Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind comparison with placebo

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Purpose: *Postoperative nausea and vomiting (PONV) is a distressing adverse effect of general anaesthesia. The aim of the current study was to compare the antiemetic activity of different 5-hydroxytryptamine$_3$ receptor antagonists with that of metoclopramide and placebo.*

Methods: *In a prospective, randomized, double-blind study we have compared the antiemetic activity of the prophylactic administration of ondansetron 4 mg, tropisetron 5 mg and granisetron 3 mg with that of metoclopramide 10 mg and placebo in 132 patients undergoing laparoscopic cholecystectomy. All study drugs and placebo were given as a short iv infusion ten minutes before the induction of anaesthesia. Perioperative anaesthetic care was standardized in all patients. Nausea and vomiting were assessed by direct questioning of the patient at 1, 4, 9, 12, 18 and 24 hr after recovery from anaesthesia. If patients experienced nausea and/or vomiting, rescue antiemetic treatment (metoclopramide 10 mg iv) was administered.*

Results: *For the 24-hr recovery period after surgery, the percentages of emesis-free patients were 65.5%, 52%, 48%, 29.2% and 27.6% in the ondansetron, granisetron, tropisetron, metoclopramide and placebo groups, respectively. Prophylactic antiemetic treatment with ondansetron resulted in a lower incidence ($P = 0.02$) of PONV than with metoclopramide or placebo. The times at which rescue antiemetic was first received were longer ($P < 0.01$) in ondansetron group than in the placebo and metoclopramide groups. There were no statistical differences between ondansetron, tropisetron and granisetron groups.*

Conclusions: *Ondansetron, when given prophylactically resulted in a significantly lower incidence of PONV than metoclopramide and placebo. Metoclopramide was ineffective.*

Key words
ANAESTHESIA: laparoscopic cholecystectomy;
PHARMACOLOGY: ondansetron, tropisetron, granisetron, metoclopramide;
COMPLICATIONS: nausea, vomiting;
VOMITING: antiemetics, postoperative.

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Accepted for publication 26th October, 1995.

Objectif: *Les nausées et vomissements postopératoires (NVP) sont des effets secondaires pénibles de l'anesthésie générale. L'objectif de cette étude était de comparer l'activité antiémétique de différents antagonistes des récepteurs de la 5-hydroxytryptamine avec celle de la métoclopramide et d'un placebo.*

Méthode: *Au cours d'une étude randomisée, prospective et en double aveugle, les auteurs ont comparé l'effet antiémétique procuré par l'administration préventive d'ondanestron 4 mg, de tropisetron 5 mg et de granisetron 3 mg avec celle de la métoclopramide 10 mg et d'un placebo chez 132 patients*

opérés pour une cholécystectomie par laparoscopie. Tous les médicaments à l'étude de même que le placebo ont été administrés par perfusion iv 10 min avant l'induction. La prise en charge anesthésique périopératoire a été standardisée chez tous les sujets. Les nausées et vomissements ont été évalués par l'interrogatoire personnel du patient à 1, 4, 9, 12, 18 et 24 h après le réveil. Lorsque les patients avaient des nausées et/ou des vomissements, un antiémétique de sauvetage (métoclopramide 10 mg iv) était administré.

***Résultats**: Pour une période de 24 h après l'intervention, le pourcentage de patients sans complication émétique a été respectivement de 65,5%, 52%, 48%, 29,2% et 27,6% pour le groupe ondansetron, granisetron, tropisetron, métoclopramide et placebo. L'ondansetron administré préventivement a produit une incidence plus faible (P = 0,02) de NVP que la métoclopramide et le placebo. Le délai précédant l'administration de l'antiémétique de sauvetage a été plus long (P < 0,01) dans le groupe ondansetron que dans les groupes métoclopramide et placebo. Il n'y a eu aune différence entre les groupes ondanestron, tropisetron et granisetron.*

***Conclusion**: L'ondanestron administré préventivement a produit une incidence plus faible de NVP que la métoclopramide et le placebo. La métoclopramide n'a pas été efficace.*

