranges tested in these studies is inadequate. Randomized, dose-finding studies which evaluate higher doses of metoclopramide are clearly needed to establish the optimal dose of metoclopramide for the prevention of PONV.

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