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Additive anti-emetic efficacy of prophylactic ondansetron with droperidol in out-patient gynecological laparoscopy

Purpose: To determine the efficacy of ondansetron and droperidol, alone and in combination, administered for prophylaxis of postoperative nausea and vomiting (PONV) in women undergoing general anesthesia for out-patient gynecological laparoscopy.

Methods: Following Institutional Ethics Board approval and patient consent, 160 female out-patients scheduled for laparoscopy were randomly allotted in a double-blind fashion to receive: i) saline (placebo), ii) 4 mg ondansetron, iii) 1.25 mg droperidol, or iv) 4 mg ondansetron and 1.25 mg droperidol combination intravenously on induction. Following a standardized general anesthesia, patients were interviewed and assessed for PONV at various times.

Results: During the first 24 hr after surgery, the incidence of PONV in the placebo group was 71%. This was reduced to 61% with droperidol alone ($P = 0.334$), to 46% with ondansetron alone ($P = 0.027$), and to 23% with the combination group ($P < 0.001$). A statistically significant difference was observed between combination and droperidol ($P < 0.001$) and between combination and ondansetron ($P = 0.036$). There were fewer requests for rescue medication from the combination group (7.7%) than from the ondansetron and placebo groups.

Conclusion: The results of this study suggest that the combination of 4 mg ondansetron and 1.25 mg droperidol is more efficacious as a prophylactic anti-emetic than either agent alone during the 24 hr post-surgery. This additive effect may be due to the different mechanisms of action of ondansetron and droperidol.

Objectif: Déterminer l'efficacité de l'ondansétron et du dropéridol, seuls ou combinés, administrés comme prophylaxie des nausées et vomissements postopératoires (NVPO) chez des patientes sous anesthésie générale lors d'une laparoscopie gynécologique en clinique externe.

Méthode : Après avoir obtenu l'autorisation du Comité d'éthique médicale et le consentement des patientes, on a procédé à l'étude de 160 femmes, réparties au hasard en double aveugle, qui ont reçu avant la laparoscopie ambulatoire prévue : i) une solution salée (placebo), ii) 4 mg d'ondansétron, iii) 1,25 mg de dropéridol, ou iv) une combinaison intraveineuse de 4 mg d'ondansétron et de 1,25 mg de dropéridol à l'induction de l'anesthésie. Après l'anesthésie générale standard, les patientes ont été interrogées sur les NVPO à différents temps.

Résultats : Pendant les 24 premières heures postopératoires, l'incidence des NVPO ont été de 71 % dans le groupe placebo. Cette incidence a été réduite à 61 % avec de dropéridol employé seul ($P = 0,334$), à 46 % avec l'ondansétron seul ($P = 0,027$) et à 23 % avec la combinaison des deux médicaments ($P < 0,001$). Une différence statistiquement différente a été observée entre la combinaison et le dropéridol ($P < 0,001$) et entre la combinaison et l'ondansétron ($P = 0,036$). On enregistre moins de demandes de médication de rattrapage provenant des patientes qui ont reçu la combinaison de médicaments (7,7 %) que de celles qui ont reçu l'ondansétron ou le placebo.

Conclusion : Les résultats de l'étude suggèrent que la combinaison de 4 mg d'ondansétron et de 1,25 mg de dropéridol est plus efficace comme prophylaxie antiémétique que chacun des médicaments utilisés seuls pendant les 24 premières heures postopératoires. Cet effet additionnel pourrait être attribué aux différents mécanismes d'action de l'ondansétron et du dropéridol.

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NAUSEA, the sensation of the urge to vomit, and vomiting or emesis, the involuntary expulsion of gastric contents, are common postoperative complications following general anesthesia.¹ One of the highest incidences of postoperative nausea and vomiting (PONV) occurs after gynecological laparoscopy, ranging from approximately 40 - 77%.² Postoperative nausea and vomiting predisposes patients to increased pain, bleeding, dehydration, electrolyte imbalance and retardation in wound healing, as well as being the principle source of prolonged discharge and unplanned postoperative hospital admission.³ It is not surprising that PONV following outpatient gynecological surgery has been considered more debilitating than the surgery itself by patients⁴ and needs to be addressed further as emphasized by Stockall with research comparing new vs old anti-emetic therapies.⁵

