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2012

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How to cite

SCHAUB, Isabelle et al. Low-dose droperidol (≤ 1 mg or ≤ 15 $\mu\text{g kg}^{-1}$) for the prevention of postoperative nausea and vomiting in adults: quantitative systematic review of randomised controlled trials. In: European journal of anaesthesiology, 2012, vol. 29, n° 6, p. 286–294. doi: 10.1097/EJA.0b013e328352813f

This publication URL: <https://archive-ouverte.unige.ch/unige:31968>

Publication DOI: [10.1097/EJA.0b013e328352813f](https://doi.org/10.1097/EJA.0b013e328352813f)

Low-dose droperidol (≤ 1 mg or $\leq 15 \mu\text{g kg}^{-1}$) for the prevention of postoperative nausea and vomiting in adults: quantitative systematic review of randomised controlled trials

Isabelle Schaub, Christopher Lysakowski, Nadia Elia and Martin R. Tramèr

Context Droperidol is widely used for the prevention of postoperative nausea and vomiting (PONV) in European countries. It is unclear how efficacious low-dose droperidol is in the prevention of PONV.

Objectives To test the efficacy of low-dose droperidol in the prevention of PONV in adults and to test for dose-responsiveness.

Design Systematic review of randomised controlled trials with meta-analyses.

Data Sources Comprehensive search in electronic databases (*Medline, Embase, Central*) up to June 2011. Additional trials were obtained from bibliographies of retrieved reports. No language restriction was applied.

Eligibility Criteria Randomised trials testing prophylactic intravenous droperidol ≤ 1 mg or $\leq 15 \mu\text{g kg}^{-1}$ compared with placebo (or no treatment) in adults undergoing general anaesthesia and reporting on PONV.

Results We analysed 25 trials (2957 patients). Doses varied from 0.25 to 1.0 mg. For prevention of early nausea (within 6 h postoperatively), relative risk (RR) was 0.45 (95% CI, 0.35 to 0.58); number needed to treat (NNT) was 7, 4, and 2 for low,

medium and high baseline risk (i.e. control event rate 25, 50, 75%). For prevention of early vomiting, RR was 0.65 (95% CI, 0.57 to 0.74), NNT 11, 6, and 4. For prevention of late nausea (within 24 h), RR was 0.74 (95% CI, 0.62 to 0.87), NNT 15, 8, and 5. For prevention of late vomiting, RR was 0.61 (95% CI, 0.47 to 0.80), NNT 10, 5, and 3. Droperidol decreased the risk of headache but increased the risk of restlessness. For these outcomes there was no evidence of dose-responsiveness. There were no differences in the incidences of sedation or dizziness. Two patients receiving droperidol 0.625 mg had extrapyramidal symptoms. Cardiac toxicity data were not reported.

Conclusion Prophylactic doses of droperidol of 1 mg or below are antiemetic. Because adverse drug reactions are likely to be dose-dependent, there is an argument to stop using doses of more than 1 mg.

Eur J Anaesthesiol 2012; 29:286–294

Published online 9 April 2012

Keywords: droperidol, emesis, nausea, vomiting

Introduction

Droperidol has been one of the most popular antiemetic drugs in the surgical setting for several decades. However, in 2001, the US Food and Drug Administration (FDA) strengthened its cautions regarding the use of droperidol by issuing a 'black box' warning, the most serious warning for a FDA-approved drug (<http://www.fda.gov/safety/MedWatch/Safetyinformation/Safety>). The FDA noted that the use of droperidol had been associated with QT segment prolongation and/or torsades de pointes, and, in some cases, had resulted in fatal cardiac arrhythmia. However, the impact of antiemetic doses of droperidol on cardiac arrhythmia has remained contentious and the FDA decision has been challenged ever since. There is support for this approach from two clinical studies that failed to show any significant difference in QT length with intravenous droperidol 0.625 and 1.25 mg compared to placebo.^{1,2} In two other studies, the effect of droperidol 0.75 mg on QT prolongation was similar to ondansetron 4 mg,³ and the combination of droperidol 1 mg and ondansetron 4 mg did not further prolong QT.⁴

