Systematic Review

Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting

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Purpose: To estimate the efficacy and harm produced by droperidol in the prevention of postoperative nausea and vomiting (PONV).

Methods: Systematic search (MEDLINE, EMBASE, Cochrane library, hand-searching, bibliographies, all languages, up to May 1999) for randomised comparisons of droperidol with placebo in surgical patients. Relevant end points were prevention of early PONV (up to six hours postoperatively), and late PONV (24 hr), and adverse effects. Combined data were analysed using relative risk and NNT.

Results: In 76 trials, 5,351 patients received 24 different regimens of droperidol. The average incidence of early and late PONV in controls was 34% and 51%, respectively. Droperidol was more efficacious than placebo in preventing PONV. In adults, the anti-nausea effect was short-lived, and there was no dose-responsiveness; with 0.25 to 0.30 mg the number-needed-to-treat (NNT) to prevent early nausea was 5. For both early and late anti-vomiting efficacy there was dose-responsiveness; best efficacy was with 1.5 mg to 2.5 mg (NNT, 7). In children, there was dose-responsiveness; best efficacy was with 75 $\mu\text{g}\cdot\text{kg}^{-1}$ (NNT to prevent early and late vomiting, 4). Two children had extrapyramidal symptoms with droperidol (NNT in children, 91; in any patient, 408). There was dose-responsiveness for sedation and drowsiness (with 2.5 mg the NNT was 7.8). Droperidol prevented postoperative headache (NNT, -25).

Conclusions: Droperidol is anti-emetic in the surgical setting. The effect on nausea is short-lived but more pronounced than the effect on vomiting. Sedation and drowsiness are dose-dependent, extrapyramidal symptoms are rare, and there is a protective effect against headache.

Objectif : Évaluer l'efficacité et les effets négatifs du dropéridol utilisé pour la prévention de nausées et de vomissements postopératoires (NVPO).

Méthode : Recherche documentaire systématique (MEDLINE, EMBASE, bibliothèque Cochrane, recherche manuelle, bibliographies, dans toutes les langues jusqu'à mai 1999) pour établir des comparaisons randomisées de dropéridol avec un placebo chez des patients de chirurgie. Les paramètres étudiés ont été la prévention des NVPO précoces (jusqu'à six heures après l'opération) et tardifs (24 h) et les effets indésirables. Les données combinées ont été analysées en utilisant le risque relatif et le nombre nécessaire au traitement (NNT).

Résultats : Pour 76 essais, 5 351 patients ont reçu 24 régimes différents de dropéridol. L'incidence moyenne de NVPO précoces et tardifs chez les témoins a été de 34 % et 51 %, respectivement. Le dropéridol a été plus efficace que le placebo pour prévenir les NVPO. Chez les adultes, l'effet anti-nausée a été de courte durée et il n'y a pas eu de réponse en fonction de la dose; avec 0,25 à 0,30 mg, le NNT pour prévenir les nausées précoces a été de 5. Pour prévenir efficacement les vomissements précoces et tardifs, il y avait une réponse dépendante de la dose; la plus efficace a été de 1,5 mg à 2,5 mg (NNT, 7). Chez les enfants, pas de réponse selon la dose; l'efficacité maximale a été notée avec 75 $\mu\text{g}\cdot\text{kg}^{-1}$ (NNT pour prévenir les vomissements précoces et tardifs, 4). Deux enfants ont présenté des symptômes pyramidaux avec le dropéridol (NNT chez les enfants, 91; chez tous les patients, 408). Il n'y avait pas de réponse selon la dose pour la somnolence (avec 2,5 mg, le NNT était de 7,8). Le dropéridol a empêché les céphalées postopératoires (NNT, -25).

Conclusion : Le dropéridol est antiémétique en chirurgie. L'effet sur les nausées est bref, mais plus prononcé que l'effet sur les vomissements. La sédation et la somnolence sont dose-dépendantes; les symptômes extrapyramidaux sont rares et il y a un effet protecteur contre les céphalées.

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DROPERIDOL is a butyrophenone. Butyrophenones produce central nervous system (CNS) depression, and they are potent anti-emetics.¹ Droperidol produces its action centrally at sites where dopamine, norepinephrine, and serotonin act. As a principal mechanism it has been suggested that droperidol may occupy GABA receptors at the postsynaptic membrane; this may reduce synaptic transmission and result in a build-up of dopamine in the intersynaptic cleft.¹ A subsequent imbalance in dopamine and acetylcholine is thought to occur, which results in an alteration of normal transmission of signals in the CNS, as, for instance, in the emetic centre in the chemoreceptor trigger zone. This is thought to be the mechanism by which droperidol exerts its anti-emetic effect.²

Droperidol was first reported to have anti-emetic efficacy in men in 1963.³ Since then, droperidol has been widely used as an anti-emetic in perioperative medicine. Textbooks suggested that 10 to 20 $\mu\text{g}\cdot\text{kg}^{-1}$ (0.6 to 1.2 mg for a 60 kg patient) may be the optimal dose for the prevention of postoperative nausea and vomiting (PONV).¹ Higher doses (2.5 to 5 mg intramuscularly or intravenously) have been proposed for the treatment of established PONV.⁴ However, the anti-emetic dose-responsiveness for droperidol efficacy has not been established for prevention of PONV or for the treatment of established PONV. More recently, the use of newer anti-emetic drugs such as 5-HT₃ receptor antagonists has been advocated for the control of PONV. A frequent argument in favour of the use of newer anti-emetic drugs is the apparent increased risk of major adverse reactions with the use of older anti-emetic drugs, such as droperidol. Indeed, as a drug which acts at dopamine receptors, droperidol has the potential of provoking extrapyramidal reactions.⁵

The aim of this quantitative review of systematically searched randomised controlled trials, was first, to estimate droperidol's anti-emetic efficacy compared with placebo in the prevention of PONV; second, to test the evidence of dose-responsiveness; third, to compare anti-nausea with anti-vomiting efficacy; and fourth, to investigate droperidol's potential risk for toxic effects in the surgical setting.