Postoperative nausea and vomiting (PONV) are among the most common and distressing symptoms occurring after surgery.[1] Postoperative patients are willing to be more sedated and to experience more pain, if only they are spared the psychological and physical distress of nausea and vomiting.[2] It is believed that the frequency of the emetic symptoms (nausea and vomiting) has changed little in the past 30 yr.[3]

Laparoscopic cholecystectomy has emerged as a popular alternative to traditional laparotomy and cholecystectomy in the management of cholelithiasis.[4] Taylor *et al.* reported that postoperative antiemetic therapy was needed in 53% of patients after laparoscopic cholecystectomy.[5]

Ondansetron, tropisetron and granisetron are selective 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonists that have been used for the treatment of PONV.[6–8] However, no direct comparison has been published on the efficacy of the aforementioned serotonin antagonists. We have conducted this prospective, randomized, double-blind study to compare the antiemetic activity of the prophylactic administration of ondansetron, tropisetron and granisetron with that of metoclopramide and placebo in patients undergoing laparoscopic cholecystectomy.

Methods

After obtaining informed consent and approval from the local Ethics Committee, we studied 132 ASA group I or II patients of both sexes, aged 21–68 (mean 37.4 [10.6 SD]) yr and weighing 40–101 (mean 72.5 [12.9]) kg. All patients were undergoing elective laparoscopic cholecystectomy. We excluded patients who were receiving drugs known to have antiemetic effects (such as tricyclic antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids and trimethobenzamides). We also excluded patients who had experienced nausea or vomiting or who had taken antiemetic treatment in the 48 hr before surgery. No premedication was given and patients were fasted from midnight before surgery.

In the operating room, the ECG, haemoglobin oxygen saturation by pulse oximetry, and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C. Neuromuscular function was monitored by a peripheral nerve stimulator.

Before induction of anaesthesia and after the establishment of venous access, patients were randomized to receive either ondansetron 4 mg, tropisetron 5 mg, granisetron 3 mg, metoclopramide 10 mg or placebo (normal saline). All study drugs and placebo were diluted by a pharmacist to a fixed volume of 50 ml and marked only with a coded label to maintain the double-blind nature of the study and were administered intravenously over ten minutes. Thereafter, anaesthesia was induced in all patients with fentanyl 2 $\mu g \cdot kg^{-1}$, thiopentone 5 $mg \cdot kg^{-1}$ and atracurium 0.5 $mg \cdot kg^{-1}$. After tracheal intubation, anaesthesia was maintained with 70% nitrous oxide in oxygen and isoflurane (0.5–1.2%). Additional fentanyl was administered as needed to maintain haemodynamic stability. After intubation the concentrations of the nitrous oxide, oxygen, carbon dioxide and isoflurane were determined continuously by a multiple-gas anaesthesia monitor (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia ($P_{ET}CO_2$ 35–40 mmHg). After tracheal intubation, all patients had an orogastric tube placed to ensure baseline emptying of the stomach of air and gastric contents. All orogastric tubes were removed at the end of surgery and before tracheal extubation.

Abdominal insufflation for the laparoscopic procedure was accomplished with carbon dioxide. During the operation, muscle relaxation was provided as needed by intermittent injection of atracurium. At the end of surgery, residual neuromuscular block was antagonized by neostigmine 0.05 $mg \cdot kg^{-1}$ and atropine 0.02 $mg \cdot kg^{-1}$.

All observations were by one anaesthetist who had been instructed in the study design and score system and

TABLE I Demographic data.

	Ondansetron (4 mg)	*Tropisetron (5 mg)*	*Granisetron (3 mg)*	*Metoclopramide (10 mg)*	*Placebo (NaCl 0.9%)*
n	29	25	25	24	29
Age (yr)	41.3 ± 13.1 (22–65)	39.2 ± 8.4 (27–68)	36.9 ± 8.9 (25–56)	35.2 ± 10.6 (21–58)	34.0 ±8.6 (22–55)
Weight (kg)	72.2 ± 12.9 (40–90)	76.8 ± 13.4 (48–97)	72.4 ± 12.2 (45–98)	71.3 ± 11.9 (45–95)	69.9 ± 13.5 (43–101)
Sex (M/F)	6/23	5/20	6/19	3/21	4/25
Duration of anaesthesia (min)	128.3 ± 42 (70–260)	113.4 ± 29.9 (60–180)	112.4 ± 36.5 (60–190)	126.5 ± 36.6 (60–180)	129.5 ± 34.5 (80–210)
Intraoperative fentanyl (μg)	189.7 ± 61.4 (100–400)	193 ± 60.2 (100–375)	162 ± 38.9 (100–250)	219.8 ± 73.3 (100–400)	195.7 ± 69.5 (100–400)

