Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting

[L'halopéridol est aussi efficace que l'ondansétron dans la prévention des nausées et vomissements postopératoires]

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Purpose: Recent warnings regarding the safety of droperidol have limited use of this drug as an antiemetic. Haloperidol, a butyrophenone derivative similar to droperidol, has not been rigorously evaluated as an antiemetic. The aim of this study was to compare the prophylactic antiemetic efficacy of haloperidol *vs* ondansetron for the prevention of postoperative nausea and vomiting (PONV) after general anesthesia.

Methods: Ninety non-smoking female patients were eligible to participate in this randomized double-blinded study. Approximately 30 min before the end of surgery, patients were randomly assigned to receive either haloperidol 2 mg *iv*, or ondansetron 4 mg *iv*, respectively. The incidence of PONV, average pain and sedation scores, recovery times, and changes of the rate-corrected QT (QTc) interval were observed postoperatively.

Results: The proportion of patients who experienced PONV in the first 24 hr was similar in the two groups (28% and 26% for haloperidol and ondansetron groups, respectively). The incidence of PONV was significantly less in both groups than predicted according to the patients' underlying risks (53% for the haloperidol group, $P = 0.016$; 51% for the ondansetron group, $P = 0.015$). Pain scores, sedation scores, and recovery times were similar in the two groups, and no prolongation of the QTc interval was observed in either group.

Conclusions: Haloperidol 2 mg *iv* given 30 min before the end of surgery is effective in preventing PONV, with efficacy comparable to ondansetron 4 mg *iv* for the first 24 hr after general anesthesia.

Objectif : De récentes mises en garde quant à l'innocuité du dropéridol ont limité l'utilisation de ce médicament comme antiémétique. L'halopéridol, un dérivé du butyrophénone similaire au dropéridol, n'a pas été évalué rigoureusement en tant qu'antiémétique. L'objectif de cette étude était de comparer l'efficacité antiémétique prophylactique de l'halopéridol vs l'ondansétron dans la prévention des nausées et vomissements postopératoires (PONV) après une anesthésie générale.

Méthode : Quatre-vingt-dix patientes non fumeuses satisfaisaient aux conditions de participation à cette étude randomisée à double insu. Environ 30 min avant la fin de la chirurgie, les patientes ont été randomisées à recevoir respectivement soit 2 mg iv d'halopéridol, soit 4 mg iv d'ondansétron. Après l'opération, l'incidence de PONV, les moyennes des scores de douleur et de sédation, les temps de rétablissement et les changements de l'intervalle QT à taux corrigé (QTc) ont été observés.

Résultats : La proportion de patientes souffrant de PONV dans les premières 24 h était semblable dans les deux groupes (28 % et 26 % pour les groupes halopéridol et ondansétron respectivement). L'incidence de PONV était significativement plus basse que prévue dans les deux groupes en considérant les risques préopératoires sous-jacents des patientes (53 % pour le groupe halopéridol, $P = 0,016$; 51 % pour le groupe ondansétron, $P = 0,015$). Les scores de douleur et de sédation, ainsi que les temps de rétablissement étaient similaires dans les deux groupes, et aucune prolongation de l'intervalle QTc n'a été observée dans l'un ou l'autre groupe.

Conclusion : L'halopéridol 2 mg iv administré 30 min avant la fin de la chirurgie est efficace dans la prévention de PONV, et présente une efficacité comparable à l'ondansétron 4 mg iv durant les premières 24 h après une anesthésie générale.

POSTOPERATIVE nausea and vomiting (PONV) are among the most unpleasant experiences following surgery performed under general anesthesia.[1] Droperidol, a butyrophenone antiemetic, was commonly used as an antiemetic for PONV.[2] However, on December 5, 2001, the U.S. Food and Drug Administration issued a "black box warning" suggesting that unexpected cardiovascular death could occur at normal therapeutic doses of droperidol.[3] Of particular concern was the possibility of QT prolongation leading to torsades de pointes.[4] Despite the argument of many clinicians that the warning was inappropriate, this announcement led to a marked withdrawal of droperidol from the market and search for a cost-effective alternative.