Methods

Systematic search

We did a systematic search for full reports of randomised controlled trials that tested the effect of prophylactic droperidol (experimental intervention) compared with placebo or "no treatment" (control intervention) on PONV after both general anesthesia or combined, spinal and general anesthesia. Relevant trials

had to report end points of interest in dichotomous form (i.e. presence or absence of the endpoint with both droperidol and control). We searched the MEDLINE (from 1966, last search May 1999), COCHRANE Library (issue 2, 1999), and EMBASE (from 1982, last search March 1999) databases without restriction to the English language, and using different search strategies with the free text key words «droperidol»; «nausea» or «vomiting» or «emesis»; «random»; and «surgery» or «anesthesia» or «anesthesia» or «post-operative». Additional trials were identified from reference lists of retrieved reports, and review articles on PONV and droperidol, and by manually searching locally available anesthesia journals. Data from abstracts, letters, review articles, and animal studies were not considered. We did not analyse efficacy data of droperidol as a treatment of established PONV. We did not consider data from active comparisons (i.e. trials without a placebo or "no treatment" arm).⁶

Critical appraisal

Independently, authors read each report that met the inclusion criteria, and scored them for inclusion and methodological validity using the three-item, five-point, Oxford-scale.⁷ The minimum score of an included randomised controlled trial was one, the maximum score was 5. Consensus was reached by discussion.

Data extraction

We took information about patients, surgery, dose, and route of administration of droperidol, study end points, and adverse effects from each included report. We extracted the cumulative incidence of PONV within six hours after surgery and within 24 hr. Incidences of PONV during the two time periods (0 to 6 hr, and 0 to 24 hr) were used as indicators of "early" (short-term) and "late" (long-term) anti-emetic efficacy, respectively. Thus, data of the "early" period may be included in the (cumulative) "late" period. A true "delayed" period (for instance, 6-24 hr) could not be analysed, since the original trials did not report data on such a period. When multiple doses of droperidol were given (for instance, a first dose at induction and a subsequent dose 12 hr after surgery), we considered the first dose (in this case the dose given at induction) for estimation of early efficacy, and the cumulative dose (in this case the sum of both doses) for late efficacy. When several events were reported at different times, we analysed the cumulative values nearest to the sixth and twenty-fourth post-operative hours. Two different PONV events, both early and late, were extracted in dichotomous form: nausea, and vomiting (including retching). These events were treated separately. We did not take into

account nausea scores, number of, or time to first vomiting episodes, number of patients needing anti-emetic rescue medication, delay until discharge, post hoc analyses, stratified data analyses (by sex, for instance), or scores of patient satisfaction, because these endpoints were inconsistently reported.

Qualitative analysis

We used the scatter of event rates (incidence of PONV) with droperidol (i.e. experimental event rate) against event rates with control (i.e. control event rate) as a graphical means to explore consistency of droperidol's efficacy and homogeneity of the data.⁸ On such plots, a scatter lying predominantly between the line of equality and the axis of the control intervention would suggest consistent efficacy with droperidol and relative homogeneity.

Quantitative analysis

We defined anti-emetic efficacy as prevention of a PONV event with droperidol or control. We combined data only when they represented clinically homogenous subgroups (i.e., the same PONV event, the same observation period, the same dose and route of administration of droperidol, and only adults or only children).

We used both relative benefit and number-needed-to-treat as estimates of antiemetic efficacy and harm. As an estimate of the statistical significance of a difference between droperidol and control we calculated relative risks with 95% confidence intervals (CI).⁹ For combined data, a fixed effect model that considers within-study variation¹⁰ was used when data from no more than two trials were combined or when there was no significant heterogeneity (i.e., $P > 0.1$). In all other situations, we used a random effects model.¹¹ If any cell of a sample was zero, then 0.5 was added to all cells of that sample to calculate the relative risk.¹² When the 95%CI around the relative risk did not include 1, we assumed a statistically significant difference between droperidol and control. As an estimate of the clinical relevance of a treatment effect we calculated the number-needed-to-treat (NNT)¹³ using the weighted means of the pooled experimental and control event rates.¹⁴ A positive NNT indicated how many patients had to be exposed to droperidol for one patient to show a particular endpoint (for instance, not to vomit), who would not have shown this endpoint (for instance, who would have vomited) had they all received a placebo. We made a pre-hoc decision that a NNT of 5 or less to prevent PONV compared with placebo would represent a clinically relevant degree of efficacy in this clinical setting.¹⁵ A negative NNT suggested that the

endpoint happened more often with placebo compared with droperidol. A 95%CI around the NNT point estimate was obtained by taking the reciprocals of the values defining the 95%CI for the absolute risk reduction.¹⁶ In tables the actual upper and lower limits of the 95%CI around the NNT, independent if they were positive or negative, are reported. The 95%CI will contain exclusively positive numbers if the difference between droperidol and control is statistically significant (i.e. $P < 0.05$) in favour of droperidol; it will contain exclusively negative values if this difference is statistically significant in favour of control. 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 infinity).

Dose-responsiveness

There was an attempt to test the evidence for dose-responsiveness using pre-set criteria.¹⁷ A statistically significant difference between two doses would be assumed when the 95%CI of the corresponding NNTs did not overlap; this was then interpreted as strong evidence of a dose-response. An increase in efficacy of at least 20% (i.e., a decrease of the NNT of 5 to 4, for instance) was considered as a clinically relevant improvement, and, therefore, would justify an increase in the dose, even when 95%CIs overlapped.

Sensitivity analysis

We calculated relative risk and NNT for nausea and vomiting outcomes separately for the best-documented regimens within two predefined ranges of control event rates: early outcomes within 20% to 60% of control event rate, and late outcomes within 40% to 80% of control event rate.¹⁸ Data outside these ranges were excluded from the sensitivity analysis. Thus, we could estimate droperidol's relative efficacy compared with other anti-emetic interventions without the need for direct comparisons.

