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Is Low-dose Haloperidol a Useful Antiemetic?

A Meta-analysis of Published and Unpublished Randomized Trials

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The antiemetic efficacy of haloperidol was studied using data from 15 published (1962–1988) and 8 unpublished randomized trials; 1,397 adults received haloperidol, and 1,071 were controls. Settings were postoperative nausea or vomiting (1,994 patients), gastroenterology (261), chemotherapy (189), and radiation therapy (24). The relative benefit to prevent postoperative nausea or vomiting during 24 h with 0.5–4 mg haloperidol compared with placebo was 1.26–1.51 (number needed to treat, 3.2–5.1), without evidence of dose responsiveness; 0.25 mg was not antiemetic. With 1 mg haloperidol, the relative benefit to stop postoperative nausea or vomiting during 2–4 h compared with placebo was 1.53 (95% confidence interval, 1.17–2.00; number needed to treat, 6); with 2 mg, the relative benefit was 1.73 (1.11–2.68; number needed to treat, 4). In gastroenterology, 2 mg haloperidol was more effective than 1 mg. For chemotherapy and radiation therapy, no conclusions could be drawn. With 4 mg, one patient had extrapyramidal symptoms. With 5 mg, sedation was increased, with a relative risk of 2.09 (95% confidence interval, 1.73–2.52; number needed to treat, 4.4). There were no reports on cardiac toxicity. Postoperatively and in gastroenterology, haloperidol is antiemetic, with minimal toxicity. For other clinical settings and for children, valid data are unavailable.

BUTYROPHENONES are powerful antiemetics. Haloperidol, a butyrophenone with a high affinity for dopamine D_2 receptors, has been available[1] since 1958 and received Food and Drug Administration approval as an antipsychotic drug in 1967. It has been used not only in psychiatry but also in medical and surgical patients for the control of severe agitation. Early studies showed that haloperidol effectively protected against apomorphine-induced emesis.[2] Subsequently, haloperidol has been widely used as an antiemetic for more than 40 yr, often despite a lack of evidence-based clinical data on efficacy and side effects. A recent systematic review addressed the usefulness of haloperidol as an antiemetic in palliative care; however, the authors did not find any relevant randomized controlled trial in the literature and therefore were unable to draw a meaningful conclusion.[3] Haloperidol, which is an old and inexpensive drug, may prove to be an interesting and cost-effective alternative to newer and more costly antiemetics. However, before haloperidol can be recommended for this indication, its antiemetic dose range, minimal effective dose, and adverse effects must be defined. The aim of this study was to address these issues using systematically searched valid data from published and unpublished randomized controlled trials.

Materials and Methods

This quantitative systematic review was performed following QUOROM (Quality of Reporting of Meta-analyses) recommendations.[4]

Search Strategy

We identified relevant articles in all languages through searches in MEDLINE, Cinahl, HealthSTAR, Oldmedline, Embase, Lilacs, Web of Science, Biologic Abstracts, and the Cochrane Controlled Trials Register using different search strategies with multiple free text keywords. Electronic searches were conducted until July 2003 and were complemented by screening bibliographies of retrieved articles, textbooks, and reviews. If there was ambiguity about data, we contacted the investigators and asked for clarification. The manufacturer of haloperidol (Janssen-Cilag AG, Baar, Switzerland) was asked for relevant studies, including unpublished data.

Study Selection

Relevant randomized trials compared haloperidol as an antiemetic (experimental intervention) with another antiemetic, placebo, or no treatment (control intervention) and reported on dichotomous data regarding the presence or absence of nausea or vomiting or haloperidol-related adverse reactions. Reports using pseudorandomization or with historic controls, experimental studies in volunteers, or animal studies were not considered. Studies that included less than 10 patients/group were ex-

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cluded.[5] We included unpublished reports of valid randomized trials when the description of methods and results was adequate.

Assessment of Validity

Retrieved reports were screened for inclusion by one of the authors (M. B.), who excluded irrelevant reports at that stage. Each author then independently scored all eligible reports, whether published or unpublished, for methodologic validity using the five-point Oxford scale that takes into account randomization, blinding, and description of withdrawals.[6] The minimum score of an included randomized study was 1, and the maximum score was 5. As with similar previous analyses,[7] consensus was reached by discussion.

Data Extraction

We extracted information on clinical setting, number of randomized and analyzed patients, dose and route of administration of study drugs, efficacy endpoints, and adverse effects from each included report. Data from different clinical settings were analyzed separately. Nausea and vomiting were considered as different endpoints. Retching was regarded as vomiting. For postoperative nausea and vomiting (PONV), we distinguished between an "early" observation period (cumulative incidence to 6 h after surgery) and a "late" period (cumulative incidence to 24 h).[7] For chemotherapy and radiation therapy, an "acute" period (cumulative incidence to 24 h after a cycle), was separated from a "delayed" period (beyond 24 h).[8] Definitions on adverse effects were taken as provided by the investigators. We only considered dichotomous data on presence or absence of nausea or vomiting or on presence or absence of adverse effects. We ignored nausea scores, delay until first emesis episodes, numbers of patients needing rescue treatment, and data on patient satisfaction because these data were inconsistently reported. Because there is no accepted standard antiemetic, we decided that the primary efficacy information would come from trials with a placebo–control group.