Haloperidol, a major tranquilizer (antipsychotic, neuroleptic) which has a chemical structure similar to that of droperidol, has been considered a possible substitute for droperidol.[5] Haloperidol has been used commonly for treating schizophrenia and related psychoses.[6] It has also been used in the treatment of chemotherapy-, radiotherapy-, and opioid-related nausea and vomiting.[6] Recently, a meta-analysis reported that haloperidol was effective in the prevention of PONV,[5] however, the supporting evidence was dated (1962 to 1972) and incomplete. Therefore, we conducted a double-blinded, randomized clinical trial to test the prophylactic antiemetic efficacy of haloperidol in comparison with ondansetron, a well established antiemetic agent, for the prevention of PONV after general anesthesia.

Methods

With institutional approval and the written informed consent of the patients, 90 ASA grade I and II female patients scheduled for gynecologic, urologic, thyroid, breast, or plastic surgeries were enrolled in this randomized, double-blinded study. Excluded were patients with obvious airway problems, obesity (body mass index > 25 kg·m^{-2}), those who were pregnant, and those who had a chronic cough, psychiatric illness, or clinically significant major organ disease. Finally, anyone who had consumed an antiemetic medication within 24 hr prior to commencing the study was excluded.

In the preoperative holding area, patients were allocated randomly to one of the two groups (n = 45 for each group) using a computer-generated random number table. Approximately 30 min before the end of surgery, patients in the haloperidol group received haloperidol 2 mg $iv;$ patients in the ondansetron group received ondansetron 4 mg iv. Study drugs were prepared to equal volumes of 2 mL in identical labelled syringes by personnel blinded to the study protocol, and were administered in a double-blind fashion.

Anesthesia was standardized. Induction of anesthesia was achieved with fentanyl 2 μg·kg^{-1} iv and propofol 3 mg·kg^{-1} iv and tracheal intubation was facilitated by the administration of rocuronium 0.8 mg·kg^{-1} iv. Anesthesia was maintained with sevoflurane 2–5% (inspired concentrations) in oxygen. Ventilation was mechanically controlled, and adjusted to maintain end-tidal CO_2 values between 35 – 45 mmHg throughout surgery. Additional rocuronium was administered as required. All patients received ketorolac 30 mg iv before the end of surgery to control postoperative pain. For reversal of residual neuromuscular block, a combination of glycopyrrolate 0.6 mg and neostigmine 3 mg was administered intravenously and the trachea was extubated when the patient was awake. No opioids were administered during the operation.

In accordance with previously published guidelines on the conduct of PONV studies, three postoperative time periods were evaluated: the 0–2, 2–24, and 0–24 hr following anesthesia.[7] For the first two hours after anesthesia in the postanesthesia care unit (PACU), nausea score, episodes of vomiting, the presence or absence of nausea and vomiting, levels of pain and sedation experienced by patients, and adverse effects such as cardiac dysrhythmias, headache and extrapyramidal effects were recorded by a trained investigator without knowledge of which treatment the patients had received. The intensity of each nausea episode was graded as mild (discomfort noticed but no disruption of anticipated normal activity), moderate (discomfort sufficient to affect anticipated normal activity), or severe (inability to perform normal activity). A vomiting episode was defined as vomiting/retching events occurring in rapid sequence within a one-minute period. If the interval between two bouts of emesis exceeded one minute, they were considered separate episodes. If there were more than four episodes within the 24-hr observation period, the vomiting was considered severe.[8] The rescue medication (metoclopramide 25 mg iv) could be administered to any patient who experienced an episode of moderate or severe nausea, an episode of vomiting, or who requested rescue antiemetic medication. Twenty-four hours following discharge from the PACU, the cumulative incidence of nausea or/and vomiting and the rescue antiemetic utilization were recorded.