Results

Included and excluded trials

We considered 93 trials for analysis, but subsequently excluded 19. Of these, four^{19–22} were inappropriately randomised; in five trials^{23–27} the number of patients per group was not indicated; in three, several doses of droperidol were given both as a prophylaxis of PONV and as a treatment of established PONV;^{28–30} in three, data of adults and children were pooled and could not be separated;^{31–33} two were duplicate reports of previously published full reports;^{34,35} one studied the effect of the hormonal cycle on PONV;³⁶ and in one, six patients only were analysed per group.³⁷

FIGURE 1 Early (0-6 hr) and late (0-24 hr) emetic event rates (incidence of nausea and vomiting) with droperidol (any dose and any route of administration, in children and adults) compared with control (placebo or no treatment). Symbols are comparisons between droperidol arms and control arms. Symbols do not take into account trial size. One trial may report one or two different emetic events (see key), both "early" and "late". Dotted lines indicate equality. A scatter lying predominantly between the line of equality and the control axis indicates consistent efficacy with droperidol compared with placebo or no treatment, and relative homogeneity of the data set.

We analysed data from 74 randomised controlled trials, published in 74 reports.³⁸⁻¹¹¹ There were data on 13,352 patients, of whom 5,351 (43%) received droperidol, 3,372 received a placebo or "no treatment", and 4,629 received another anti-emetic intervention. A "no treatment" control was used in fourteen trials,^{59,63,65,66,73,75,76,80,83,98,108-111} all others used placebos. Data from "no treatment" groups were regarded as placebos.¹¹² The median number of patients per trial was 165 (range, 40 to 2,061). The median validity score was 3 (range, 1 to 5). Twenty-four different droperidol regimens were tested: oral, intramuscular and intravenous routes; fixed doses (full milligram) and variable doses (micrograms per kilogram); single, and double administrations per 24 hr. Forty-seven trials were in adults, twenty-nine of them in women only. Twenty-nine trials were done in children.

Qualitative analysis

The event rate scatter for both early and late outcomes suggested improved efficacy with droperidol compared with placebo (Figure 1). The average incidence of early nausea with droperidol and placebo was 16% (range, 3% to 41%) and 33% (range, 15% to 80%), respectively. The average incidence of early vomiting with droperidol and placebo was 14% (range, 0% to 56%) and 29% (range, 6% to 86%), respectively. The average incidence of late

FIGURE 2 Antiemetic efficacy of droperidol in placebo-controlled trials. Intravenous doses in adults. Early outcomes (0-6 hr postoperatively) and late outcomes (0-24 hr postoperatively). Nausea = white squares, vomiting (including retching) = dark circles. Symbol sizes are proportional to the number of analysed data. Vertical lines are 95% confidence intervals.

FIGURE 3 Antiemetic efficacy of droperidol in placebo-controlled trials. Intravenous doses in children. Early outcomes (0-6 hr postoperatively) and late outcomes (0-24 hr postoperatively). Only vomiting outcomes are shown. Symbol sizes are proportional to the number of analysed data. Vertical lines are 95% confidence intervals.

nausea with droperidol and placebo was 45% (range, 1% to 86%) and 58% (range, 11% to 96%), respectively. The average incidence of late vomiting with droperidol was 28% (range, 4% to 83%) and 46% (range, 12% to 97%), respectively.

Quantitative analysis

Nine different fixed doses (0.25 mg, 0.5 mg, 0.625 mg, 0.75 mg, 1 mg, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg) and nine variable doses (5, 10, 14, 15, 20, 25, 40, 50, or 90 $\mu\text{g}\cdot\text{kg}^{-1}$), orally or intravenously, were test-

ed in adults. We extrapolated variable doses in adults to fixed doses assuming an average bodyweight of 60 kg. In children, only variable doses (5, 10, 20, 40, 50, 75, 200, or 300 $\mu\text{g}\cdot\text{kg}^{-1}$), orally or intravenously, were given. Most pediatric trials analysed prevention of vomiting only. Because of the variety of different regimens, we combined doses to arbitrarily defined subgroups of dose ranges for both adults and children.

EARLY EVENTS (0-6 HR) IN ADULTS

All outcomes indicated an improvement with droperidol compared with placebo, except for prevention of vomiting with 0.5 mg to 0.75 mg *iv* in 88 treated patients, and for prevention of both nausea and vomiting with 2.5 mg *im* in 50 treated patients (Table Ia). There was no evidence of dose-responsiveness for early anti-nausea efficacy with intravenous doses (Table Ia, Figure 2); 95% CIs overlapped and NNT point estimates did not improve with increasing doses. For the lowest dose range tested, 0.25 mg to 0.30 mg, the NNT to prevent nausea was about 5, and higher doses did not further increase this efficacy (Table Ia). There was, however, some weak evidence of dose-responsiveness for early anti-vomiting efficacy with intravenous doses (Table Ia, Figure 2). For the two lowest dose ranges tested, 0.25 to 0.3 mg, and 0.5 to 0.75 mg, the NNT to prevent early vomiting was about 10; for the most frequently reported dose ranges, 1 mg to 1.25 mg, and 1.5 to 2.5 mg, the NNT improved (i.e. decreased) to about 7 (Table Ia). All confidence intervals overlapped; however, the NNT point estimates improved by 45%.

There was, in a limited number of patients, some evidence of dose-responsiveness for *im* doses (Table Ia). For 2.5 mg, NNTs to prevent early nausea and vomiting were very high or did not indicate any statistical significance; for 5 mg, NNTs improved to about 7. For all doses and routes of administration, droperidol's anti-nausea effect was more pronounced (i.e. NNTs were lower) than its anti-vomiting effect (Table Ia, Figure 2).