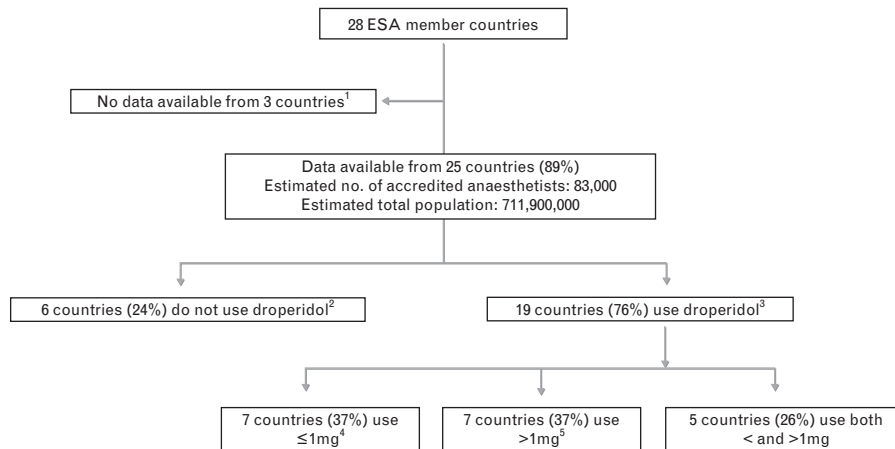
In 2007, despite the FDA warning, an international consensus panel still recommended intravenous droperidol 0.625 and 1.25 mg as a first-line antiemetic, alone or in combination with other antiemetic drugs, for the prevention of postoperative nausea and vomiting (PONV).⁵ These recommendations were based on data from a large multicentre study comparing these two doses⁶ and a meta-analysis of studies that mainly tested doses of 1.25 mg or above.⁷ Unfortunately, the 2007 consensus panel did not specify whether the lower of the two recommended doses (0.625 mg) was as efficacious as, or less efficacious than, the higher dose (1.25 mg), and it remained unclear whether doses below 0.625 mg had any worthwhile antiemetic efficacy.

We may assume that the cardiac risk of droperidol is dose-dependent and that, therefore, anaesthetists increasingly tend to use minimal effective doses. To better understand the importance of droperidol use for PONV prophylaxis in Europe today, we contacted all 28 Council members of the European Society of Anaesthesiology and asked them about the use of droperidol as an antiemetic in their country (Fig. 1). In 19 of 25 European countries, representing an estimated number of 83 000 anaesthetists and a population of over 711 million, droperidol is regularly used. In some countries (for instance, Spain, United Kingdom), droperidol was only recently reapproved after an intermediate withdrawal due to the

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Fig. 1



Use of droperidol in Europe in 2011. ¹Bulgaria, Israel, Latvia. ²Croatia, Ireland, Poland, Romania, Serbia, Turkey. ³Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Norway, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, The Netherlands, United Kingdom. ⁴Range 0.5–1 mg. ⁵Range 1.25–2.5 mg. ESA, European Society of Anaesthesiology.

FDA black box warning. Reported doses vary between 0.5 and 2.5 mg. However, in only seven of 19 countries (37%) are doses of droperidol of ≤ 1 mg commonly used.

In this systematic review of randomised controlled trials (RCT), we set out to test the efficacy of low-dose droperidol (arbitrarily defined as doses ≤ 1 mg) for the prevention of PONV in adults.

Methods

Systematic search

We performed a comprehensive search for published reports of RCTs testing intravenous single-dose regimens of droperidol for the prevention of PONV after general anaesthesia in adults. We searched in *Medline*, *Embase* and *Central* using different search strategies with combinations of the key words 'nausea', 'vomiting', 'emesis', 'droperidol', 'surgery', 'an(a)esthesia', 'postoperative' and the LIMIT 'Type of article: RCT'. The last electronic search was in June 2011. Additional trials were obtained from bibliographies of retrieved reports. There was no language restriction.

Inclusion and exclusion criteria

We considered full-published reports of placebo-controlled comparisons that tested intravenous single-dose droperidol regimens 1 mg or less or $15 \mu\text{g kg}^{-1}$ or less. Studies that were not published as full reports (for instance, abstracts or letters), review articles and animal studies, as well as trials without a placebo or 'no treatment' group, were excluded. Grey literature was not searched. We also excluded trials when droperidol was used for the treatment of established PONV, when droperidol was combined with another antiemetic or

when it was used as an antiemetic in a patient-controlled analgesia device.

Quality scoring and data extraction

We screened the abstracts of all retrieved reports and excluded articles that clearly did not meet our inclusion criteria. We independently read the included reports and assessed their quality of data reporting using a modified 6-points 4-items Oxford scale.⁸ Discrepancies were resolved by discussion.

We extracted information about patients, surgery, droperidol regimen, efficacy endpoints and adverse effects from each included study. To facilitate comparisons between trials, we extrapolated all variable doses ($\mu\text{g kg}^{-1}$) to fixed doses (mg) using average body weight of patients as reported in the original trials. When a trial did not report on average body weight of the study participants we used the median of all average body weights of all trials.

We extracted cumulative incidences of nausea, and vomiting (including retching), within 6 h after surgery and within 24 h. Cumulative incidences during the two time periods were used as indicators of short-term or 'early' (0–6 h) and long-term or 'late' (0–24 h) antiemetic efficacy. Consequently, early events were included in late events.

Data analyses

We analysed dichotomous data by calculating relative risks (RRs) with 95% CIs.