Postoperative pain intensity was rated by the patients using a 10-cm visual analogue scale (VAS), with 0 symbolizing no pain and 10 the worst pain imaginable. When patients complained of excessive

TABLE I Patient characteristics and variables related to PONV

Group	Haloperidol (n = 43)	Ondansetron (n = 43)	P
Age (yr); mean ± SD	43 ± 13	40 ± 13	0.502
Weight (kg); mean ± SD	58 ± 5	56 ± 5	0.228
History of PONV *n* (%)	8 (19)	10 (23)	0.596
History of motion sickness *n* (%)	20 (47)	17 (40)	0.514
Duration of anesthesia (min); mean ± SD	154 ± 58	138 ± 73	0.283
Surgical type			
Gynecologic *n* (%)	10 (23)	12 (28)	0.621
Urologic *n* (%)	12 (28)	8 (19)	0.307
Breast *n* (%)	à8 (19)	6 (14)	0.559
Thyroid *n* (%)	8 (19)	10 (23)	0.596
Plastic *n* (%)	5 (12)	7 (16)	0.534
Risk factors; mean ± SD	2.7 ± 0.5	2.6 ± 0.5	0.323
Risk of PONV (%); mean ± SD	54.7 ± 9.5	51.9 ± 9.9	0.503
Postoperative pain scores (VAS)			
0–2 hr; mean ± SD	3.2 ± 0.9	3.5 ± 0.9	0.113
2–24 hr; mean ± SD	2.4 ± 0.9	2.5 ± 0.7	0.790

PONV = postoperative nausea and vomiting; risk of PONV = estimated risk of PONV according to a validated score.[11] VAS = visual analogue scale.

TABLE II Frequency of PONV and requirement for rescue antiemetics

Group	Haloperidol (n = 43)	Ondansetron (n = 43)	P
0–2 hr			
Nausea only *n* (%)	6 (14)	9 (21)	0.394
Vomiting *n* (%)	5 (12)	1 (2)	0.090
Total PONV *n* (%)	11 (26)	10 (23)	0.802
Rescue antiemetics *n* (%)	7 (16)	4 (9)	0.333
2–24 hr			
Nausea only *n* (%)	6 (14)	8 (19)	0.559
Vomiting *n* (%)	4 (9)	3 (7)	0.694
Total PONV *n* (%)	10 (23)	11 (26)	0.802
Rescue antiemetics *n* (%)	8 (19)	6 (14)	0.559
0–24 hr			
Nausea only *n* (%)	7 (16)	8 (19)	0.777
Vomiting *n* (%)	5 (12)	3 (7)	0.458
Total PONV *n* (%)	12 (28)	11 (26)	0.808
Rescue antiemetics *n* (%)	10 (23)	8 (19)	0.596

PONV = postoperative nausea and vomiting.

pain and requested analgesia, ketorolac 30 mg *iv* every six hours was given. Sedation was assessed during the first 15, 30, 60, 90 and 120 min in the PACU using the five-point Observer's Assessment of Alertness/ Sedation (OAA/S) scale (where 1 = awake/alert and 5 = deep sleep).[9] Recovery times from discontinuation of anesthesia until opening of the patient's eyes (awakening time), ability to follow commands (e.g., squeezing of the investigator's hand), and orientation to person or place, as well as the time to achieve a modified Aldrete score of 10 were recorded.

A 12-lead electrocardiogram was obtained before the operation. The standard electrocardiographic lead II was continuously monitored at a speed of 25 mm·sec^{-1} and amplification of 0.1 mV·mm^{-1}. Heart rate was calculated from three R-R intervals preceding the measured QT intervals. The QT intervals were measured manually from the onset of the QRS complexes to the end of the T wave and corrected for the patient's heart rate using the formula of Bazett (QTc = $QT/R-R^{0.5}$).[10] The QTc interval was measured ten minutes after administration of the study medication.

Our primary goal was to compare the prophylactic antiemetic efficacy of haloperidol *vs* ondansetron following general anesthesia. For ethical reasons there was no placebo group. Instead, the observed incidences were compared to the predicted incidences based upon Apfel' risk score.[11] The primary efficacy endpoint was the incidence of PONV. The secondary endpoint was the safety of treatment.