It is believed that anti-emetic agents act on the chemoreceptor trigger zone (CTZ) located in the area postrema which contains abundant receptors of various classes (e.g. dopaminergic, muscarinic, opioid, serotonergic).⁶ Once the anti-emetic agent blocks its specific class of receptors, signaling from the CTZ to the emetic centre is hindered and PONV is reduced.⁷

For prophylaxis of PONV during outpatient gynecological laparoscopy under general anesthesia, two of the most commonly used anti-emetics are ondansetron, a serotonin hydroxytryptamine (HT) receptor antagonist highly specific for the 5HT₃ receptor class,⁸ and droperidol, primarily a dopamine₂ receptor antagonist⁶ with minor effects on the histamine receptor.⁹ However, both ondansetron and droperidol have limited efficacy in decreasing the incidence of PONV. Ondansetron lowers the PONV incidence range to 20 to 45 %¹⁰⁻¹² and only has minor transient side effects.^{13,14} Droperidol lowers the PONV incidence range to 22 to 60%^{15,16} and is associated with sedation, hypotension, and extrapyramidal reactions.¹⁷

The many causes of PONV may be better addressed by antagonizing more than one class of receptors through the use of a combination of anti-emetic drugs. Some benefits of combination anti-emetic use include reduced side effects and toxicity of each anti-emetic agent, and increased efficacy by providing various mechanisms of action.¹⁴

The use of combination anti-emetic therapy was first used and is now prevalent in the oncology literature. Although there are differences between chemotherapy-induced and anesthesia-induced nausea and vomiting, there are similarities in their basic mechanism involving the CTZ and emetic centre. Therefore the wealth of knowledge from the oncology literature cannot be ignored.

The present double-blind study was designed to appraise prospectively the efficacy of ondansetron and droperidol, alone and in combination, administered for prophylaxis of PONV in women undergoing general anesthesia for outpatient gynecological laparoscopy.

Methods

Following Institutional Review Board approval, and after explaining the nature of the study, written informed consent was obtained from 160 ASA physical status I-III female outpatients scheduled to undergo elective laparoscopic gynecological procedures under general anesthesia. Female outpatients between the ages of 16 and 65 yr were eligible. Exclusion criteria were laboratory or clinical evidence of cardiovascular, hematologic, pulmonary, renal, hepatic, neurological or endocrine abnormalities, pregnancy, morbid obesity (those who were more than 25% above ideal body weight), a history of substance abuse, anti-emetic or psychoactive medication within 24 hr before surgery, previous allergic reactions to serotonin antagonists, and the need for a nasogastric tube postoperatively. To identify patients with a predisposition to PONV, patients were asked about previous anesthetic experiences, motion sickness, and menstrual cycle patterns.¹⁸

Upon consent, each patient was randomized to one of four intravenous treatment categories: i) saline, ii) 4 mg ondansetron, iii) 1.25 mg droperidol, and iv) the combination of 4 mg ondansetron and 1.25 mg droperidol. All four medications were diluted to a final volume of 4 ml with normal saline and were administered upon induction of anesthesia. Each of these therapy medications was prepared by either the operating room pharmacist (not otherwise involved in the study) or by the research coordinator, and presented to the attending anesthesiologist in a numbered syringe which correlated with the patients study number. In this way, the anesthesiologist, study investigator, patient, operating room attendants, and recovery room nurses, were all blinded to the identity of the prophylactic treatment.

All patients received a standardized anesthetic technique (Table II) consisting of 1.25 - 4.0 mg·kg⁻¹ propofol *iv* with or without 1-3 mg midazolam *iv* for anesthesia induction. Nitrous oxide 70% in oxygen, isoflurane (0.5 - 1.0%) and/or enflurane were used for maintenance. Intraoperative opioids included 50 - 350 µg fentanyl *iv* or 1.0 - 1.5 mg alfentanil *iv*. Muscle relaxants that were permitted in the study consisted of 1.25 - 2.50 mg·kg⁻¹ succinylcholine *iv*, 1.0 - 3.0 mg d-tubocurarine *iv*, 1.0 - 7.0 mg vecuronium *iv*, and 0.20 - 0.45 atracurium mg·kg⁻¹ *iv*. Reversal agents entailed 1.0 - 5.0 mg neostigmine *iv*, and/or

1.5 - 3.0 mg edrophonium *iv*, 0.6 - 2.0 mg atropine *iv*, and 0.2 - 0.6 mg glycopyrrolate *iv*. Postoperative opioids were codeine, morphine, meperidine.