Heterogeneity between studies was formally tested using the Cochrane χ^2 test for heterogeneity. If the *P*-value for heterogeneity was more than 0.1, studies were considered

homogeneous and the estimates were aggregated using a Mantel-Haenszel fixed effect model. If the *P*-value of the heterogeneity test was less than 0.1, studies were considered heterogeneous and reasons for heterogeneity were investigated. In particular, using a model of meta-regression, we investigated whether differences in effects were due to differences in the doses of droperidol. If no source of heterogeneity was identified, we pooled the data using a random effects model.

We computed numbers needed to treat (NNT) to benefit one individual. Because NNT depend on the true underlying, or baseline, risk and because we were unable to identify that risk for all study groups, we used three hypothetical control event rates strata, 25, 50, and 75%, as surrogates of a low, medium and high-baseline risk, respectively. We then calculated for each baseline risk stratum the NNT with 95% CI using the aggregate (meta-analytical) RR and the hypothetical control event rate. Negative NNT were regarded as numbers needed to harm.

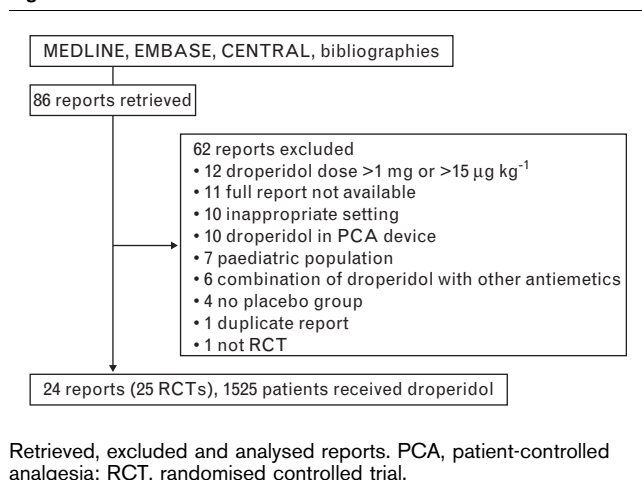
Data were processed and analysed using Excel 2007 (Microsoft, Redmond, USA), Revman 5.0.24 (The Nordic Cochrane Centre, Copenhagen, Denmark), and STATA (STATA release 11, StataCorp LP, Texas, USA).

Results

Retrieved and analysed trials

We retrieved 86 reports; 62 were subsequently excluded (Fig. 2). One was a duplicate of a full report already published.^{6,9} We excluded the duplicate⁹ and analysed the original.⁶ We eventually analysed data from 25 trials published in 24 reports between 1984 and 2008 (Table 1).^{1,6,10–31} In total, 1525 patients received droperidol and 1432 received placebo. The median quality score of the trials was 3 (range, 1 to 6).

Fig. 2



Tested regimens

Most trials tested fixed doses and only a few tested weight-adjusted doses (Table 1). The median of all average body weights of patients in all trials was 67 kg. When all weight-adjusted doses were converted to fixed doses, the range was 0.25–1.0 mg (median, 0.625 mg).

Two large multicentre studies were published concomitantly in one report;⁶ they each tested droperidol 0.625 mg in 256 patients. In these large trials, the median control event rate (i.e. the incidence of nausea and vomiting in control patients) was 54% (range, 53 to 55%) for early outcomes and 70% (range, 63 to 82%) for late outcomes (Fig. 3).⁶ The other 23 trials were all single-centre; they tested droperidol 0.25–1.0 mg in 17–86 patients (median, 38). In these smaller trials, the median control event rate was 25% (range, 2 to 63%) for early outcomes and 40% (range, 7 to 96%) for late outcomes (Fig. 3).

Antiemetic efficacy

Eight trials reported on prevention of early nausea.^{19,21,24,26,27,29–31} The tested dose-range was 0.25–0.94 mg. There was no evidence of statistical heterogeneity between study estimates ($P = 0.783$). Overall, the RR of early nausea comparing the risk in patients receiving droperidol with those receiving placebo was 0.45 (95% CI, 0.35 to 0.58) (Fig. 4, Supplemental Digital Content 1, <http://links.lww.com/EJA/A26>).

Ten trials (nine reports) reported on the prevention of early vomiting.^{6,19,21,24,26,28–31} The tested dose range was 0.25–1.0 mg. There was no evidence of statistical heterogeneity ($P = 0.587$). Overall, the RR of early vomiting comparing the risk in patients receiving droperidol with those receiving placebo was 0.65 (95% CI, 0.57 to 0.74). More than 80% of the weight was attributed to the two large multicentre trials that were documented in one report.⁶ Excluding these two trials changed the overall RR estimate to 0.53 (95% CI, 0.36 to 0.78) (Fig. 4, Supplemental Digital Content 2, <http://links.lww.com/EJA/A26>).