Data Synthesis

We calculated relative benefit (RB) and relative risk with 95% confidence interval (CI) for data on efficacy and adverse effects, respectively.[9] For rare events (*e.g.*, extrapyramidal reactions), we used the Peto odds ratio, which ignores trials with zero cells.[10] We calculated the number needed to treat (NNT)/number needed to harm with 95% CI as an estimate of the clinical relevance of a treatment effect.[11] NNTs were used to compare degrees of efficacy of different doses, of the same dose during different observation periods, or of different efficacy endpoints (antinausea *vs.* antivomiting efficacy); however, this was done only when control event rates of relevant subgroups were similar. We used a fixed-effect model to combine data across studies because the data seemed to be clinically homogenous. Formal heterogeneity testing was done when data from at least three trials were combined.

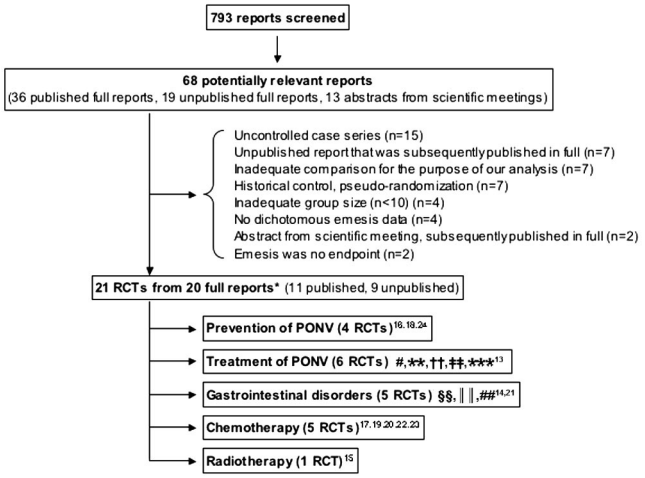

Fig. 1. Flowchart of retrieved, excluded, and analyzed reports. * One report[24] contained data from two randomized controlled trials (RCTs). PONV = postoperative nausea and vomiting. For explanation of symbols #,,††,‡‡,§§,‖‖,##,***, see footnotes on page 1456.**

We tested for dose–responsiveness using conservative assumptions as in previous similar analyses.[12] First, if the 95% CI around the RB of one dose did not overlap with the point estimate of the RB of another dose, we assumed that there was a significant difference in the efficacy of the two doses. Second, if one dose of haloperidol was not significantly different from placebo (*i.e.*, the 95% CI around the RB included 1) and higher doses were consistently more effective than placebo, we regarded this as evidence of dose–responsiveness. We further assessed for consistency in the increase in efficacy with increasing dose. If control event rates were similar, we used the NNT for that purpose. A decrease in the NNT by more than 20% (*e.g.*, from 5 to 4) was regarded as a relevant improvement and would therefore justify an increase in the dose.[12] The optimal dose of haloperidol would have an acceptable adverse effect profile, and any further increase would not lead to a relevant improvement (*i.e.*, a decrease in the NNT $> 20\%$). Analyses were performed with RevMan 4.2 (Cochrane Library, Update Software, Oxford, United Kingdom) and with Microsoft® Excel 98 for Mac®.

Results

Search Results

We screened 793 reports. Sixty-eight were potentially relevant for the purpose of this study; of those, 48 were subsequently excluded for various reasons (fig. 1). We eventually analyzed data from 21 randomized trials

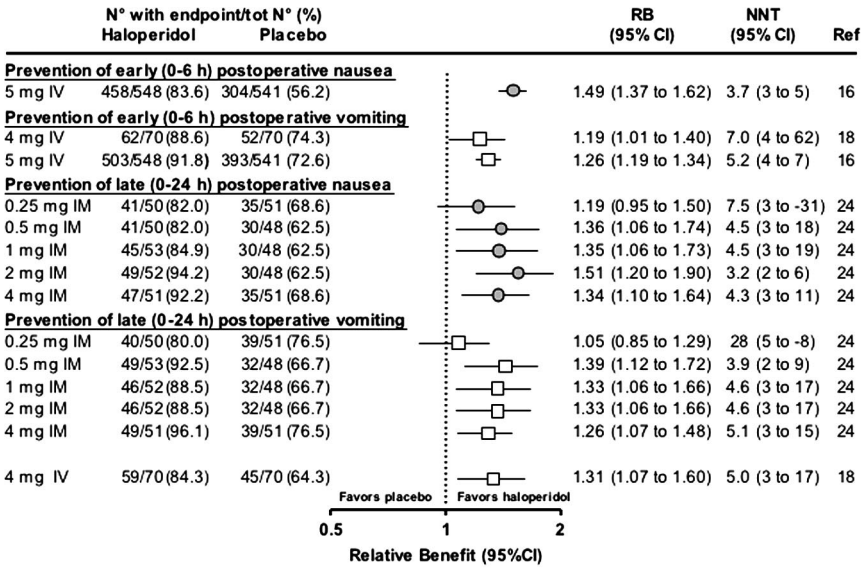

Fig. 2. Prevention of postoperative nausea and vomiting with parenteral single-dose haloperidol regimens. All data are from individual trials and were not combined (*i.e.*, no meta-analyses were performed). *Gray circles* = nausea; *white squares* = vomiting. CI = confidence interval; IM = intramuscular; IV = intravenous; NNT = number needed to treat; RB = relative benefit; Ref = reference.