Sample size was based upon Apfel' risk score, with an expected incidence of PONV in this study was in the region of 60%.[12] A 50% reduction in the incidence of PONV (from 60% to 30%) in the treatment groups was considered to be clinically relevant. With an α error of 0.05 (two-sided) and a β error of 0.2 (power = 0.8), 43 patients were required in each group. Forty-five patients per group would compensate for potential dropouts. Data were analyzed using Chi-squared analysis and Fisher's exact test (two sided). The 5% level of probability ($P < 0.05$) was taken as significant. Commercial SPSS 10.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results
Ninety patients were screened, and of the 90 patients enrolled in the study, four were later withdrawn for incomplete data collection. The remaining 86 completed the protocol. Patient characteristics, duration of anesthesia, surgical types, the risk factors for PONV,[11] estimated risk of PONV[12] and postoperative pain scores (VAS) at the three different time intervals were similar in the two groups (Table I).

Patients in both groups reported a low incidence of PONV (≤ 30%) within 24 hr postoperatively. No significant difference was found between groups with respect to the following variables: the incidences of nausea, vomiting, total PONV, and use of rescue antiemetics during the periods 0–2, 2–24, and 0–24 hr postoperatively (Table II). In addition, the observed incidences of 24 hr PONV in both groups were significantly less than the predicted incidences (53% for

TABLE III Predicted and observed incidence of postoperative nausea and vomiting

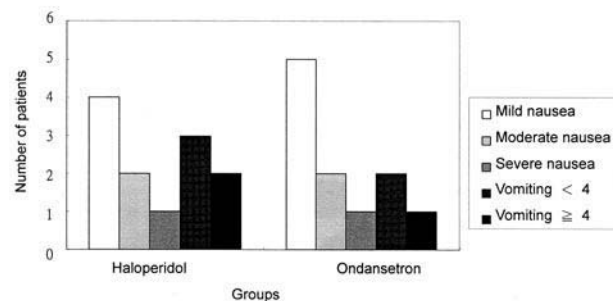| Group	Haloperidol (n = 43)	Ondansetron (n = 43)
Predicted incidence n (%)	23 (53)	22 (51)
Observed incidence n (%)	12 (28)	11 (26)
P	0.016	0.015

FIGURE Number of patients in mild, moderate and severe nausea categories and vomiting episodes during the first 24 hr postoperatively.

TABLE IV Sedation scores and recovery times in the post-anesthesia care unit

Group	Haloperidol (n = 43)	Ondansetron (n = 43)	P
Sedation scores			
At 15 min	2.1 ± 0.6	1.9 ± 0.7	0.199
At 30 min	1.7 ± 0.7	1.6 ± 0.7	0.518
At 60 min	1.3 ± 0.6	1.3 ± 0.5	0.839
At 90 min	1.1 ± 0.4	1.2 ± 0.4	0.564
At 120 min	1.1 ± 0.3	1.1 ± 0.4	0.506
Recovery times (min)			
Awakening	6.6 ± 2.1	6.1 ± 2.2	0.311
Obey to comments	8.5 ± 2.2	7.8 ± 1.9	0.157
Orientation	11.7 ± 2.8	11.3 ± 2.7	0.531
Aldrete 10	20.8 ± 3.3	20.1 ± 3.5	0.339

Data presented as means ± SD.

a prophylactic antiemetic effect on PONV similar to that of ondansetron 4 mg.

For antiemetic purposes, the dose of haloperidol is much lower than that required for use as an antipsychotic.[5] A meta-analysis suggested that haloperidol 0.5 to 4 mg is more efficacious than placebo, but a dose-response could not be established within that dose range.[5] The authors suggested that parental single doses between 1 and 2 mg are efficacious, with minimal toxicity, for the prevention of PONV. In a previous study, haloperidol 2 mg iv was used in patients undergoing orthopedic or endoscopic urologic procedures to prevent intrathecal morphine-related PONV.[14] However, the incidence of PONV was relatively high (55% frequency). In a more recent study, haloperidol 1 mg iv proved to be an effective antiemetic for the early (0–2 hr) prevention of nausea and vomiting.[15] Yet, the overall 24 hr incidence of PONV (41%) did not improve compared with placebo (56% incidence). In these studies, study medications were administered at the start of anesthesia. However, droperidol is most effective when administered at the end of surgery.[16,17] Given that haloperidol is pharmacologically similar to droperidol for the control of nausea and vomiting, and the time to peak plasma concentration from iv injection is only five to 15 min,[6] it seemed logical that haloperidol might be more effective when administered at the end of surgery, thereby producing a more sustained antiemetic effect in the postoperative period. In our study, a higher dose of haloperidol (2 mg) was given 30 min before the anticipated end of surgery, resulting in a 24 hr incidence of PONV that is only 28% for an at-risk population. Whether a higher dose, or administering