Values are mean ± SD (range).

who was unaware of the patients' group assignments. Nausea and vomiting were assessed by direct questioning of the patient at 1, 4, 9, 12, 18 and 24 hr after recovery from anaesthesia, defined as the first response to spoken command. Retching was not assessed separately. If patients experienced nausea and/or vomiting, rescue antiemetic treatment (metoclopramide 10 mg *iv*) was administered. Patients who received rescue antiemetics were classified as treatment failures and considered to have experienced both nausea and vomiting. Verbal analogue scores, on a scale of 0–10 (none to most severe) for pain intensity were obtained postoperatively at the aforementioned times. Meperidine 50 mg *im* was administered for postoperative analgesia whenever pain score was ≥5. Times of oral intake and ambulation were also noted.

Data Processing and Statistical Analyses

All statistical analyses were carried out using BMDP statistical package, release 7.01 (University of California Press, Berkeley, California, 1994). The times at which rescue antiemetic treatment (metoclopramide 10 mg *iv*) was administered were treated as being analogous to survival data. "Survival" curves were plotted to indicate the proportion of patients in each group who had received no rescue antiemetic by a given time after operation. The times at which rescue antiemetic were first received for the five groups were compared using four nonparametric linear rank tests: The Mantel-Cox (log-rank), Tarone-Ware, Breslow, and Peto-Prentice statistics. These tests compare the observed rate at which patients needed rescue antiemetic with the rate that might be expected if prophylactic administration of ondansetron, tropisetron, granisetron, metoclopramide and placebo were equally effective.

Factors measured in this study that were considered to have a possible effect on the proportion of patients experiencing PONV were also examined by a stepwise regression (maximum partial likelihood ratio) based on a stratified Cox proportional hazards model (using BMDP 2L programme). Stratification was based on the type of prophylactic antiemetic treatment given. With maximum partial likelihood ratio method, covariates are entered or removed on the basis of significance probabilities calculated from a large sample partial likelihood ratio test. The preoperative variables included in the model were: patient age, body weight, smoking, concentration of volatile anaesthetic (isoflurane), doses of fentanyl given intraoperatively, duration of anaesthesia, time from induction to recovery from anaesthesia. In addition, the postoperative data collected at 1, 4, 9, 12, 18 and 24 hr after recovery from anaesthesia and included in the analysis were: doses of rescue antiemetic given (metoclopramide), postoperative pain score, doses of meperidine given for postoperative analgesia, ambulation and timing of oral intake. Where appropriate, data were also analyzed by Kruskal-Wallis nonparametric analysis of variance and by Chi-square statistic. For all statistical comparisons, differences were considered significant when P value <0.05.

Results

Demographic data are shown in Table I. There were no differences among the groups in age, sex, weight, doses of intraoperative fentanyl, duration of anaesthesia and recovery times, incidence and severity of pain, doses of

TABLE II Incidence of postoperative nausea and vomiting (PONV)

	Ondansetron (4 mg)	*Tropisetron (5 mg)*	*Granisetron (3 mg)*	*Metoclopramide (10 mg)*	*Placebo (NaCl 0.9%)*
n	29	25	25	24	29
Patients with PONV (%)	10 (34.5%)	13 (52%)	12 (48%)	17 (70.8%)	21 (72.4%)

The incidence of no PONV was lower in the ondansetron group as compared with metoclopramide and placebo groups ($P = 0.02$). There were no differences among ondansetron, tropisetron and granisetron groups.

meperidine administered for postoperative analgesia, times of postoperative ambulation or oral intake. The incidence of PONV is shown in Table II. Prophylactic antiemetic treatment with ondansetron resulted in a lower incidence ($P = 0.02$) of PONV than with metoclopramide or placebo. However, no differences in the incidence of PONV were observed between tropisetron, granisetron, metoclopramide or placebo groups. Likewise, there were no differences between ondansetron, tropisetron and granisetron groups. Stratified stepwise analysis disclosed that none of the preoperative or postoperative variables included in the model had an effect on the incidence of PONV. Therefore, the difference observed among the groups was due to the type of antiemetic therapy used.