Twelve trials (11 reports) reported on the prevention of late nausea.^{1,6,10,14,15,19,23,25,28,30,31} Two of these provided the cumulative incidences of nausea or vomiting within 48 h.^{23,28} These data were combined with cumulative 24 h data. The tested dose range was 0.63–1.0 mg. The study estimates were heterogeneous ($P = 0.002$). However, there was no evidence of dose-responsiveness. Overall, the RR of late nausea in patients receiving droperidol compared with those receiving placebo was 0.74 (95% CI, 0.62 to 0.87). More than 40% of the weight was attributed to the two large multicentre trials.⁶ Excluding these two trials changed the RR estimate to 0.59 (95% CI, 0.41 to 0.83) (Fig. 4, Supplemental Digital Content 3, <http://links.lww.com/EJA/A26>).

Thirteen trials reported on the prevention of late vomiting.^{1,6,10,14–16,19,20,23,28,30,31} The tested dose range was

Table 1 Included randomised controlled trials

Reference	Comparison (number of analysed patients)	Surgery	Modified Oxford scale			
			R	C	B	D
Badaoui <i>et al.</i>¹⁰	Saline (25) Ondansetron 4 mg (24); not considered Droperidol 1 mg (19)	Laparoscopic cholecystectomy	2	0	1	0
Beattie <i>et al.</i>¹¹	Placebo (26) Droperidol 10 µg kg ⁻¹ (26) Droperidol 20 µg kg ⁻¹ (24); not considered Droperidol 30 µg kg ⁻¹ (24); not considered	Laparoscopic tubal ligation	1	0	1	0
Contreras-Dominguez <i>et al.</i>¹²	Saline (25) Droperidol 0.625 mg (25) Metoclopramide 20 mg (25); not considered Tropisetron 5 mg (25); not considered Granisetron 1 mg (25); not considered Dexamethasone 4 mg (25); not considered	Emergency appendicectomy	2	0	1	0
Cozanitis <i>et al.</i>¹³	Ranitidine 300 mg (60); not considered Droperidol 0.75 mg (60) Saline (60)	Abdominal hysterectomy	1	0	1	0
Eberhart <i>et al.</i>¹⁴	Placebo (35) Droperidol 10 µg kg ⁻¹ (35) Dolasetron 12.5 mg (36); not considered Droperidol + dolasetron (35); not considered	Cataract	2	0	2	1
Eberhart <i>et al.</i>¹⁵	Placebo (78) Droperidol 10 µg kg ⁻¹ (74) Dolasetron 12.5 mg (80); not considered Droperidol + dolasetron (80); not considered	Vitroretinal	2	1	2	1
Fassoulaki <i>et al.</i>¹⁶	Saline (49) Droperidol 0.5 mg (32) Droperidol 2.5 mg (30); not considered Droperidol 5 mg (19); not considered	ENT	1	0	2	1
Fortney <i>et al.</i>⁶						
Study 1	Placebo (256) Droperidol 0.625 mg (256) Droperidol 1.25 mg (253); not considered	Outpatient procedures <2 h	1	0	1	0
Study 2	Ondansetron 4 mg (257); not considered Placebo (254) Droperidol 0.625 mg (256) Droperidol 1.25 mg (252); not considered Ondansetron 4 mg (253); not considered	Outpatient procedures <2 h				
Foster <i>et al.</i>¹⁷	Saline (35) Droperidol 0.5 mg (38) Droperidol 1 mg (40)	Outpatient gynaecological	1	1	1	1
Jorgensen and Coyle¹⁸	Saline (19) Droperidol 10 µg kg ⁻¹ (20) Droperidol 20 µg kg ⁻¹ (20); not considered	Short procedures	1	1	2	1
Joris <i>et al.</i>¹⁹	30% O ₂ (50) 80% O ₂ (50); not considered 30% O ₂ + droperidol 0.625 mg (50)	Thyroid	1	0	1	0
Klahsen <i>et al.</i>²⁰	Saline (17) Droperidol 1 mg (17) Droperidol 1 mg + 0.02 per mg of morphine in PCA (19); not considered Droperidol 1 mg + 0.04 per mg of morphine in PCA (18); not considered	Open abdominal gynaecological	1	1	2	1
Kreisler <i>et al.</i>²¹	Saline (76) Droperidol 0.625 mg (74)	Procedures >2 h	1	0	1	0
Lim <i>et al.</i>²²	Droperidol 2.5 mg (51); not considered Droperidol 1.25 mg (59); not considered Droperidol 0.25 mg (86) Metoclopramide 10 mg (58); not considered Placebo (71)	Outpatient termination of pregnancy	1	0	1	0
Martin <i>et al.</i>²³	67% N ₂ O (18) 67% N ₂ O + droperidol 15 µg kg ⁻¹ (21) 100% O ₂ (21); not considered	Outpatient procedures	1	0	0	0
Millar and Hall²⁴	Saline (49) Droperidol 0.25 mg (48) Droperidol 0.5 mg (47); not considered	Outpatient termination of pregnancy	2	1	2	1
Morin <i>et al.</i>²⁵	Saline (38) Droperidol 0.625 mg (37) Droperidol 1.25 mg (37); not considered Droperidol 2.5 mg (34); not considered	Gynaecological laparoscopy	1	0	1	1
O'Donovan and Shaw²⁶	Saline (46) Droperidol 0.25 mg (41) Droperidol 1.25 mg (37); not considered	Outpatient dental	1	0	1	1