that were published in 20 full reports#,**,††,‡‡,§§,||||,##,***,[13–24]; one report[24] contained data from two dose-finding studies. In these trials, 1,397 adults received different regimens of haloperidol, and 1,694 were controls.

Twelve reports (13 trials, 1,994 patients) were published between 1962 and 1988.[13–24] Eight unpublished reports (8 trials, 474 patients) were provided by the manufacturer. The latter were phase II and III trials as part of the manufacturer's US registration program for haloperidol as an antiemetic in the early 1980s.#,**,††,‡‡,§§,||||,##,*** The registration trials had similar designs, and some of these studies were subsequently published in full. Haloperidol was tested for the prevention or treatment of PONV, for the treatment of emesis due to gastrointestinal diseases, and for the control of chemotherapy- and radiation therapy–induced sickness. There were no randomized trials on emesis in palliative care, acquired immunodeficiency syndrome, hyperemesis gravidarum, or motion sickness, and there were no trials in children.

Dannemiller FJ: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized patients following operative procedures. McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

** DeBakker A: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized patients following operative procedures (trial A). McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

†† DeBakker A: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized patients following operative procedures (trial B). McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

‡‡ DeBakker A: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized patients following operative procedures (trial C). McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

§§ Everett SF: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized and nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders. McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

|||| Leslie RE: A double-blind evaluation of the antiemetic properties of Haldol in nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders (trial A). McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

Leslie RE: A double-blind evaluation of the antiemetic properties of Haldol in nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders (trial B). McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

*** Ritter R, Watson RL: A double-blind evaluation of the antiemetic properties of Haldol in hospitalized patients following operative procedures. McNeil Laboratories; January 1974. Available at: http://www.hcuge.ch/anesthesie/data.htm. Accessed July 12, 2004.

Methodologic Quality of the Included Studies

The median quality score was 3 (range, 1–4). All studies were randomized and blinded; however, in one study only,[13] the authors provided details on how randomization was done, and in two,[13,21] the method of blinding was described.

Quantitative Data Synthesis

Prevention of PONV. Four trials published in three reports studied the efficacy of single-dose haloperidol regimens for the prevention of PONV in 1,586 surgical patients (table 1 and fig. 2).[16,18,24] Five fixed intramuscular doses (0.25, 0.5, 1, 2, and 4 mg) and two fixed intravenous doses (4 and 5 mg) were compared with placebo.

Data on prevention of nausea up to the sixth hour after surgery came from one large study (1,089 patients) that tested 5 mg intravenous haloperidol.[16] The average incidence of early nausea was 16.4% with haloperidol and 43.8% with placebo (RB, 1.49 [95% CI, 1.37–1.62]; NNT, 3.7). Data on prevention of early vomiting came from two studies that tested 4 mg intravenous haloperidol in 140 patients[18] and 5 mg intravenous haloperidol in 1,089 patients.[16] The lower limit of the 95% CI of the 5-mg dose was identical with the point estimate of the 4-mg dose; the corresponding NNTs were 5.2 and 7, respectively. The differential effect of haloperidol on nausea and on vomiting could be studied with the 5-mg dose (fig. 2). The antinausea effect was significantly more

pronounced than the antivomiting effect (*i.e.*, the 95% CIs of the RBs did not overlap); the corresponding NNTs were 3.7 and 5.2, respectively.

Three studies (2 reports, 497 patients) reported on antiemetic efficacy during 24 h after surgery. Two dose-finding studies tested 0.25–4 mg intramuscular haloperidol.[24] One tested 4 mg intravenous haloperidol.[18] The lowest dose, 0.25 mg, was not different from placebo. Higher doses (0.5, 1, 2, and 4 mg) were significantly more efficacious than placebo, but there was no evidence of dose–responsiveness within that dose range; RB point estimates were between 1.34 and 1.51 (NNT, 3.2–4.5) for antinausea efficacy and between 1.26 and 1.39 (NNT, 3.9–5.1) for antivomiting efficacy. Antivomiting efficacy of the 4-mg dose was tested using the intravenous[18] and the intramuscular route[24]; there was no evidence of any difference.