After surgery, the time of recovery room arrival was recorded. The anesthesiologists and PACU nurses were instructed to treat nausea and pain as needed to ensure patient comfort. Consequently, the patient was assessed by the study investigator for nausea, vomiting, need for anti-emetic medication, and overall satisfaction (determined by patient responses to how they perceived themselves to be), through verbal responses at various time intervals: 30, 90, 150, 210 min after recovery room arrival. After 24 hr, a telephone follow-up was also conducted to examine the patient's condition subsequent to discharge. At each of these evaluations, the patient's complaints of nausea, vomiting, retching, pain, and drowsiness were all measured using a visual analog scale (VAS) during hospital stay and for the telephone interview, the patients complaints were measured by incidence. The VAS score was indicated by the patient on a 10 cm unmarked line with the extremes being "none" and "worst ever". At any time during the hospital stay, if the patient felt any nausea and/or experienced any vomiting, a "rescue" anti-emetic treatment could be requested and was administered by one of the supervising nurses. The patient was previously informed at time of consent of the availability of "rescue" anti-emetic treatment upon request. The "rescue" medication administered was either 25 mg dimenhydrinate *iv* or 5 to 10 mg metoclopramide *iv*, and in one case, 4 mg ondansetron *iv*, according to the anesthesiologist's instructions.

Upon completion of the study, each patient's record was grouped with others belonging to the same prophylactic treatment. The data were analyzed with GraphPad Prism (GraphPad Software Inc., San Diego, CA) computer program using analysis of variance and χ^2 . Where a difference between groups was found in the analysis of variance, Bonferroni corrections were used to isolate the group(s) producing the difference and to avoid error of multiple comparisons. P values < 0.05 were considered statistically significant. Only following data analysis was the code broken to reduce bias. Comparisons were made among the hospital stay, post-discharge, and the combined hospital stay and post-discharge periods. PONV data was analyzed based on first incidence of PONV so each patient is only counted once. The use of rescue medication only occurs after first incidence of PONV and does not affect the results.

In determining the number of patients required to be in each study group, the dichotomous outcome

technique represented in "Experimental Design" by Cochran & Cox (Wiley, 1950) was used. Since in the absence of any anti-emetic treatment, the incidence of PONV after gynecological surgery can be as high as around 70 %, ^{12,19} it was calculated that in order to decrease this incidence by 50%, 33 participants in each group would be required. This power test of significance was at the 5% level with a probability of 90%.

Results

There were eight study patients (two from the placebo group, three from the ondansetron group, two from the droperidol group, and one from the combination group) excluded from the study because they were inadvertently given thiopental for induction of anesthesia. Thiopental has been known to cause postoperative nausea and vomiting.²⁰ Three study patients (one in the droperidol group, one in the ondansetron group, and one in the combination group) were admitted due to surgical complications unrelated to the study. Retching scores were combined with the vomiting scores. No differences in demographic data among the four treatment groups in regards to age, height, weight, history of PONV after previous general anesthesia, duration of anesthesia, and history of motion sickness were found (Table I). There were also no differences among study groups in administration of midazolam, opioids given intraoperatively and postoperatively, all known to have anti-emetic or emetic properties. However, the combination group did receive more nitrous oxide 70% than the other groups (Table II) which may lead to increased PONV.¹ The length of hospital stay was not recorded as it would have been influenced primarily by our institution's discharge criteria and not to PONV.

During hospital stay, all three pharmacologically treated groups (droperidol, ondansetron, and combination) were more effective than placebo in preventing PONV ($P = 0.006$, $P = 0.028$, $P < 0.001$) (Figure 1). When comparing the treatment groups amongst themselves, the combination group fared better than ondansetron alone ($P = 0.026$) and decreased PONV was seen from the combination group relative to droperidol alone but the difference was not significant ($P = 0.093$). No significant difference was also found between the ondansetron and droperidol groups ($P = 0.569$). When nausea and vomiting data were separated, the postoperative nausea results remained similar but no significant differences were found among the pharmacologically treated groups when only postoperative vomiting data were considered.