Table 1 (continued)

Reference	Comparison (number of analysed patients)	Surgery	Modified Oxford scale			
			R	C	B	D
Pandit <i>et al.</i> ²⁷	Saline (20)	Outpatient laparoscopic	2	0	1	0
	Droperidol 5 µg kg ⁻¹ (20)					
	Droperidol 10 µg kg ⁻¹ (20)					
	Droperidol 20 µg kg ⁻¹ (20); not considered					
	Metoclopramide 5 mg (20); not considered					
	Metoclopramide 10 mg (20); not considered					
	Metoclopramide 10 mg + droperidol 10 µg kg ⁻¹ (20); not considered					
Paxton <i>et al.</i> ²⁸	Saline (28)	Gynaecological laparoscopy	1	0	1	1
	Droperidol 1 mg (29)					
	Ondansetron 4 mg (32); not considered					
Tang <i>et al.</i> ²⁹	Saline (40)	Outpatient gynaecological procedures	2	1	2	0
	Droperidol 0.625 mg (41)					
	Droperidol 1.25 mg (40); not considered					
	Ondansetron 4 mg (40); not considered					
Valanne and Korttila ³⁰	Placebo (50)	Oral	1	0	1	1
	Droperidol 14 µg kg ⁻¹ (49)					
Wang <i>et al.</i> ³¹	Saline (47)	Outpatient laparoscopic surgery	2	1	2	1
	Droperidol 0.625 mg (44)					
	Haloperidol 1 mg (45); not considered					
White <i>et al.</i> ¹	Saline (20)	ENT	2	1	2	0
	Droperidol 0.625 mg (20)					
	Droperidol 1.25 mg (20); not considered					

R, randomisation (1 = yes but not specified; 2 = yes and adequate e.g. table of random numbers); B, blinding (0 = none, 1 = patient-blinded, 2 = patient-blinded and observer-blinded); C, concealment (0 = none, 1 = yes); D, drop-outs (0 = none, 1 = yes); PCA, patient-controlled analgesia.

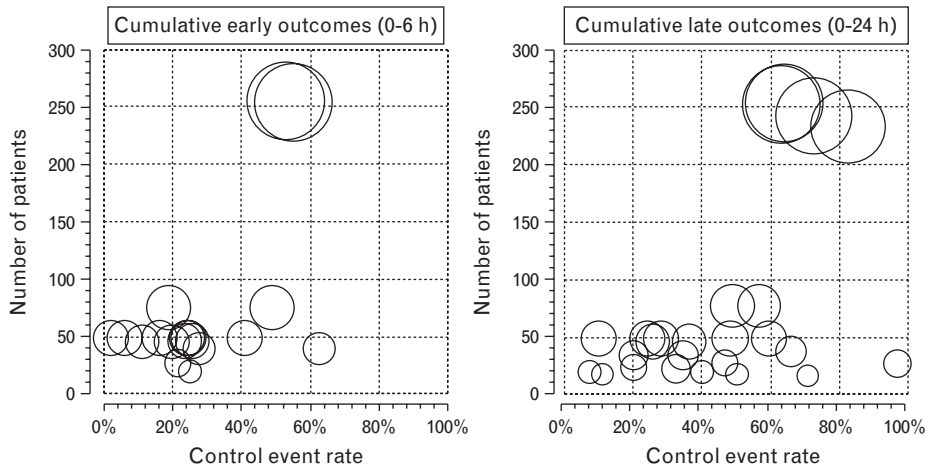
0.5–1.0 mg. The study estimates were heterogeneous ($P < 0.001$). However, there was no evidence of dose-responsiveness. Overall, the RR of late vomiting in patients receiving droperidol compared with those receiving placebo was 0.61 (95% CI, 0.47 to 0.80). About 40% of the weight was attributed to the two large multi-centre trials.⁶ Excluding these two trials changed the RR estimate to 0.50 (95% CI, 0.32 to 0.79) (Fig. 4,

Supplemental Digital Content 4, <http://links.lww.com/EJA/A26>).

Six trials (295 patients received droperidol 0.25–0.75 mg) reported on a composite nausea and vomiting endpoint only.^{11–13,17,18,22} These data were not analysed further.