LATE EVENTS (0-24 HR) IN ADULTS

All outcomes indicated an improvement with droperidol compared with placebo, except for prevention of late nausea and vomiting with 5.4 mg (= 90 $\mu\text{g}\cdot\text{kg}^{-1}$) droperidol given orally in 30 patients, and for prevention of late vomiting with 3-5 mg *im* in 66 patients (Table Ib). For anti-nausea efficacy there was some evidence of dose-responsiveness with the two best documented dose ranges: 0.5 to 0.75 mg had a NNT of 11 to prevent late nausea in more than 550 patients, and 1 to 1.25 mg had a NNT of about 7 in more than 1,000 patients; 95% CIs overlapped (Table Ib, Figure 2). For

anti-vomiting efficacy, interpretation was more difficult because of the variability in the average control event rates. The lowest dose range tested, 0.5 to 0.75 mg, seemed to provide best efficacy (NNT 3.4). The average control event rate was 52%. Higher doses did not achieve the same degree of efficacy; NNTs with doses as high as 5 mg were no better than about 7 (Table Ib). The average control event rate, however, was only 27%. Intramuscular and oral doses were poorly documented.

EARLY EVENTS (0-6 HR) IN CHILDREN

All outcomes showed an improvement with droperidol compared with placebo. There was some evidence of dose-responsiveness for early anti-vomiting efficacy with *iv* doses (Table Ic, Figure 3). For the lowest dose range tested, 10-20 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT to prevent early vomiting was 7.8. For 40-50 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT decreased to 6.6 (with a CI including 307). For the most frequently tested dose, 75 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT further decreased to 4.2. Although confidence intervals overlapped, the NNT point estimates improved by 86%. Intramuscular and oral regimens were poorly documented.

LATE EVENTS (0-24 HR) IN CHILDREN

All outcomes showed a statistically significant improvement with droperidol compared with placebo. There was evidence of dose-responsiveness for late anti-vomiting efficacy with *iv* doses (Table Id, Figure 3). For the lowest dose-range, 5-20 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT to prevent late vomiting was 7.3. For 50 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT decreased to 4.4. For the most frequently used dose, 75 $\mu\text{g}\cdot\text{kg}^{-1}$, the NNT further decreased to 3.8. Confidence intervals overlapped; however, NNT point estimates improved by 92%.

Sensitivity analyses

CONTROL EVENT RATE BANDING

Some trials reported early incidences of nausea or vomiting with placebo below the 20% or above the 60% boundary of the comparator control event-rate ranges.^{40,46,50,53,54,59,61,83,84,88,96,98,105,107,109} Some trials reported late incidences of nausea or vomiting with placebo below the 40% or above the 80% boundary, respectively.^{38,39,42,70,78,91,93} Data from these trials were excluded from the sensitivity analysis with truncated control event rates (Table IIa). In both adults and children, results on dose-responsiveness were maintained despite restriction of the analysed data to a pre-defined range of control event rates.

TIME OF ADMINISTRATION

There was an intention to test the impact of the time point of administration of droperidol on its anti-emetic efficacy. This was done with the largest subgroup of

TABLE I Prophylactic antiemetic efficacy of droperidol in placebo-controlled randomised trials: efficacy data in adults and children.