When both hospital stay and post-discharge data are considered (the 24 hr time period) the combina-

TABLE I Patient demographic data

	<i>Placebo</i>	<i>Droperidol</i>	<i>Ondansetron</i>	<i>Combination</i>	<i>P</i>
n	38	38	37	39	0.5686
Age (yr)	33.8 ± 7.8	31.6 ± 6.9	33.1 ± 5.0	32.9 ± 7.1	0.2946
Height (cm)	162.1 ± 5.6	162.0 ± 6.4	161.0 ± 6.4	163.9 ± 7.9	0.3697
Weight (kg)	6.3 ± 12.8	63.2 ± 12.8	60.5 ± 11.8	62.6 ± 11.4	0.3697
Previous General Anesthetic	32	26	31	31	0.2964
History of PONV	12	14	13	10	0.7302
History of Motion Sickness	10	13	14	19	0.2306
Duration of Anesthesia (min)	60 ± 21	60 ± 24	59 ± 27	60 ± 28	0.9467
Day of Menstrual cycle	16 ± 8	17 ± 17	14 ± 9	18 ± 14	0.7296

Data expressed as mean ± standard deviation, or number of patients (n)

TABLE II Anesthetics and opioids used intraoperatively and postoperatively

	<i>Placebo</i>	<i>Droperidol</i>	<i>Ondansetron</i>	<i>Combination</i>	<i>P</i>
<i>Anesthetics</i>					
Induction agents					
Propofol	100 (38)	100 (38)	100 (37)	100 (39)	1.0000
Midazolam	74 (28)	82 (31)	76 (28)	72 (28)	0.7723
Maintenance agents					
Nitrous oxide 70%	84 (32)	89 (34)	97 (36)	100 (39)	0.0303
Enflurane	16 (6)	29 (11)	22 (8)	31 (12)	0.3962
Isoflurane	82 (31)	61 (23)	76 (28)	64 (25)	0.1516
Muscle relaxant	61 (23)	61 (23)	73 (27)	44 (17)	0.0753
Reversal agents	87 (33)	82 (31)	89 (33)	92 (36)	0.5411
<i>Opioids</i>					
Intraoperative	100 (38)	100 (38)	100 (37)	100 (39)	1.0000
Postoperative	79 (30)	74 (28)	81 (30)	67 (26)	0.4708

Data expressed as percentage of patients (number)

TABLE III Incidence of PONV and of rescue medication administration during various time periods

	<i>Placebo</i>	<i>Droperidol</i>	<i>Ondansetron</i>	<i>Combination</i>	<i>P</i>
n	38	38	37	39	
Hospital Stay (3.5 hr)	63 (24)	32 (12)	38 (14)	15 (6)	0.0002
Post-discharge	32 (12)	46 (17)	31 (11)	13 (5)	0.0625
Total 24 hr Period	71 (27)	61 (23)	46 (17)	23 (9)	0.0002
Need of Rescue Medication	26 (10)	16 (6)	30 (11)	8 (3)	0.0625

Data expressed as percentage of patients (number)

tion group fared better than the ondansetron, droperidol, and placebo groups ($P < 0.04$, $P < 0.001$, $P < 0.001$). However, during the same 24 hr period, the group receiving droperidol alone no longer exhibited greater efficacy from placebo ($P = 0.334$) (Figure 2). Again, no difference is seen between the single antiemetic droperidol and ondansetron groups ($P = 0.206$). Postoperative nausea data reflected these

results while postoperative vomiting data showed significant differences between the combination and placebo groups.

The VAS scores representing the severity of patients' pain showed no difference among the groups. The VAS scores for drowsiness were higher for the group receiving droperidol alone ($P = 0.0009$). The VAS scores for nausea were higher for the place-

FIGURE 1 * $P < 0.05$ compared with placebo, † $P < 0.05$ compared with combination.

Incidence of PONV during hospital stay (3.5 hr). More placebo-grouped women had PONV than patients in the other three study groups (droperidol, ondansetron, and combination) ($P = 0.006$, $P = 0.028$, $P < 0.001$). The combination group of ondansetron and droperidol also had significantly less PONV than ondansetron alone ($P = 0.026$) and a trend toward less PONV than droperidol alone ($P = 0.093$).

FIGURE 2 * $P < 0.05$ compared with placebo, † $P < 0.05$ compared with combination.