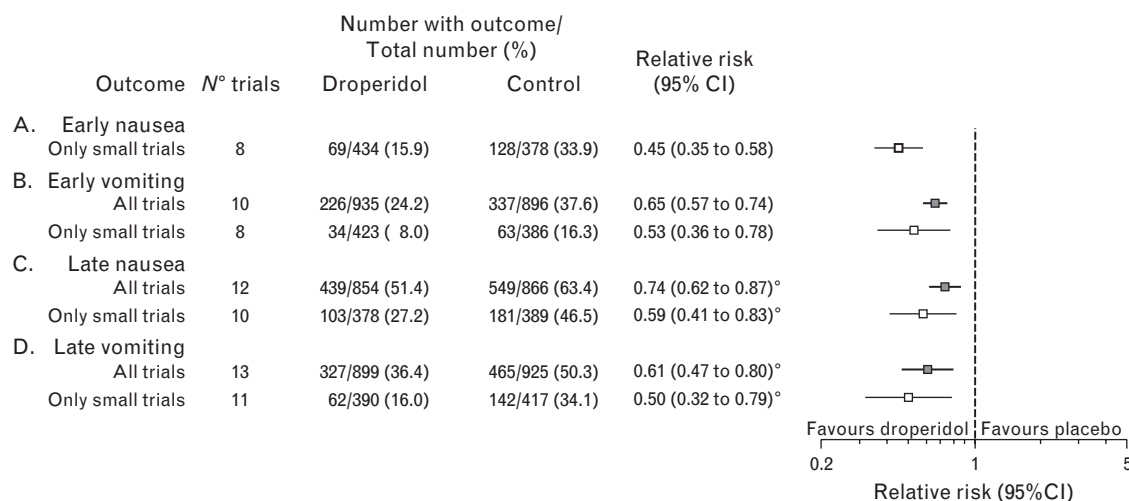
Individual meta-analyses (Forrest plots) on early and late nausea and vomiting are freely accessible from the

Fig. 3



Trial size and baseline risk. Each bubble represents one comparison; sizes of bubbles are proportional to the number of participants in the comparisons. Control event rate is cumulative incidence of nausea or vomiting in patients receiving placebo during the first 6 h (early outcomes, left panel) and during the first 24 h (late outcomes, right panel), postoperatively. Y-axis = sum of number of patients in placebo and droperidol groups of each comparison. The large bubbles are from two multicentre trials.⁶

Fig. 4



Summary meta-analyses of early and late antiemetic efficacy. Early, cumulative incidence of nausea or vomiting up to 6 h; late, up to 24 h. 'All trials' include data from two large multicentre trials;⁶ these did not report data on prevention of early nausea. ^oRandom effects model (*P* for heterogeneity <0.1); in all other cases, fixed effect model.

authors' web page (<http://anesthesiologic.hug-gc.ch/data.htm>).

Numbers needed to treat for antiemetic efficacy

NNT consistently decreased (i.e. the antiemetic efficacy improved) with increasing control event rates (i.e. with increasing baseline risks; Table 2).

For early outcomes, and within each baseline risk stratum, NNT point estimates tended to be lower for nausea compared with vomiting, suggesting that antinausea efficacy was superior to antivomiting efficacy. For late outcomes, and within each baseline risk stratum, NNT point estimates tended to be lower for vomiting compared with nausea suggesting that antivomiting efficacy was superior to antinausea efficacy. Ninety-five percentage CI around the NNT for early nausea did not overlap with those for

late nausea; however, 95% CI around the NNT for early vomiting overlapped with those for late vomiting.

Further beneficial and harmful effects

Significantly fewer patients treated with droperidol were reported to have a headache postoperatively; the NNT point estimate was 24 (Table 3, Supplemental Digital Content 5, <http://links.lww.com/EJA/A26>).^{1,6,13–15,17,21,22,24–26,30} Significantly more patients receiving droperidol were restless; the number needed to harm was nine (Table 3, Supplemental Digital Content 6, <http://links.lww.com/EJA/A26>). For both outcomes, there was no evidence of dose-responsiveness. There were no statistically significant differences in the incidence of sedation or dizziness. Six trials (301 patients received droperidol) reported on the presence or absence of extrapyramidal symptoms.^{13,15,16,20,21,31} In one trial, two of

Table 2 Numbers needed to treat to benefit one individual according to three baseline risks