Event	Trials		Event rates		Number without event/total number		Relative Risk	P	Number-needed-to-treat	References
	No	Drop	Plac	Drop	Plac	95% CI				
Ia. Early events (0-6 hr) in adults										
0.25-0.30 mg iv										
nausea	3	17%	36%	91/109	74/115	1.30 (1.11 to 1.52)	0.46	5.2 (3.3 to 12.6)	86;90;92	
vomiting	2	7%	17%	83/89	79/95	1.13 (1.01 to 1.25)	n/a	9.9 (5.2 to 106)	86;90	
0.5-0.75 mg iv										
nausea	3	25%	46%	81/108	59/109	1.39(1.14 to 1.70)	0.61	4.8 (3.0 to 12)	86;92;104	
vomiting	2	16%	26%	74/88	66/89	1.13 (0.97 to 1.32)	n/a	10 (4.6 to -51)	86;104	
1-1.25 mg iv										
nausea	9	15%	31%	383/450	213/317	1.21 (1.12 to 1.31)	0.99	6.1 (4.5 to 9.4)	43;55;64;72;89;90;92;104;107	
vomiting	1 2	7%	20%	557/596	371/462	1.14 (1.04 to 1.26)	0.04	7.6 (5.8 to 11)	43;52;55;64;72;89;90;94;104;105;107;111	
1.5-2.5 mg iv										
nausea	4	16%	33%	124/147	101/150	1.25 (1.10 to 1.43)	0.16	5.9 (3.8 to 13)	66;67;81;99	
vomiting	6	13%	28%	227/261	190/262	1.20 (1.10 to 1.31)	0.89	6.9 (4.7 to 13)	52;66;67;82;91;99	
2.5 mg im										
nausea	1	20%	24%	40/50	38/50	1.05 (0.85 to 1.30)	n/a	25 (4.9 to -8.2)	8 5	
vomiting	1	16%	12%	42/50	44/50	0.95 (0.81 to 1.12)	n/a	-25 (-6 to 10)	8 5	
5 mg im										
nausea	1	3%	19%	68/70	57/70	1.19 (1.06 to 1.34)	n/a	6.4 (3.9 to 17)	10 6	
vomiting	2	6%	19%	118/125	99/122	1.16 (1.06 to 1.28)	n/a	7.5 (4.7 to 19)	98;106	
Ib. Late events (0-24 hr) in adults										
0.5-0.75 mg iv										
nausea	3	68%	77%	180/554	129/555	1.39 (1.14 to 1.69)	0.09	11 (6.9 to 25)	49;87;104	
vomiting	3	23%	52%	85/110	61/127	1.60 (1.31 to 1.96)	0.40	3.4 (2.4 to 5.7)	48;87;104	
1-1.25 mg iv										
nausea	1 3	47%	62%	551/1048	343/905	1.41 (1.28 to 1.55)	0.69	6.8 (5.2 to 9.7)	40;49;53;55;58;64;72;83;89;94;104;107	
vomiting	1 2	26%	38%	444/596	286/459	1.17 (1.04 to 1.32)	0.08	8.2 (5.6 to 15)	40;53;55;58;64;72;89;94;100;104;107	
1.5-2.5 mg iv										
nausea	3	16%	33%	146/173	117/174	1.24 (1.11 to 1.39)	0.61	5.8 (3.8 to 12)	67;87;88	
vomiting	4	48%	62%	101/193	82/214	1.43 (1.20 to 1.71)	0.18	7.1 (4.2 to 23)	48;67;87;91	
3.75-5 mg iv										
nausea	3	6%	15%	182/193	207/244	1.12 (0.97 to 1.29)	0.85	11 (6.7 to 26)	88;99;109	
vomiting	3	12%	27%	101/115	144/197	1.20 (1.01 to 1.43)	0.52	6.8 (4.3 to 16)	48;99;109	
3-5 mg im										
nausea	2	9%	29%	107/118	75/105	1.55 (1.15 to 2.09)	n/a	5.1 (3.4 to 11)	98;109	
vomiting	1	8%	13%	61/66	48/55	1.06 (0.94 to 1.20)	n/a	19 (6.2 to -18)	10 9	
5.4 mg po										
nausea	1	27%	29%	22/30	20/28	1.03 (0.75 to 1.41)	n/a	53 (4.0 to -4.7)	5 9	
vomiting	1	13%	18%	26/30	23/28	1.06 (0.84 to 1.32)	n/a	22 (4.3 to -7.1)	5 9	
IC. Early events (0-6 hr) in children										
10-20 µg·kg ⁻¹ iv										
vomiting	3	14%	27%	172/200	134/172	1.17 (1.06 to 1.29)	0.76	7.8 (4.8 to 21)	41;80;96	
40-50 µg·kg ⁻¹ iv										
vomiting	3	27%	42%	55/75	46/79	1.34 (1.09 to 1.64)	0.74	6.5 (4.0 to 18)	38;42;61	
75 µg·kg ⁻¹ iv										
vomiting	1 1	25%	49%	273/365	195/382	1.47 (1.20 to 1.82)	0.06	4.2 (3.3 to 5.9)	39;41;46;57;69;70;75;76;78;103;110	
50 µg·kg ⁻¹ im										
vomiting	1	4%	18%	47/49	42/51	1.16 (1.01 to 1.34)	n/a	7.4 (3.9 to 58)	8 4	
200 µg·kg ⁻¹ im										
vomiting	1	8%	22%	101/110	84/108	1.18 (1.05 to 1.32)	n/a	7.1 (4.3 to 21)	4 5	
200 µg·kg ⁻¹ po										
vomiting	1	31%	49%	48/70	37/73	1.44 (1.13 to 1.85)	n/a	5.6 (3.0 to 48)	10 8	
ID. Late events (0-24 hr) in children										
5-20 µg·kg ⁻¹ iv										
vomiting	2	25%	39%	168/225	125/205	1.22 (1.07 to 1.39)	n/a	7.3 (4.5 to 20)	80;101	
50 µg·kg ⁻¹ iv										
vomiting	2	37%	59%	38/60	28/69	1.51 (1.09 to 2.11)	n/a	4.4 (2.5 to 17)	56;61	
75 µg·kg ⁻¹ iv										
vomiting	1 0	34%	60%	217/326	126/315	1.55(1.17 to 2.06)	<0.05	3.8 (2.8 to 5.2)	46;69-71;73;75;76;95;103;110	
300 µg·kg ⁻¹ po										
vomiting	1	27%	56%	30/41	15/34	1.66 (1.09 to 2.53)	n/a	3.4 (2.0 to 13)	7 4	

In adults, variable doses (µg·kg⁻¹) were extrapolated to fixed doses (mg) assuming an average body weight of 60 kg.

Event rates are incidences of nausea and vomiting respectively. *P* = heterogeneity.

TABLE II Prophylactic antiemetic efficacy of droperidol in placebo-controlled randomised trials: subgroup analyses in adults and children