The times at which rescue antiemetic (metoclopramide) was first received are displayed in the form of survival curves in the Figure. The curves indicate the proportion of patients who had no PONV by a given elapsed time since recovery from anaesthesia. Recovery to first rescue antiemetic times were longer ($P < 0.01$) in the ondansetron group than in the placebo or metoclopramide groups. There was no difference between the tropisetron and granisetron groups. Similarly, there was no difference among the ondansetron, granisetron and tropisetron groups.

No major adverse effects were observed in the study groups.

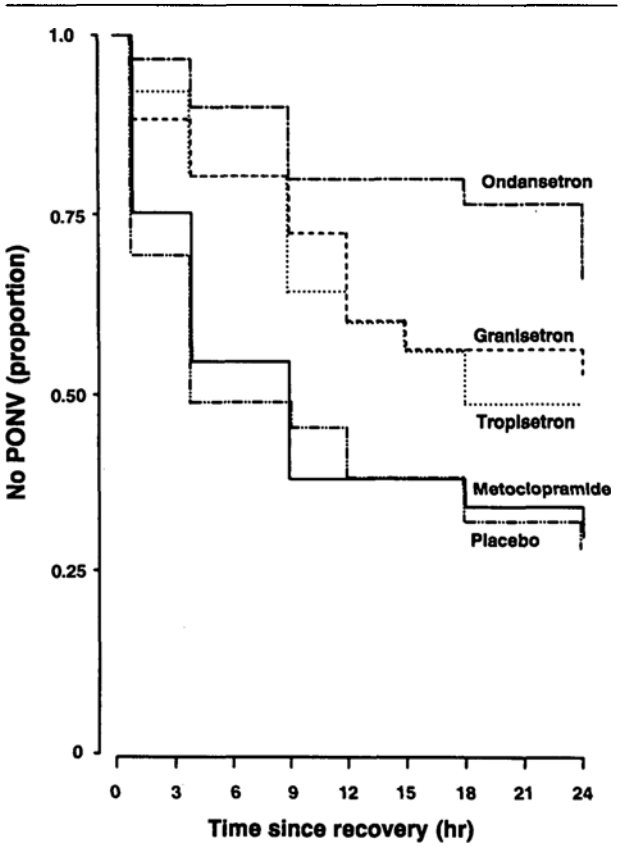

FIGURE "Survival" curves for the ondansetron 4 mg, tropisetron 5 mg, granisetron 3 mg, metoclopramide 10 mg or placebo (normal saline) groups. Proportion of patients in each group who had no PONV and had not required any rescue antiemetic therapy after recovery from anaesthesia. The times at which rescue antiemetic was first received were longer ($P < 0.01$) in ondansetron group than in the placebo and metoclopramide groups. There was no difference among the ondansetron, granisetron and tropisetron groups.

Discussion

The results of this study demonstrated that prophylactic administration of ondansetron 4 mg reduced the incidence of PONV in patients undergoing laparoscopic cholecystectomy by approximately 50% compared with metoclopramide and placebo. No differences in the incidence of PONV could be demonstrated among ondansetron, granisetron and tropisetron groups. Although the incidence of PONV after tropisetron 5 mg and granisetron 3 mg was less than that seen in the metoclopramide and placebo groups (Table II), this difference was not statistically significant.

Orkin[2] found that the patient's preference for postoperative recovery was based primarily on whether emetic symptoms were present or not. Furthermore, PONV is a leading cause of delayed discharge or hospital readmission after ambulatory surgical procedures.[9] In this study, nausea and vomiting were combined into a single outcome parameter. Rescue antiemetic treatment (metoclopramide 10 mg *iv*) was administered if the patient experienced nausea and/or vomiting. Patients who received

rescue antiemetics were classified as treatment failures and considered to have experienced both nausea and vomiting.