Treatment of Established PONV. One published trial[13] and five unpublished trials#,**,††,‡‡,*** (fig. 3) reported on the therapeutic efficacy of single-dose haloperidol regimens in 408 nauseous or vomiting surgical patients. Study designs were identical; tested regimens were 1 and 2 mg intramuscular; observation periods were 30 min and 2–4 h. Haloperidol, 1 mg intramuscular, was not antinauseous during the first 30 min after administration, but the 2-mg intramuscular dose was. Neither dose was efficacious against vomiting during the same short observation period. However, both 1 and 2 mg intramuscular haloperidol prevented further vomiting at 2–4 h after treatment; with the 1-mg dose, the RB was 1.53 (95% CI, 1.17–2.00; NNT, 6), and with the 2 mg dose, the RB was 1.73 (95% CI, 1.11–2.68; NNT, 4).

Nausea and Vomiting Related to Gastrointestinal Diseases. Two published trials[14,21] and three unpublished trials§§,||||,## reported on the efficacy of 1 and 2 mg intramuscular haloperidol for the treatment of nausea and vomiting due to gastrointestinal diseases in 261 patients (fig. 4). The inclusion criteria and patient demographics were poorly described. However, the study designs were identical. The observation periods were 0–2, 2–4, 4–8, and 8–12 h. Both regimens were efficacious during all observation periods (with the exception of 2 mg during the 0- to 2-h period), and efficacy decreased consistently over time. For the cumulative incidence of vomiting over 12 h, there was some evidence of increased efficacy with the 2-mg dose.

Nausea and Vomiting Related to Chemotherapy and Radiation Therapy. Five published trials in 189 patients undergoing chemotherapy[17,19,20,22,23] and one in 24 patients undergoing radiation therapy‖[15] tested the efficacy of haloperidol. None were sponsored by the manufacturer. Five had a crossover design. The regimen contained cisplatin in four of five chemotherapy trials. Six different oral and parenteral, single- or multiple-dose haloperidol regimens were tested against two different metoclopramide regimens in two trials and against prochlorperazine, δ-9-tetrahydrocannabinol, benzquinamide, or placebo each in one trial. No comparison was tested more than once. In one small chemotherapy trial, haloperidol was superior to benzquinamide in the prevention of acute vomiting.[19] In the radiation therapy trial, haloperidol was superior to placebo in the prevention of delayed vomiting.[15]

‖ Details of the trials are available at: http://www.hcuge.ch/anesthesie/data. Accessed July 12, 2004.

Adverse Effects in Placebo-controlled Trials

Twelve placebo-controlled trials from the postoperative and gastrointestinal settings reported on a large variety of adverse effects. All trials tested single-dose haloperidol regimens.

Extrapyramidal Symptoms. Presence or absence of extrapyramidal symptoms was reported in two studies with data on 1,842 surgical patients.[16,24] One of those trials tested 0.25–4 mg intravenous haloperidol.[24] Of 258 patients randomly assigned to receive haloperidol, one who had received 4 mg had mild puckering of the lips, and the investigators considered this to be evocative for extrapyramidal symptoms.[24] There were no such events in 99 controls. In the other trial, there were no extrapyramidal symptoms in 548 surgical patients who had received 5 mg intravenous haloperidol and in 541 controls.[16] Therefore, of 806 patients exposed to 0.25–5 mg intravenous haloperidol, 1 (0.1%) had extrapyramidal symptoms with 4 mg. No other trial reported extrapyramidal symptoms.

Sedation and Drowsiness. Sedation or drowsiness was reported in two trials, although in none were clear definitions of these outcomes provided. In one large surgical trial, 239 of 548 patients (43.6%) who had received 5 mg intravenous haloperidol were reported to be sedated postoperatively as compared with 113 of 541 controls (20.9%); the relative risk was 2.09 (95% CI, 1.73–2.52), and the number needed to harm was 4.4 (95% CI, 3.6–5.8).[16] In one gastroenterology trial, 1 of 55 patients (1.8%) who had received 1 mg intravenous haloperidol was reported to be drowsy as compared with none of 50 controls (odds ratio, 6.75 [95% CI, 0.13–342]).[14]

Arterial Hypotension. Five surgical studies reported on the presence or absence of episodes of arterial hypotension.#,**,||||,***[18] Hypotension, as defined by the investigators, occurred in 17 of 224 (7.6%) patients treated with 1–4 mg haloperidol as compared with 16 of 205 controls (7.8%); the odds ratio was 1.05 (95% CI, 0.49–2.22).

Other Adverse Effects. Other adverse effects that were reported in placebo-controlled trials were arterial hypertension,[18,24] blurred vision,[14,24] chills and shivering,[24] bradycardia,**[24] tachycardia,***[21] and nystagmus.[13] None was significantly associated with administration of haloperidol. There were no reports of cardiac arrhythmias.