<i>Event</i>	<i>Trials</i>	<i>Event rates</i>		<i>Number without event/total number</i>		<i>Relative Risk</i>	<i>P</i>	<i>Number-needed-to-treat</i>	<i>References</i>
	<i>No</i>	<i>Drop</i>	<i>Plac</i>	<i>Drop</i>	<i>Plac</i>	<i>95% CI</i>		<i>95% CI</i>	
IIa. CONTROL EVENT RATE BANDING									
Early events (0-6 hr) with CER 20-60% in adults									
<i>0.5-0.75 mg iv</i>									
nausea	2	19%	36%	54/67	44/69	1.26 (1.02 to 1.56)	0.40	5.9 (3.2 to 49)	86;92
vomiting	2	16%	26%	74/88	66/89	1.13 (0.97 to 1.32)	0.67	10 (4.6 to -51)	86;104
<i>1-1.25 mg iv</i>									
nausea	5	15%	34%	280/331	130/197	1.22 (1.09 to 1.36)	0.90	5.4 (3.8 to 9.2)	43;72;89;90;92
vomiting	6	14%	33%	166/193	130/193	1.27 (1.14 to 1.42)	0.37	5.4 (3.7 to 9.6)	43;52;55;94;104;111
<i>1.5-2.5 mg iv</i>									
nausea	4	16%	33%	124/147	101/150	1.25 (1.10 to 1.43)	<0.05	5.9 (3.8 to 13)	66;67;81;99
vomiting	4	17%	34%	144/173	114/171	1.25 (1.11 to 1.41)	<0.05	6.0 (3.9 to 13)	52;66;91;99
Early events (0-6 hr) with CER 20-60% in children									
<i>10-20 µg·kg⁻¹ iv</i>									
vomiting	3	14%	27%	172/200	134/172	1.17 (1.06 to 1.29)	0.76	7.8 (4.8 to 21)	41;80;96
<i>40-50 µg·kg⁻¹ iv</i>									
vomiting	3	27%	42%	55/75	46/79	1.34 (1.09 to 1.64)	0.74	6.6 (3.3 to 307)	51;62;79
<i>75 µg·kg⁻¹ iv</i>									
vomiting	7	26%	44%	190/256	147/262	1.32 (1.17 to 1.50)	0.39	5.5 (3.8 to 9.9)	41;57;69;75;76;103;110
Late events (0-24 hr) with CER 40-80% in adults									
<i>0.5-0.75 mg iv</i>									
nausea	3	68%	77%	180/554	129/555	1.68 (1.18 to 2.38)	0.09	11 (6.9 to 25)	49;87;104
vomiting	2	27%	62%	53/73	34/89	1.95 (1.45 to 2.62)	n/a	2.9 (2.1 to 5.0)	48;104
<i>1-1.25 mg iv</i>									
nausea	6	54%	73%	391/842	189/696	1.67 (1.45 to 1.93)	0.80	5.2 (4.2 to 6.9)	49;64;72;87;89;104
vomiting	6	29%	50%	277/389	125/248	1.37 (1.13 to 1.67)	0.08	4.8 (3.5 to 7.6)	58;64;72;94;100;104
Late events (0-24 hr) with CER 40-80% in children									
<i>5-20 µg·kg⁻¹ iv</i>									
vomiting	1	26%	44%	74/100	56/100	1.32 (1.07 to 1.63)	n/a	5.6 (3.2 to 20)	80;101
<i>50 µg·kg⁻¹ iv</i>									
vomiting	2	37%	59%	38/60	28/69	1.51 (1.09 to 2.11)	n/a	4.4 (2.5 to 17)	56;61
<i>75 µg·kg⁻¹ iv</i>									
vomiting	7	29%	51%	159/225	101/207	1.42 (1.21 to 1.68)	0.487	4.6 (3.2 to 7.8)	69;73;75;76;95;103;110
IIb. TIME OF ADMINISTRATION									
Children: 75 µg·kg ⁻¹ <i>i v</i> prevention of early vomiting									
<i>At induction</i>									
vomiting	8	25%	43%	219/290	171/302	1.34 (1.20 to 1.51)	<0.05	5.3 (3.8 to 8.7)	41;46;57;69;76;78;103;110
<i>Intra- or postoperatively</i>									
vomiting	3	28%	70%	45/75	24/80	2.34 (1.64 to 3.34)	<0.05	2.4 (1.8 to 3.6)	39;70;75
Children: 75 µg·kg ⁻¹ <i>i v</i> prevention of late vomiting									
<i>At induction</i>									
vomiting	8	30%	55%	177/251	117/261	1.49 (1.14 to 1.95)	<0.05	3.9 (3.0 to 5.7)	46;69;71;73;76;95;103;110
<i>Intra- or postoperatively</i>									
vomiting	3	47%	73%	40/75	20/74	1.93 (1.30 to 2.89)	0.1	3.8 (2.4 to 9.0)	39;73;75

In adults variable doses (µg·kg⁻¹) were extrapolated to fixed doses (mg) assuming an average body weight of 60 kg.

Event rates are incidences of nausea and vomiting respectively. CER = control event rate. P = heterogeneity.

Numbers of trials do not add up because in some trials more than one dose of droperidol was tested.

patients who received the same regimen of droperidol either at induction or later (for instance, at the end of surgery), with the same endpoint and the same observation period. This subgroup was in children receiving droperidol 75 µg·kg⁻¹ *iv*, with vomiting as the endpoint (Table IIb).

In eight trials, droperidol 75 µg·kg⁻¹ was given at induction. In those, the NNT to prevent early vomiting was 5.3. In three trials, 75 µg·kg⁻¹ droperidol was given either intraoperatively, or at the end of surgery, or postoperatively (in the recovery room). In those, the NNT to prevent early vomiting was 2.4.

Confidence intervals of the NNTs of the two subgroups did not overlap. The control event rate for the first subgroup was 43%, for the second was 70%, suggesting that droperidol's efficacy when given at the end of surgery may have been exaggerated. The relative risk, however, showed the same tendency as the NNT, although 95% CIs of the relative risk did not overlap. For late outcomes, no impact of the time of administration was apparent (Table IIb).

Adverse drug reactions

EXTRAPYRAMIDAL SYMPTOMS, RESTLESSNESS, AND ABNORMAL MOVEMENTS

Presence or absence of extrapyramidal symptoms was described in 12 trials with a total of 815 treated adults and children (Table IIIa). In two children⁶⁹ who had received 75 µg·kg⁻¹ droperidol, extrapyramidal symptoms were reported; the NNT point estimate for extrapyramidal symptoms in children alone was 91. When the data of adults and children of all 12 trials were combined, the NNT point estimate was 408. Restlessness or abnormal movements were reported in 7% of adults treated with droperidol, and in 5% of controls (Table IIIa). When all neurological outcomes (i.e. extrapyramidal symptoms, restlessness, abnormal movements) were combined, the NNT point estimate was 88. None of these results was statistically significant.

SEDATION AND DROWSINESS

Postoperative sedation and drowsiness were reported in 15 trials in adults (Table IIIb), and in one trial in children,³⁹ with a total of 2,098 patients. In adults, there was some evidence of dose-responsiveness. With the lowest range of doses, 0.25-0.625 mg, there was no increased risk of sedation or drowsiness with droperidol compared with placebo. With increasing doses, the NNT decreased (i.e. the additional risk of sedation or drowsiness increased); all differences between droperidol and controls were statistically significant. With 5 mg droperidol *iv*, the NNT was 7; 95% CIs overlapped.

HEADACHE

Postoperative headache was reported in 151 of 1,057 (14%) adults receiving droperidol, and in 167 of 913 controls (18%) (Table IIIc). The NNT for postoperative headache with droperidol compared with placebo was -25. This difference in favour of droperidol was statistically significant. Droperidol doses ranged between 0.25 mg and 5.4 mg (90 µg·kg⁻¹); there was a lack of evidence for dose-responsiveness.