haloperidol group, P = 0.016; 51% for ondansetron group, P = 0.015; Table III). Also, the severities of nausea and vomiting were similar between groups (Figure). Mean sedation levels and times to awakening were also similar in the two groups (Table IV). No patient experienced headache or extrapyramidal symptoms.

The QTc intervals before administration of study medications were similar in both groups (haloperidol group: 423.85 ± 19.37 msec, ondansetron group: 423.33 ± 15.76 msec; P = 0.892). Ten minutes after administration of the study medication, the QTc intervals were not different between groups (haloperidol group: 427.38 ± 12.43 msec, ondansetron group: 428.05 ± 15.29 msec; P = 0.827). No patient in either group had a QTc value > 470 msec, and no cardiac dysrhythmias were observed.

Discussion
Ondansetron 4 mg iv administered immediately before the end of surgery has established efficacy in preventing PONV.[13] In this double-blind, randomized clinical trial, we found that haloperidol 2 mg iv administered before the end of surgery produced

haloperidol at the end of surgery will increase the anti-emetic efficacy warrants further investigation.

A concern regarding haloperidol is its potential to cause sedation, and in rare instances, extrapyramidal symptoms.[5] However, sedation is a rare adverse event and many clinicians consider the drug to be non-sedating.[6] In this study, haloperidol 2 mg was associated with a low level of sedation which was similar to that of ondansetron 4 mg. No extrapyramidal symptoms were reported.

Based upon the Apfel' risk score for PONV,[11] all patients had either two or three risk factors (female, non-smoking, history of motion sickness or previous PONV). The expected risks for PONV were 40 to 60%. Since this simplified risk score has been validated, and the study medications are already known to be effective for PONV, it was considered not ethically justified to exclude high risk patients prophylactic treatment against PONV. Therefore, we did not include a placebo group in the study design. Instead, observed incidences were compared to predicted incidences in both treatment groups based upon the risk score. The results showed that 26% of patients in the ondansetron group reported PONV in the first 24 hr postoperatively, which was significantly less than predicted according to the patients' underlying risks (51%). In addition, haloperidol showed similar efficacy to ondansetron for this indication.

Previous prospective investigations have shown that the different incidences of PONV are associated more with individual PONV risk factors and less by the operation itself.[18] Furthermore, study designs that analyze only one type of surgery have already been criticized.[7] Therefore, we used Apfel's simplified risk score instead of selecting patients undergoing just one type of surgery. In our study, the type of surgery and the number of risk factors were found to be similar between groups (Table I). We believe that the study results are directly related to the study medications.

Previous studies have suggested that high dose haloperidol may cause QTc prolongation.[19,20] In a meta-analysis, 1,397 patients received different regimens of haloperidol, however, there were no reports of cardiac dysrhythmias.[5] 5-HT$_3$] are also known to prolong the QTc interval at high dosages.[21] Several cases of cardiac dysrhythmias after administration of ondansetron have been reported.[22,23] In the current study, the QTc interval was not significantly different between groups ten minutes after administration of the study medication, and there was no evidence of any adverse effect on cardiac rhythm. According to sex-related thresholds (QTc > 470 msec in women),[24] no prolonged QTc interval was found in any patient.

The use of ondansetron as a first line antiemetic has been criticized because of its high cost.[25] Our hospital pharmacy's acquisition cost for a 4-mg ampoule of ondansetron is Can $26.9, whereas, a 2-mg of haloperidol is Can $0.41.

In conclusion, the prophylactic *iv* administration of haloperidol 2 mg 30 min before the anticipated end of surgery effectively reduces the incidence of PONV without any adverse effect on cardiac rhythm. Treatment using ondansetron, a relatively more costly 5-HT$_3$ antagonist, did not provide superior benefit compared to haloperidol in the present study.

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