Table 1. Single-dose Haloperidol Regimens in Surgery and Gastrointestinal Diseases

Reference	Year of Publication	Oxford Scale: Randomized	Oxford Scale: Double Blind	Oxford Scale: Dropouts	Patients
Prevention of postoperative nausea and vomiting					
Dyrberg[16]	1962	1	1	0	772 females, 317 males Age > 15 yr
Maggi *et al.*[18]	1964	1	0	0	76 females, 64 males Age range, 20–70 yr
Tornetta,[24] studies I and II	1972	1	1	0	All females Age mean, 38.2 yr (range, 17–80 yr) Weight mean, 62.3 kg
		1	1	0	All females Age mean, 37.4 (range, 18–77 yr) Weight mean, 64.8 kg
Treatment of established postoperative nausea and vomiting					
Barton *et al.*[13]	1975	2	2	0	60 females, 2 males Age mean, 28.7 yr (range, 13–86 yr) Weight mean, 62.1 kg
Dannemiller#	Unpublished	1	1	1	27 females, 11 males Age mean, 31.0 yr (range, 13–60 yr) Weight mean, 66.2 kg
DeBakker**	Unpublished	1	1	1	83 females, 18 males Age mean, 40.8 yr (range, 17–73 yr) Weight mean, 67.0 kg
DeBakker††	Unpublished	1	1	1	49 females, 8 males Age mean, 39.9 yr (range, 15–75 yr) Weight mean, 65.8 kg
DeBakker‡‡	Unpublished	1	1	1	32 females, 6 males Age mean, 43.5 yr (range, 18–71 yr) Weight mean, 66.5 kg
Ritter and Watson***	Unpublished	1	1	1	98 females, 14 males Age mean, 33.8 yr (range, 15–66 yr) Weight mean, 65.7 kg
Treatment of established gastrointestinal nausea and vomiting					
Christman et al.[14]	1974	1	1	0	80 females, 25 males Age mean, 47.1 (range, 18–80 yr) Weight mean, NA
Everett§§	Unpublished	1	1	1	12 females, 8 males Age mean, 52.2 (range, 20–86 yr) Weight mean, 65.5 kg
Leslie‖‖	Unpublished	1	1	1	35 females, 9 males Age mean, 56.2 (range 17–85 yr) Weight mean, 69.5 kg
Leslie##	Unpublished	1	1	1	38 females, 26 males Age mean, 57.4 (range, 18–85 yr) Weight mean, 79.2 kg
Robbins and Nagel[21]	1975	1	2	1	25 females, 3 males Age mean, 83.4 (range, 72–95 yr) Weight mean, 54.5 kg

(*Continues*)

For explanation of symbols #,**,††,‡‡,***,§§,‖‖,##, see footnotes on page 1456.

IM = intramuscular; IV = intravenous; NA = not applicable; N_2O = nitrous oxide.

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Adverse Effects in Active-controlled Trials

Four chemotherapy trials reported on presence or absence of adverse effects.[17,20,22,23] There was a large variety in the rates of adverse effects with both haloperidol and control regimens. For example, extrapyramidal symptoms, reported as twitching, dystonia, akathisia, or rigor, occurred in 4–100% of patients receiving haloperidol and in 0–50% of those receiving metoclopramide or prochlorperazine.[17,22] Further adverse effects that occurred more frequently with haloperidol were sedation, fatigue, and drowsiness. None were significantly associated with administration of haloperidol. There were no reports of cardiac arrhythmias.

Table 1. (*Continued*)

Setting	Anesthesia	Comparison (No. of Patients)	Time Point of Administration	Follow-up	Sponsor
Prevention of postoperative nausea and vomiting					
Different surgeries	Morphine premedication, barbiturate, N_2O, relaxant	1. Haloperidol, 5 mg IV (548) 2. Placebo, IV (541)	During surgery	24 h	NA
Different surgeries	Fluothane, penthrane, N_2O, thiobarbiturate, succinylcholine, mefedine	1. Haloperidol, 4 mg IV (70) 2. Placebo, IV (70)	End of surgery	24 h	NA
Dilatation and curettage	Meperidine atropine–scopolamine, methohexital, cyclopropane, succinylcholine	1. Haloperidol, 0.5 mg IM (53) 2. Haloperidol, 1 mg IM (52) 3. Haloperidol, 2 mg IM (52) 4. Placebo, IM (48) 1. Haloperidol, 0.25 mg IM (50) 2. Haloperidol, 4 mg IM (51) 3. Placebo, IM (51)	Before induction	24 h	Janssen-Cilag Int.
Treatment of established postoperative nausea and vomiting					
Different surgeries	Cyclopropane, thiopental, N_2O, halothane, fluroxene, ether	1. Haloperidol, 1 mg IM (32) 2. Placebo, IM (30)	After nausea or vomiting episode	3 h	Janssen-Cilag Int.
Different surgeries	Not reported	1. Haloperidol, 2 mg IM (19) 2. Placebo, IM (19)	In recovery room, after vomiting	4 h	Janssen-Cilag Int.
Different surgeries	Not reported	1. Haloperidol, 1 mg IM (51) 2. Placebo (50)	After onset of vomiting	2 h	Janssen-Cilag Int.
Different surgeries	Not reported	1. Haloperidol, 2 mg IM (29) 2. Placebo (28)	After onset of vomiting	4 h	Janssen-Cilag Int.
Different surgeries	Not reported	1. Haloperidol, 1 mg IM (13) 2. Haloperidol, 2 mg IM (12) 3. Placebo (13)	After onset of vomiting	4 h	Janssen-Cilag Int.
Different surgeries	Not reported	1. Haloperidol, 1 mg IM (59) 2. Placebo (53)	In recovery room, after vomiting	4 h	Janssen-Cilag Int.
Treatment of established gastrointestinal nausea and vomiting					
Institutionalized or office patients	NA	1. Haloperidol, 1 mg IM (55) 2. Placebo (50)	After onset of vomiting	12 h	Janssen-Cilag Int.
Nonhospitalized patients	NA	1. Haloperidol, 2 mg IM (10) 2. Placebo (10)	After onset of vomiting	12 h	Janssen-Cilag Int.
Nonhospitalized patients	NA	1. Haloperidol, 1 mg IM (23) 2. Placebo (21)	After onset of vomiting	12 h	Janssen-Cilag Int.
Nonhospitalized patients	NA	1. Haloperidol, 2 mg IM (31) 2. Placebo (33)	After onset of vomiting	12 h	Janssen-Cilag Int.
Geriatric patients	NA	1. Haloperidol, 1 mg IM (14) 2. Placebo (14)	After onset of vomiting	12 h	Janssen-Cilag Int.