DIZZINESS AND VERTIGO

In eight trials, 115 of 910 (13%) adults treated with droperidol, 0.25 mg to 1.25 mg, reported dizziness and vertigo compared with 92 of 771 (12%) controls (Table IIId). The NNT for dizziness and vertigo with

TABLE III Adverse drug reactions with droperidol in adults and children

<i>Endpoint</i>	<i>Trials</i>	<i>Event rates</i>		<i>Number with endpoint/total number</i>		<i>Relative Risk</i>	<i>Number-needed-to-harm</i>		<i>References</i>
	<i>No</i>	<i>Drop</i>	<i>Placebo</i>	<i>Drop</i>	<i>Placebo</i>	<i>95% CI</i>	<i>95% CI</i>	<i>ADR</i>	
Extrapyramidal symptoms, restlessness and abnormal movements									
<i>Extrapyramidal symptoms</i>									
adults and children, any dose	12	0.2%	0.0%	2/815	0/663	1.16 (0.00 to >100)	408 (171 to -1061)		38;47;52;54;56;57;63;65;69;70;72;75;78
children only, any dose	5	1.0%	0.0%	2/182	0/184	1.80 (0.00 to >100)	91 (38 to -241)		57;69;70;75;78
<i>Restlessness or abnormal movements</i>									
adults, any dose	9	7%	5%	41/563	20/424	1.50 (0.89 to 2.54)	39 (18 to -263)		47;50;65;72;81;82;104;106;111
All	20	3%	2%	43/1326	20/952	1.31 (0.04 to 39.5)	88 (41 to -566)		
Sedation and drowsiness									
0.25-0.625 mg, <i>iv</i>	3	12%	14%	79/645	89/635	0.88 (0.66 to 1.16)	-57 (52 to -18)		49;77;90
1.25 mg, <i>iv</i>	7	17%	13%	143/846	106/829	1.35 (1.03 to 1.78)	24 (13 to 139)		47;49;52;77;90;100;105
2.5 mg, <i>iv</i>	5	40%	27%	108/272	79/293	1.46 (1.18 to 1.80)	7.8 (4.9 to 20)		52;77;81;82;88
5 mg, <i>iv</i>	1	25%	10%	24/97	10/96	2.38 (1.20 to 4.70)	7.0 (4.0 to 26)		88
2.4-5 mg, <i>im</i>	4	33%	29%	68/207	59/204	1.15 (0.92 to 1.44)	26 (7.8 to -20)		85;98;102;106
Headache									
adults, any dose	11	14%	18%	151/1057	167/913	0.71 (0.57 to 0.87)	-25 (-14 to -137)		49;52;54;55;59;72;90;91;97-99
Dizziness and vertigo									
adults, any dose	8	13%	12%	115/910	92/771	0.71 (0.33 to 1.52)	142 (26 to -41)		49;52;54;55;72;90;97;100

Numbers of trials do not add up, because some trials reported more than one adverse drug reaction, and because in some trials more than one dose of droperidol was investigated.

droperidol was 142 compared with placebo; a result, which was not statistically significant.

OTHER ADVERSE REACTIONS

Other adverse reactions, possibly related to droperidol, were anxiety,^{49,50,100} hypotension,^{49,65,106} visual disturbances,^{72,91,105} nightmares,^{72,84} oculogyric crisis,¹⁰⁸ and urinary retention.^{97,99} For none of these reactions was there a statistically significant difference between droperidol and placebo.

Discussion

Droperidol has been used as an anti-emetic in perioperative medicine for almost 40 yr. Extensive clinical experience with a drug is no guarantor for that drug to be clinically really useful. Metoclopramide, for instance, despite having been used extensively in anesthetic practice, is not anti-emetic in the recommended doses in the perioperative period.¹¹³

This systematic review suggests strongly that droperidol, contrary to metoclopramide, is indeed anti-emetic compared with placebo in the surgical setting. It has to be stressed though, that these trials represent clinical settings with a moderate to high risk of PONV. The incidence of early PONV in placebo patients was on average 34%, and of late PONV was about 50%. Even higher control event rates have been reported in ondansetron trials.¹⁷ Because of these differences in the average of control event rates (and thus in the underlying risk) we performed a sensitivity analysis with truncated data¹⁸ (Table IIa) to enable indirect comparisons of droperidol with other anti-emetic interventions.

The meta-analytical approach enabled us to test the evidence for dose-responsiveness over a wide range of doses in both adults and children, and to compare relative anti-nausea and anti-vomiting efficacy. The major methodological problem was the important variability in control event rates among trials (Figure 1). This variability may be a reflection of different underlying risks. Again, the sensitivity analysis with truncated data was used to circumvent the variability. Results on dose-responsiveness were unchanged whether data were analysed across all trials or within the restricted range of control event rates.

In adults, there were three main results. First, there was dose-responsiveness for the anti-vomiting but not the anti-nausea effect of droperidol. With the lowest range of doses tested, 0.25-0.30 mg, about five patients need to be treated for one not to feel nauseated at short-term who would have felt nauseated had they all received a placebo (Table Ia). Increasing the dose did not improve the early anti-nausea efficacy of

droperidol. However, to maintain this degree of efficacy long-term, higher doses were needed (Table Ib). Thus, repeated boluses of low doses of droperidol (for instance, 0.5 mg *iv* 12-hourly) should be used to control postoperative nausea. This strategy has been advocated by others, and it has been shown to be cost-effective.¹⁰⁴ For anti-vomiting efficacy, the two lowest ranges of doses tested, 0.25-0.30 mg, and 0.5-0.75 mg *iv*, were clearly not efficacious. With increasing doses, droperidol's anti-vomiting efficacy improved considerably, although doses beyond 2.5 mg did not further increase efficacy (Table Ib).