Baseline risk	Control event rate	Endpoint	Number needed to treat (95% CI)
Early outcomes (up to 6 h postoperatively)			
Low	25%	Prevention of nausea	7.3 (6.2 to 9.5)
		Prevention of vomiting	11 (9.3 to 15)
Medium	50%	Prevention of nausea	3.6 (3.1 to 4.8)
		Prevention of vomiting	5.7 (4.7 to 7.7)
High	75%	Prevention of nausea	2.4 (2.1 to 3.2)
		Prevention of vomiting	3.8 (3.1 to 5.1)
Late outcomes (up to 24 h postoperatively)			
Low	25%	Prevention of nausea	15 (11 to 31)
		Prevention of vomiting	10 (7.5 to 20)
Medium	50%	Prevention of nausea	7.7 (5.3 to 15)
		Prevention of vomiting	5.1 (3.8 to 10)
High	75%	Prevention of nausea	5.1 (3.5 to 10)
		Prevention of vomiting	3.4 (2.5 to 6.7)

CI, confidence interval. Baseline risks and corresponding control event rates were arbitrarily chosen. Relative risks to compute numbers needed to treat were taken from Figure 4.

Table 3 Further beneficial and harmful effects

Outcome	Number with outcome/total number (%)		Relative risk (95% CI)	Number needed to treat (95% CI)	References
	Droperidol	Control			
Headache	121/834 (14.5)	149/811 (18.4)	0.77 (0.62 to 0.96)	24 (14 to 136)	1,6,14,15,21,24,26
Restlessness	42/243 (17.3)	10/212 (4.7)	3.30 (1.65 to 6.58)	−9.0 (−33 to −4.0)	1,15,17,21
Dizziness	50/256 (19.5)	31/230 (13.5)	1.41 (0.94 to 2.12)	−13	6,13,14,22,24–26
Sedation	168/859 (19.6)	157/813 (19.4)	0.99 (0.84 to 1.16)	510	1,21,24,26,30

CI, confidence interval. Definitions of outcomes were taken as reported in the original trials. When an outcome was reported at different time points after surgery, the highest cumulative incidence was extracted. A negative number needed to treat is a number needed to harm. 95% Confidence intervals around numbers needed to treat/harm are shown for statistically significant results only.

74 patients receiving droperidol 0.625 mg presented such symptoms.²¹ There were no reports of QT prolongation or cardiac arrhythmia.

Discussion

An international consensus panel recommended droperidol 0.625 or 1.25 mg for the prevention of PONV in adults undergoing general anaesthesia.⁵ Our analyses suggest that doses below 1 mg do have worthwhile antiemetic efficacy and that doses above 1 mg are not warranted.

The antinausea effect of low-dose droperidol was not maintained over the 24 h period. In contrast, the anti-vomiting efficacy was very similar at long-term (i.e. within 24 h) compared with short-term (within the first 6 h). This suggests that for the maintenance of an adequate antinausea effect during a 24 h period, one single prophylactic dose may not be sufficient.

Patients receiving droperidol complained of postoperative headache less often, something that has been described before.³² What is new knowledge is that protection against headache is apparent even at doses below 1 mg. Not unexpectedly, patients treated with droperidol were more often restless. However, for dizziness or sedation, aggregate data did not show a significant difference between those who received droperidol and controls. Finally, extrapyramidal symptoms happened but they appeared to be rare. No case of torsades de pointes or cardiac arrest was reported.

It may be argued that two previously published large-scale trials have already provided all the evidence on efficacy and harm of low-dose droperidol.⁶ However, these trials tested only one dose (0.625 mg) and they did not report on early nausea outcomes. To better understand the usefulness of an antiemetic drug, it is important to distinguish between its early and late efficacy, and also between its antinausea and anti-vomiting efficacy. Additionally, our enquiry among ESA council members revealed that, although droperidol is widely used in Europe, administered doses are often inappropriately high, including 2.5 mg in some countries. This suggests that dissemination and implementation of evidence from meta-analysis³² and large trials,⁶ and of

recommendations from international expert panels,⁵ have been insufficient. Finally, had we not included all the smaller trials, we would have missed valuable data on adverse drug reactions and would not have been able to test for dose-responsiveness.

Antiemetic efficiency clearly depends on the underlying, or baseline risk. In a high-risk population, less effort is needed to prevent one bad outcome. As expected, NNT decreased with increasing control event rates, confirming that prevention is only worthwhile when the baseline risk is high. In the hypothetical high-risk setting, NNT to prevent nausea and vomiting were between about 3.5 and 5. These numbers suggested improved efficacy. However, it may be argued that even in a high-risk setting, low-dose droperidol alone should not be regarded as a universal prophylaxis. Combinations of antiemetic drugs for optimal efficacy have been advocated before.⁵