Discussion

Haloperidol is antiemetic at doses that are considerably lower than those used for the treatment of psychosis or the control of agitation. The available evidence from published and unpublished randomized trials suggests that it may not even be worthwhile to increase the dose above 1 or 2 mg to prevent PONV. With these very low doses, the degree of antiemetic efficacy of haloperidol is markedly strong and comparable with many other antiemetic interventions that are used for the prevention and treatment of PONV.††† [7] It may be inferred from the

††† Kazemi-Kjellberg F, Henzi I, Tramèr MR: Treatment of established postoperative nausea and vomiting: A quantitative systematic review. Biomed Central Anesthesiol 2001; 1:2 (PMID: 11734064). Available at: http://www.biomedcentral.com/1471-2253/1/2. Accessed July 12, 2004.

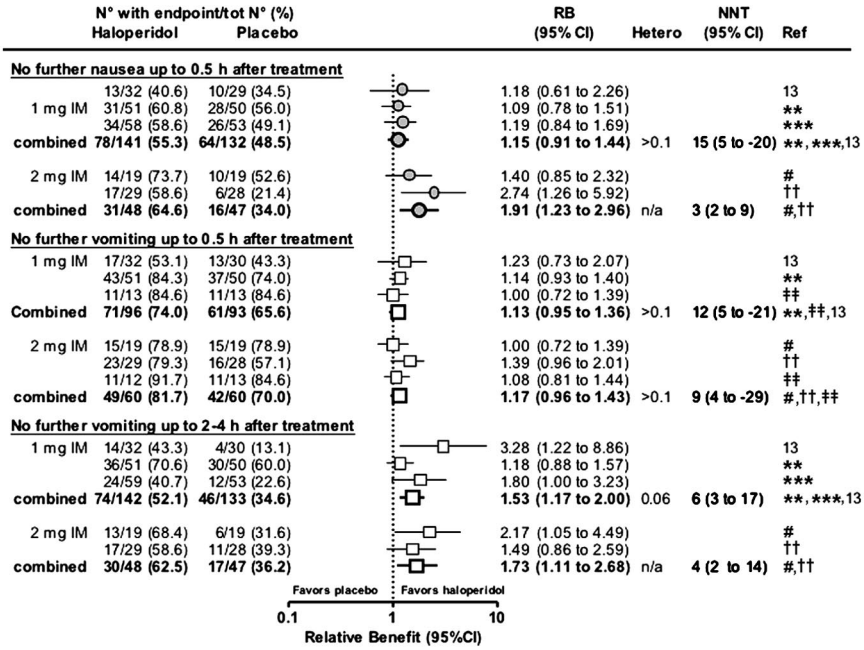

Fig. 3. Treatment of established postoperative nausea and vomiting with parenteral single-dose haloperidol regimens. *Gray circles* = nausea; *white squares* = vomiting. All data are from unpublished reports (symbols #,,††,‡‡,***, see footnotes on page 1456), except Barton *et al.*[13] Bold numbers and symbols represent combined data (meta-analyses). CI = confidence interval; Hetero = heterogeneity; IM = intramuscular; n/a = not applicable (data from only two trials); NNT = number needed to treat (a negative upper limit of the 95% CI indicates a statistically nonsignificant result); RB = relative benefit; Ref = reference.**

4-mg data (the only dose administered by the intramuscular and intravenous routes) that there is little difference between these two routes of administration. There is also strong evidence that low-dose haloperidol is effective for the control of emesis due to various gastrointestinal diseases. For chemotherapy and radiation therapy, however, the evidence was less clear. In the chemotherapy setting, several haloperidol regimens were tested against different control regimens, placebo controls were lacking, endpoint reporting was inconsistent, and only a limited amount of clinically homogenous efficacy data could be extracted from the trials. No meaningful conclusion could be drawn. In the radiation therapy setting, valid data that supported the antiemetic efficacy of haloperidol came from one small trial.