Incidence of PONV during the first 24 hr after recovery room arrival. More placebo-grouped women had PONV than patients in the ondansetron, and ondansetron with droperidol study groups ($P = 0.027$, $P < 0.01$). The combination group of ondansetron and droperidol also had significantly less PONV than either of the anti-emetic drugs alone (ondansetron or droperidol) ($P = 0.036$, $P < 0.01$).

bo group but all the scores were very low. The combination group needed less rescue medication than the other groups but this difference was not significant (Table III). The proportion of patients experiencing minor side effects during the 24 hr period after administration of study medications included shivering, headache, and dizziness, were noted but did not differ among the groups.

The occurrence of pain did not differ among the study groups in incidence or severity as a dose of fentanyl (50 - 350 μ g) was given during surgery followed by a dose of morphine (2 - 20 mg) postoperatively. Similarly, the incidence of drowsiness was high in all groups equally. There was no difference in patient's overall well-being scores (rated on a scale of poor, moderate, and comfortable).

During the post-discharge period, the combination group experienced less PONV compared to droperidol or placebo groups ($P < 0.01$, $P = 0.04$), and there was a trend toward a difference with ondansetron alone ($P = 0.052$) (Table III). However, when nausea and vomiting data are considered separately, the combination group showed less of an increase than droperidol ($P = 0.0015$, $P = 0.0174$ for nausea and vomiting respectively).

Discussion

The present study demonstrated superior efficacy of the combination of 4 mg ondansetron *iv* and 1.25 mg droperidol *iv* with either anti-emetic alone or placebo during the 24 hr period post-surgery when given prophylactically to women undergoing gynecologic laparoscopy. Study patients in the combined anti-emetic group also had fewer requests for "rescue" medication during their hospital stay and at home. Of the handful of studies that have examined the ondansetron and droperidol anti-emetic combination, one found better efficacy in preventing PONV by the combination compared with, either anti-emetic alone,²¹ droperidol alone,¹⁵ efficacy only in preventing postoperative nausea (PON),²² or no significance when compared with droperidol alone for postoperative vomiting (POV).⁸ Unfortunately, many of these studies lacked one or more of the recommended three arms of postoperative anti-emetic trials (placebo, test drug, and control drug),²³ or used two doses of droperidol,²¹ which made it difficult to interpret the results.

The droperidol group fared better than the placebo group during hospital stay. However, a large post-discharge increase in incidence of PONV (46%) (Table III) resulted in a lack of efficacy of the droperidol group in the 24 hr study period compared with place-

bo ($P = 0.334$). A similar result had been previously found in a well executed study by Cohen *et al.*²⁴ A likely reason for the lack of efficacy of droperidol over longer periods of time is its elimination half-life of approximately two hours.²⁵ Droperidol's quick onset of action may also account for its similar efficacy when compared to the combination group in the first 3.5 hr ($P = 0.093$). Ondansetron, on the other hand, has a half-life of approximately 3.4 hr.²⁶ Therefore, the coupling of the longer duration of action of ondansetron with the quicker onset of action of droperidol makes these two drugs an attractive anti-emetic combination.

Equivalent efficacy was seen between the ondansetron and droperidol groups in reducing PONV in outpatients. Similar results have also been found by Fortney *et al.*¹⁷ and Tang *et al.*¹⁶ There was also a lack of difference in adverse effects (e.g. shivering, headache, dizziness probably due to the general anesthetic agents) among the four study groups except that the group receiving 1.25 mg droperidol alone experienced more severe drowsiness (which may have delayed discharge) as is expected for droperidol. The combination group did not experience such severe drowsiness. However, the widely held concern over adverse reactions from droperidol is only associated with doses higher than 2.5 mg,^{1,27} and Tramer *et al.* did not find that droperidol was limited by adverse reactions at all.²⁸ The 4 mg dose of ondansetron was chosen as it is considered the optimal dose for prophylaxis of PONV.^{29,30} The lack of difference in requests for "rescue" medication between placebo and each of the anti-emetic drug groups alone emphasizes the need for an alternative to single dose single anti-emetic therapy for the prophylaxis of PONV - combination anti-emetic therapy.