The true incidence of PONV after laparoscopic cholecystectomy has not been reported before. In a study that was not designed primarily to address the incidence of PONV after laparoscopic cholecystectomy, Taylor *et al.*[5] reported that the requirement for postoperative antiemetic therapy was 53%. They, however, did not indicate the criteria for this therapy and whether it was given to all patients complaining of PONV or not. Our baseline incidence of PONV (72%) in the placebo group is consistent with the incidence reported in previous studies for patients who underwent other surgical procedures.[7,10–12] Zomers *et al.*[7] noted that nausea and vomiting occurred in 88% and 59%, respectively, in the placebo-treated patients. Similarly, Larijani *et al.*[12] reported that 72% of their patient in the placebo group suffered from PONV. In addition, Haigh *et al.*[10] have shown that the adjusted probabilities of experiencing nausea and vomiting in the placebo group were 0.75 and 0.61, respectively.

The aetiology of PONV is multifactorial, unlike chemotherapy-induced nausea and vomiting, so one cannot expect the same efficacy of antiemetics as that seen in chemotherapy. There are many factors both related and unrelated to anaesthesia that may influence PONV such as age,[10,13,14] sex,[1,14] body weight,[3] type and duration of operation,[10] type of induction,[15] maintenance[10] and neuromuscular blocking drug used.[10] In this study we standardized many of these factors and there were no differences in these factors among the groups studied.

The doses of granisetron (3 mg) and tropisetron (5 mg) used in this study were chosen because they had been proved to be optimal for treatment of nausea and vomiting induced by various highly emetic chemotherapy regimens[16,17] and for prevention of PONV.[7,8,18]

Recent animal data showed that granisetron was less effective in preventing morphine-induced emesis than the less selective 5-HT_3 antagonist, ondansetron.[19] In this study, the incidence of PONV after granisetron 3 mg was not different from that seen after metoclopramide or placebo (Table II). Fujii *et al.*[8] reported that the PONV scores during 0–3 hr showed no difference between metoclopramide (10 mg) and granisetron (3 mg) groups. They noted, however, differences during 3–24 hr.[8] Mikawa *et al.*[18] noted that the number of emesis-free patients undergoing gynaecologic surgery was larger in the granisetron than in the control group (83%, 78% and 20% of patients receiving granisetron 20 $\mu g \cdot kg^{-1}$ (1.1 mg) and 40 $\mu g \cdot kg^{-1}$ (2.2 mg), and saline, respectively). This is to be contrasted with 52% and 27.6% of patients receiving granisetron 3 mg (or approximately 42 $\mu g \cdot kg^{-1}$) and saline, respectively, in this study. This difference could be attributed to the differences in the study design and population of patients studied.

Ondansetron has been shown to be more effective than placebo or metoclopramide for prevention of PONV in both paediatrics and adults population.[6,10–12,20,21] Malins *et al.*[21] reported that PONV occurred in 26% of patients who received ondansetron, 42% of those who received metoclopramide and 50% of those given placebo. In accordance with our results, Desilva *et al.*[22] noted that metoclopramide was ineffective in the prevention of PONV.

In patients undergoing gynaecological surgery, Zomers *et al.*[7] reported that vomiting occurred in 26% of tropisetron (5 mg)-treated patients compared with 59% of placebo-treated patients ($P = 0.006$). The incidence of nausea was, respectively, 69% and 88% ($P = 0.05$).[7] In this study, the incidence of PONV in tropisetron (5 mg)-treated patients was 52% (P = NS).

In conclusion, we found that the incidence of PONV in placebo-treated patients after laparoscopic cholecystectomy was 72.4%. Prophylactic administration of ondansetron 4 mg decreased this incidence to 34.5% ($P = 0.02$). In addition, the times at which rescue antiemetic was first received were longer ($P < 0.01$) in the ondansetron group than in the placebo and metoclopramide groups. Metoclopramide was ineffective. No differences in the incidence of PONV could be demonstrated among ondansetron, granisetron and tropisetron groups.

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