Until recently, droperidol was perhaps the most widely used dopamine antagonist for the control of nausea and vomiting. However, droperidol has been suggested to be cardiotoxic.[25] The US Food and Drug Administration has changed the labeling requirements for droperidol injections, now including a Black Box Warning.‡‡‡ This severe restriction included both chronic high-dose droperidol regimens that are used to treat psychosis and severe agitation and single, low-dose administrations for the control of emesis. Haloperidol is a butyrophenone similar to droperidol, and these drugs have the potential to prolong the QT interval, with the risk of subsequent torsades de pointes and sudden cardiac death.[26] Observational studies have suggested that high-dose haloperidol may cause lethal cardiac arrhythmias in psychiatric patients.[27,28] High-dose haloperidol has also been suggested to cause QT prolongation in critically ill patients in the intensive care unit[29,30] or postoperatively.[31] In these uncontrolled studies, haloperidol was administered in antipsychotic doses that often exceeded several hundred milligrams per day. The QT-prolonging effect of antipsychotic drugs is dose dependent.[27,28] There is evidence from this systematic review that for the control of emesis, haloperidol (similar to droperidol[32]) may be useful in much lower doses than for the control of psychosis or agitation. In contrast to droperidol, haloperidol use has never been restricted. This raises the question of whether haloperidol is any more or less cardiotoxic than droperidol and whether low-dose haloperidol could replace low-dose droperidol as an antiemetic. In this meta-analysis, 1,397 patients received different regimens of haloperidol, and there were no reports of cardiac arrhythmias. This result must be interpreted cautiously. The number of analyzed patients may have been insufficient to detect rare adverse events. However, when the antiemetic efficacy of low-dose droperidol was reviewed systematically, there were no reports of cardiac toxicity in 5,351 patients.[32] If these randomized haloperidol trials reported correctly on the absence of arrhythmias, we may be 95% confident that with low-dose (0.25–5 mg) intravenous haloperidol, cardiac arrhythmia does not occur more often than in 0.21%.[33] We cannot exclude that in some patients QT prolongation did occur but was not diagnosed. We cannot exclude that episodes of torsades de pointes and even cardiac arrest occurred but were not reported. Most trials were relatively old, and monitoring of cardiac function may not have been an important feature at that time. There was no intention to include data from observational studies on possible cardiac toxicity of haloperidol in our analyses. Based on the available evidence from randomized controlled trials, it is impossible to

‡‡‡ FDA strengthens warning for droperidol. Available at: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01123.html. Accessed July 12, 2004.

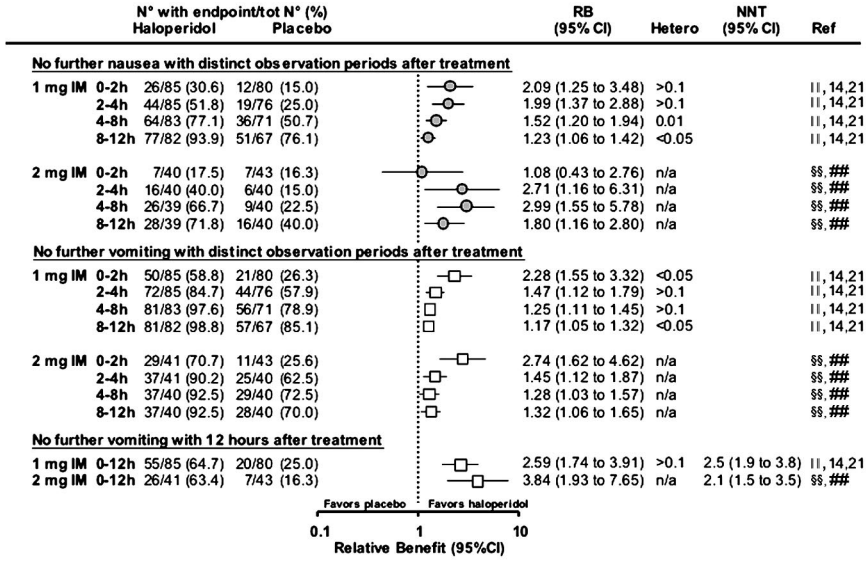

Fig. 4. Treatment of nausea and vomiting related to gastrointestinal-related diseases with single-dose haloperidol regimens. All results are from meta-analyses that each combined data from two or three trials. For explanation of symbols §§,‖ ‖,##, see footnotes on page 1456. Details of the trial are available.§§§ *Gray circles* = nausea; *white squares* = vomiting. Numbers needed to treat (NNTs) are shown only when control event rates (incidence of nausea or vomiting in controls) were similar. CI = confidence interval; Hetero = heterogeneity; IM = intramuscular; n/a = not applicable (data from only two trials); RB = relative benefit; Ref = reference.

conclude whether there is any more or less risk of cardiac arrhythmias with low-dose haloperidol *versus* low-dose droperidol. Finally, it must be emphasized that many drugs that are used in anesthesia may prolong the QT interval, *e.g.*, thiopental, isoflurane, sevoflurane, pancuronium.[34] Also, not all QT prolongation is dangerous and leads to torsades de pointes arrhythmia. It is likely that other risk factors, such as electrolyte abnormalities or metabolic conditions, must be simultaneously present to provoke cardiac arrhythmia.