Many factors are involved in triggering PONV. Some patient-related factors include age, sex, obesity, previous PONV, and motion sickness,³¹ all of which were evenly spread throughout the four treatment groups (Table I). The type of surgery, gynecological laparoscopy, and anesthetic technique were also standardized (Table II) and the duration of surgery did not vary amongst the study groups. The anesthetic technique was chosen to minimize PONV. Less PONV in the combination group may be expected if significantly more nitrous oxide 70% was not used in this group and compared to the other groups. Other factors affecting incidence of PONV are the use of propofol, midazolam, and opioid analgesics. Propofol, compared with other anesthetics, has been suggested to have anti-emetic effect³² and was therefore used for all study patients. Midazolam is another anesthetic agent that reduces persistent PONV³³ but its use did not vary among the

study groups. The use of opioid analgesics (e.g. morphine and codeine in this study) is needed to control postoperative pain but they also increase the incidence of PONV.^{34,35} especially in outpatients who become mobile more quickly.³⁶ The use of opioid analgesics did not vary among the study groups (Table II). However, one solution to minimize morphine-induced emesis is through the use of a patient-controlled analgesia (PCA) device which can deliver the optimum amount of morphine, as excessive doses of opioids result in opioid-induced emesis.³⁶ Nonsteroidal anti-inflammatory drugs may also have a role in drug-induced emesis.

In conclusion, we found that 4 mg ondansetron and/or 1.25 mg droperidol administered intravenously during induction of anesthesia reduced the frequency of PONV during the first 3.5 hr of the study (hospital stay). Only 4 mg ondansetron alone or the combination of 4 mg ondansetron and 1.25 mg droperidol reduced the frequency of PONV during the 24 hr study period. Moreover, the combination of 4 mg ondansetron and 1.25 mg droperidol further attenuated this incidence when compared to 4 mg ondansetron alone (during both 3.5 hr and 24 hr post-surgery) or 1.25 mg droperidol alone (during the 24 hr post-surgery). In the present study, the anti-emetic properties of ondansetron and droperidol appear to be additive due to their antagonistic action at different receptor types and their distinct half-lives. Further studies in combination anti-emetic therapy could include multiple doses of the combination. Recently, Warrick *et al.* used 4 mg ondansetron and 1.25 mg droperidol in combination prior to induction followed by a second dose of the combination dose for home. This treatment did not appear to alter the incidence of PONV over the 24 hr period. However, this lack of improvement may be related to the timing of the second dose rather than the efficacy of multiple doses.³⁷

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References

- 1 Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; 77: 162-84.