Second, within the standardised restricted range of control event rates (Table IIa), 1-1.25 mg droperidol in adults achieved a degree of anti-vomiting efficacy which was similar to ondansetron 4 or 8 mg in adults, analysed within the same range of control event rates.¹⁷ This equivalence, based on data from indirect comparisons, has been confirmed in randomised trials of direct comparisons between droperidol and ondansetron.⁶

Third, the anti-nausea efficacy of droperidol was consistently superior to its anti-vomiting efficacy. This stands in contrast to ondansetron, where all regimens, *iv* or *po*, consistently achieved a better effect on vomiting than on nausea.¹⁷ Thus, it may be worthwhile to study more intensively the anti-emetic efficacy of drugs or drug combinations which block both dopamine and 5-HT₃ receptors. An optimal control of both nausea and vomiting may then be achieved. There is some evidence of an increased anti-emetic efficacy with a combination of droperidol and ondansetron in the surgical setting.^{114,115} Further research is needed to establish optimal doses of this combination. Metoclopramide, however, is a molecule, which acts at both dopamine and 5-HT₃ receptors, and which theoretically combines the anti-emetic properties of droperidol and ondansetron, did not show any clinically relevant anti-emetic efficacy in the surgical setting at the doses currently used (i.e. 10 mg).¹¹³ This may be because inadequate doses of metoclopramide are used in anesthetic practice.

In children, dose-responsiveness of the anti-vomiting efficacy of droperidol was suggested both graphically (Figure 3) and quantitatively (Tables Ic, Id). Analyses with data from all trials, independent of control event rates (Table I), and a sensitivity analysis within the restricted range of control event rates (Table II), suggested that 75 µg·kg⁻¹ *iv* is likely to be the most effective prophylactic dose. Numbers-needed-to-treat indicated that four to five children must be treated for one not to vomit at short- or at long-term who would have done so had they received placebo.

This degree of anti-emetic efficacy may be regarded as clinically relevant. However, it has to be stressed that this dose, extrapolated to an adult, is excessive; it corresponds to about 5 mg *iv*, a dose which has only rarely been tested in adults. The next lower dose tested in children, 50 $\mu\text{g}\cdot\text{kg}^{-1}$, showed less efficacy both in the short- and long-term, although this dose was tested in a limited number of patients only (Tables Ic, Id). The slightly decreased efficacy at 24 hr (NNT 4.4 with 50 $\mu\text{g}\cdot\text{kg}^{-1}$ vs NNT 3.8 with 75 $\mu\text{g}\cdot\text{kg}^{-1}$) may not be perceived as being clinically relevant. Taken together with the dose-dependency of droperidol-related sedation and drowsiness (Table IIb) one may consider 50 $\mu\text{g}\cdot\text{kg}^{-1}$ to be the best prophylactic dose in children, when sedation and drowsiness should be prevented, as for instance in day case surgery.

Droperidol and other, older anti-emetic drugs have been repeatedly discredited because of their apparent increased risk of potentially major adverse drug reactions. Systematic review suggested that there was no such risk with metoclopramide.¹¹³ For metoclopramide, however, doses used in perioperative medicine are likely to be too low. The situation with droperidol is different, because this drug is clearly anti-emetic in the doses used in clinical practice. Its anti-nausea effect, for instance, is likely to be the best currently available. Thus, it may be worthwhile to balance the estimates of the anti-emetic efficacy of droperidol against its estimates for harm. Extrapyramidal symptoms, a major adverse reaction of drugs acting at the dopamine receptor, were reported in two children receiving droperidol, but in no adults. In children alone, the additional risk for extrapyramidal symptoms was about 1 in 90 (Table IIIa). When all negative adult data were added, this risk decreased to about 1 in 400. This may indicate that children are more vulnerable to droperidol-related extrapyramidal symptoms. It may also suggest that extrapyramidal symptoms are dose-related, since both affected children had received 75 $\mu\text{g}\cdot\text{kg}^{-1}$. Such high doses were rarely used in adults. There was a lack of data to test dose-responsiveness; it can only be speculated that lower doses of droperidol would decrease the risk of extrapyramidal reactions. Visual disturbances, urinary retention, and oculogyric crisis have been described. The clinical relevance of these events and their relation to droperidol, however, is unclear.

It has been known for a long time that droperidol, as a CNS depressant, produces a drowsy and placid subject who tends to fall into a sleep from which he can be readily aroused.¹¹⁶ Indeed, droperidol increased the likelihood of sedation and drowsiness; an obvious dose-response could be described. With the lowest doses tested, 0.25 to 0.625 mg, there was no difference

between droperidol and placebo (Table IIb). With increasing doses, the likelihood of droperidol-related sedation or drowsiness increased consistently. With 1.25 mg the additional risk was one in 24, with 2.5 mg it was one in 8, and with 5 mg it was even one in 7. We do not know from these data how long sedation and drowsiness lasted, and what degree of sedation or drowsiness has to be expected with different doses of droperidol. However, two conclusions can be drawn. First, these data do not support the general view, that the anti-nausea efficacy of droperidol may simply be due to sedation, since the anti-nausea effect was not dose-dependent. Second, when sedation is not warranted (for instance, in day case surgery) minimal effective doses of droperidol should be used. This is another argument in favour of using repeated low doses of prophylactic droperidol rather than one large bolus dose.

There was strong evidence for a protective effect of droperidol against postoperative headache. This puts into question general statements on the increased risk of toxicity with droperidol. We do not know if there is a relationship between an increased risk of sedation and the anti-headache effect. The favourable effect on headache is yet another reason why droperidol should be combined with a 5-HT₃ receptor antagonist, since 5-HT₃ receptor antagonists increase the risk of headache.^{17,117}

There was some evidence that the timing of administration of prophylactic droperidol may have an impact on its early anti-emetic efficacy, but not thereafter (Table IIb). Trials on the impact of timing of the administration of ondansetron on the incidence of PONV came to contradictory results.^{118,119} From a pharmacokinetic point of view it seems to be reasonable to administer a prophylactic anti-emetic intervention shortly before the patient awakes and possibly needs the anti-emetic protection.

In conclusion, droperidol is anti-emetic in the surgical setting. The anti-nausea effect is not dose-dependent, is more pronounced than the anti-vomiting effect, and is short-lived. Sedation and drowsiness are dose-dependent, extrapyramidal symptoms are rare, and there is a protective effect against headache. We speculate that improved control of PONV may be achieved with the combination of droperidol with a 5-HT₃ receptor antagonist.

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