A further concern with butyrophenones is their potential to cause neurologic adverse effects. The trials analyzed here provided some evidence that haloperidol, even at low, antiemetic doses, may cause sedation and, in rare instances, extrapyramidal symptoms. One in four patients is sedated with a single dose of 5 mg haloperidol. This suggests that 5 mg is too high a dose to control nausea and vomiting in, for example, patients undergoing ambulatory surgery. However, efficacy data also suggested that it was not worthwhile to increase doses above 2 mg to achieve a relevant antiemetic effect. In two trials, 806 adults received a single intravenous dose of 0.25–5 mg haloperidol, and, according to the original authors interpretation, one had symptoms that were suggestive of an extrapyramidal reaction. Extrapyramidal reactions with low-dose droperidol were reported only in children.[32] In the chemotherapy setting, where much higher and repetitive doses of haloperidol were used, the risk of extrapyramidal symptoms was increased, but these symptoms were also reported with metoclopramide and prochlorperazine. We did not find any association of other adverse reactions with administration of haloperidol.

Eight trials (35% of all trials) with data from 474 patients (19% of all patients) were unpublished. All were phase II and III trials that originated from the manufacturer's registration program. Inclusion of this unusually large number of unpublished data provided a methodologic challenge. Advocates of the inclusion of unpublished material into meta-analyses argue that unpublished trials are more likely to report on negative results, and therefore, every effort should be undertaken to unearth unpublished data to challenge publication bias. We were unable to confirm this assumption because all unpublished trials reported on positive results. Data on the treatment of established PONV came from five unpublished trials that included 346 patients and from one published trial that included 62 patients. Without these unpublished valid data, we would not have much knowledge about the role of haloperidol in the treatment of nausea and vomiting in surgical patients. However, it is of note that several decades passed until these data were eventually made accessible. Critics of the inclusion of unpublished material into meta-analyses may argue that these data have not undergone peer review and that their scientific validity remains unproven. For the purpose of our analyses, all data, whether published or unpublished, underwent the same rigorous process of critical appraisal. Several unpublished (and published) studies did not satisfy our high methodologic standards and were therefore excluded from the analyses.

Our systematic review has several limitations, and they are related to weaknesses in the original studies. First, trial design was sometimes unsatisfactory. Data on repetitive dose regimens were sparse. These would be especially important in settings where patients are likely to need prolonged antiemetic therapy such as in palliative care. Second, most trials were of limited methodologic quality. They did not specify the method of randomization or of concealment of treatment allocation, and only a few reported on the method of blinding. Often, it was

§§§ Details of the trial are available at http://www.hcuge.ch/anesthesia/data.

unclear whether this was due to inadequate trial design or inappropriate data reporting. Most trials were conducted in the early 1980s, when recommendations for reporting of study results did not yet exist.[35] Finally, most studies were of limited size, and observation periods were too short to identify with confidence adverse effects with single low-dose haloperidol regimens.

This systematic review may serve as an evidence base to define a rational research agenda. If haloperidol is to be considered as a true alternative to droperidol, several issues must be addressed. There were no direct comparisons between low-dose droperidol and low-dose haloperidol, but we may assume from indirect comparisons[32] that both drugs exert approximately the same degree of antiemetic efficacy. We need to know whether haloperidol exerts the same synergistic effect with 5-hydroxytryptamine$_3$ receptor antagonists as droperidol does.[36] Also, because the control of opioid-induced nausea is a particular concern in surgical patients[37] and because droperidol, when given concomitantly with morphine in a patient-controlled analgesia-pump, has shown consistent antinausea efficacy,[38] it may be worthwhile to test haloperidol for the control of opioid-induced nausea. Finally, there was a lack of valid data on the antiemetic efficacy of haloperidol in other settings where emesis is a problem, and there was a complete lack of relevant pediatric studies. Direct data from children are needed to avoid extrapolation of results from adults to children.

In conclusion, data from systematically searched, valid, published and unpublished randomized trials suggest that haloperidol is antiemetic at doses much lower than those used to treat psychiatric disorders. For the prevention and treatment of PONV and for the control of nausea and vomiting due to gastrointestinal diseases, parenteral single doses between 1 and 2 mg are efficacious, with minimal toxicity. Extrapyramidal symptoms are rare, there is no sedation, and cardiac arrhythmias have not been reported. Haloperidol is an inexpensive drug compared with the new 5-hydroxytryptamine$_3$ antagonists. Haloperidol may be an interesting alternative to more expensive antiemetic drugs, especially in healthcare systems with scarce resources.

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