- 2 Hovorka J, Korttila K, Erkola O. Nitrous oxide does not increase nausea and vomiting following gynaecological laparoscopy. *Can J Anaesth* 1989; 36: 145–8.
- 3 White PF, Shafer A. Nausea and vomiting: causes and prophylaxis. *Semin Anesth* 1987; 6: 300–8.
- 4 Hirsch J. Impact of postoperative nausea and vomiting in the surgical setting. *Anaesthesia* 1994; 49(Suppl): 30–3.
- 5 Stockall CA. Postoperative nausea and vomiting - when will it stop? (Editorial) *Can J Anesth* 1999; 46: 715–8.
- 6 Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. *Anaesthesia* 1994; 49(Suppl): 2–5.
- 7 Peroutka SJ, Snyder SH. Antiemetics: neurotransmitter receptor binding predicts therapeutic action. *Lancet* 1982; 1: 658–9.
- 8 Riley TJ, McKenzie R, Tantisira BR, Hamilton DL. Droperidol-ondansetron combination *versus* droperidol alone for postoperative control of emesis after total abdominal hysterectomy. *J Clin Anesth* 1998; 10: 6–12.
- 9 Simpson RB, Russell D. Anaesthesia for daycase gynaecological laparoscopy: a survey of clinical practice in the United Kingdom. *Anaesthesia* 1999; 54: 51–85.
- 10 Bodner M, White PF. Antiemetic efficacy of ondansetron after outpatient laparoscopy. *Anesth Analg* 1991; 73: 250–4.
- 11 Dupeyron JP, Conseiller C, Levarlet M, *et al.* The effect of oral ondansetron in the prevention of postoperative nausea and vomiting after major gynaecological surgery performed under general anaesthesia. *Anaesthesia* 1993; 48: 214–8.
- 12 Kenny GNC, Oates JDL, Leeser J, *et al.* Efficacy of orally administered ondansetron in the prevention of postoperative nausea and vomiting: a dose ranging study. *Br J Anaesth* 1992; 68: 466–70.
- 13 Russell D, Kenny GNC. 5-HT₃ antagonists in postoperative nausea and vomiting. *Br J Anaesth* 1992; 69: 63S–8S.
- 14 Wadibia EC. Antiemetics. *South Med J* 1999; 92: 162–5.
- 15 McKenzie R, Uy NTL, Riley TJ, Hamilton DL. Droperidol/ondansetron combination controls nausea and vomiting after tubal banding. *Anesth Analg* 1996; 83: 1218–22.
- 16 Tang J, Watcha MF, White PF. A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. *Anesth Analg* 1996; 83: 304–13.
- 17 Fortney JT, Gan TJ, Graczyk S, *et al.* A comparison of the efficacy, safety, and patient satisfaction of ondansetron *versus* droperidol as antiemetics for elective outpatient surgical procedures. *Anesth Analg* 1998; 86: 731–8.
- 18 Beattie WS, Lindblad T, Buckley DN, Forrest JB. Menstruation increases the risk of nausea and vomiting after laparoscopy. *Anesthesiology* 1993; 78: 272–6.
- 19 Koivuranta M, Jokela R, Kiviluoma K, Alahuhta S. The anti-emetic efficacy of a combination of ondansetron and droperidol. *Anaesthesia* 1997; 52: 863–8.
- 20 Myles PS, Hendrata M, Bennett AM, Langley M, Buckland MR. Postoperative nausea and vomiting. Propofol or thiopentone: does choice of induction agent affect outcome? *Anaesth Intensive Care* 1996; 24: 355–9.
- 21 Pueyo, F J, Carrascosa F, Lopez L, Iribarren MJ, Garcia-Pedrajas F, Saez A. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg* 1996; 83: 117–22.
- 22 Wrench IJ, Ward JEH, Walder AD, Hobbs GJ. The prevention of postoperative nausea and vomiting using a combination of ondansetron and droperidol. *Anaesthesia* 1996; 51: 776–8.
- 23 Goodman NW. Trials of postoperative antiemetics need three arms (Letter). *BMJ* 1999; 318: 942.
- 24 Cohen SE, Woods WA, Wyner J. Antiemetic efficacy of droperidol and metoclopramide. *Anesthesiology* 1984; 60: 67–9.
- 25 Fischler M, Bonnet F, Trang H, *et al.* The pharmacokinetics of droperidol in anesthetized patients. *Anesthesiology* 1986; 64: 486–9.
- 26 Pritchard JF, Bryson JC, Kernodle AE, Benedetti TL, Powell JR. Age and gender effects on ondansetron pharmacokinetics: evaluation of healthy aged volunteers. *Clin Pharmacol Ther* 1992; 51: 51–5.
- 27 Sniadach MS, Alberts MS. A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynecologic laparoscopy. *Anesth Analg* 1997; 85: 797–800.
- 28 Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. When placebo controlled trials are essential and equivalence trials are inadequate. *BMJ* 1998; 317: 875–80.
- 29 Khalil SN, Kataria B, Pearson K, *et al.* Ondansetron prevents postoperative nausea and vomiting in women outpatients. *Anesth Analg* 1994; 79: 845–51.
- 30 McKenzie R, Kovac A, O'Connor T, *et al.* Comparison of ondansetron *versus* placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. *Anesthesiology* 1993; 78: 21–8.
- 31 Broomhead CJ. Physiology of postoperative nausea and vomiting. *Br J Hosp Med* 1995; 53: 327–30.
- 32 Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. *Anesthesiology* 1989; 71: 260–77.
- 33 Di Florio T, Goucke CR. The effect of midazolam on persistent postoperative nausea and vomiting. *Anesth Intensive Care* 1999; 27: 38–40.

- 34 *Kenny GNC*. Risk factors for postoperative nausea and vomiting. *Anaesthesia* 1994; 49(Suppl): 6–10.
- 35 *Palazzo M, Evans R* Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk management. *Br J Anaesth* 1993; 70: 135–40.
- 36 *Wrench IJ, Ward JE, Walder AD, Hobbs GJ*. The prevention of postoperative nausea and vomiting using a combination of ondansetron and droperidol. *Anaesthesia* 1996; 51: 776–8.
- 37 *Warrick PD, Belo SE*. Treating rebound emesis following outpatient gynecologic laparoscopy: the efficacy of a two-dose regimen of droperidol and ondansetron. *J Clin Anesth* 1999; 11: 119–25.