As with other old antiemetic drugs,³³ droperidol is not exempt from central adverse reactions. However, in the dose range analysed, adverse effects did not seem to be a major limiting factor. Not unexpectedly, the risk of restlessness was increased; about one in nine patients receiving droperidol 0.25–1.0 mg will be restless postoperatively, who would not be if they received a placebo. It remained unclear whether this adverse effect increased postoperative morbidity or interfered with patient satisfaction. Sedation or dizziness was not an issue and this was probably due to the low-dose range that was tested. Extrapyramidal symptoms are typical adverse effects of butyrophenones and there is evidence that these may even occur with doses as low as 0.625 mg.²¹ Depending on the chosen denominator, between 0.7 (two of 301) and 2.7% (two of 74) patients receiving droperidol 0.625 mg were reported to have such symptoms postoperatively. We do not know whether the two reported cases needed treatment. There was no report of arrhythmia including QT prolongation and no case of torsades de pointes or cardiac arrest. Because none of these trials was designed to study the cardiac toxicity of droperidol, it remains unknown whether such cases occurred but were missed, or whether they were not reported, although this is unlikely given the severity of this adverse effect. Clinical studies have suggested that with droperidol doses below 1 mg, QT prolongation was no different from placebo.^{1,2}

or ondansetron 4 mg,^{3,4} but we still cannot completely rule out an increased risk of cardiac arrhythmia even with doses below 1 mg. In our analysis, 1525 patients had received droperidol 0.25–1 mg and there was no report of cardiac death; therefore, we can be 95% confident that the chance of this major adverse event happening is at most three in 1525 (or 0.2%).³⁴

We cannot be certain that our analysis does not overestimate the beneficial effect of low-dose droperidol. The literature search was comprehensive but selective publication of positive results cannot be ruled out. The quality score of studies ranged from 1–6 (median, 3) and low-quality trials tend to overestimate treatment efficacy. However, our methodological quality score appreciates the quality of data reporting of randomised trials, which, strictly speaking, does not reveal how the trials were actually performed. Authors sometimes perform adequate randomisation but fail to report on the necessary methodological details.³⁵

Small trials reported large variability in control event rates, indicating that in small trials anything may happen by random chance.³⁶ It has been argued that smaller trials should, therefore, be excluded from meta-analysis.³⁷ The two largest trials reported extraordinary high control event rates due to selective inclusion of high-risk patients, mainly women with a positive history of PONV or motion sickness.⁶ However, despite high control event rates, the large trials reported a degree of antiemetic efficacy of droperidol that was lower than in smaller trials.

We were unable to show evidence of dose-responsiveness. This may mean that there is none in the dose range between 0.25 and 1.0 mg, or that our analyses were lacking power to show a dose-response relationship. For late outcomes, the tested dose range was narrow, ranging from 0.5 to 1.0 mg only. This may be yet another explanation for why we were unable to find dose-responsiveness. The lack of late data for very low doses (i.e. ≤ 0.5 mg) may reflect the presence of publication bias; it cannot be ruled out that trials testing very low doses failed to report on late data because these were negative.

It has been suggested that the antiemetic effect of droperidol may be sex-dependent.³⁸ Although 13 trials included mixed sex, only one reported on the number of men and women needing rescue treatment separately but without providing any analyses of these data.²¹ This meta-analysis does not further our understanding on sex differences of the antiemetic effect of droperidol.

Our analyses may serve as a rational basis for future research. Knowing that low doses of droperidol are antiemetic in the surgical setting, albeit to a limited degree, begs the question as to how low-dose droperidol performs in combination with other antiemetics, for instance, 5HT₃ receptor antagonists or dexamethasone. Also, it seemed that the antinausea effect was not maintained to

the same degree as the antiemetic effect. It may be worthwhile testing, how often a prophylactic low-dose droperidol regimen needs to be repeated to maintain adequate 24 h antinausea efficacy.³⁹

In conclusion, a survey suggests that droperidol is still a popular antiemetic among European anaesthetists. Data from randomised trials provide evidence that low-dose droperidol (≤ 1 mg or $\leq 15 \mu\text{g kg}^{-1}$) is clearly efficacious for the prevention of PONV. An additional, but weak, beneficial effect is the prevention of postoperative headache. Cardiac adverse events were not reported. However, even at low doses, potentially serious central adverse effects such as extrapyramidal symptoms may occur. In view of the fact that droperidol at doses of 1 mg or less is antiemetic, and that adverse drug reactions are likely to be dose-dependent, there is an argument to stop using doses above 1 mg.

Acknowledgments

This work was supported by the Evidence-based Critical Care, Anaesthesia and Pain Treatment (EBCAP) Institute (Geneva, Switzerland) (salary of N.E.), and institutional funds from the Department of Anaesthesiology, Critical Care & Clinical Pharmacology, Geneva University Hospitals. From 2005 to 2007, the Evidence-based Critical Care, Anaesthesia and Pain Treatment (EBCAP) Institute (Geneva, Switzerland) received an unrestricted grant from SINTETICA SA, CH-6850 Mendrisio, Switzerland. SINTETICA SA is a manufacturer of droperidol. None of the authors reports any conflict of interest in relation to this study.

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