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Summary

Nausea and vomiting are common side effects of opioids administered for pain control. This double-blind, randomized, parallel-group study evaluated the anti-emetic efficacy and tolerability of single intravenous (i.v.) doses of ondansetron 8 mg, ondansetron 16 mg and metoclopramide 10 mg in the treatment of opioid-induced emesis. Adult patients undergoing low emetogenic surgical procedures, using a standardized anaesthesia regimen were assessed for 24 h following administration of study anti-emetic to treat established post-surgical opioid-induced emesis. A total of 4511 patients were enrolled of whom 1366 experienced opioid-induced emesis and received randomized study medication. Ondansetron 8 mg and 16 mg were significantly better than metoclopramide 10 mg ($P < 0.05$) for both complete control of emesis, complete control of nausea and other efficacy measures. There were no significant differences between the two ondansetron groups. All three treatments were well tolerated. In conclusion, this large, multicentre study demonstrates that ondansetron is more effective than metoclopramide in the treatment of opioid-induced emesis following administration of post-surgical opioids to control pain.

Keywords: OPIOID-INDUCED EMESIS, ondansetron, metoclopramide, post-surgical patients, nausea, vomiting.

Introduction

Ondansetron is a highly effective anti-emetic indicated for use for chemotherapy/radiotherapy-induced emesis (CRIE) and in post-surgical patients for post-operative nausea and emesis (PONV). Opioids, administered for pain management, are emetogenic agents manifesting their effects by both direct stimulation of the chemoreceptor trigger zone and, by indirect stimulation, increasing vestibular sensitivity to movement [1,2]. Opioids are commonly used in the post-surgical setting for pain management and are recognised as an important component of the emetogenic stimulus [3]. As a result of emetic side effects, patients may receive suboptimal doses of opioids with the consequence of inadequate pain management. In addition, pain itself can exacerbate the symptoms of nausea and vomiting [4], further complicating pain management in the post-surgical setting.

A number of studies have demonstrated that the co-administration of morphine and anti-emetics such as droperidol, metoclopramide and ondansetron to post-surgical patients provides effective control of

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opioid-induced nausea and vomiting [5–11]. The prime objective of the present study was to evaluate the anti-emetic efficacy of single i.v. doses of ondansetron 8 mg, ondansetron 16 mg and metoclopramide 10 mg in the treatment of opioid-induced nausea and emesis (OIE) in patients who have been administered post-surgical opioids for pain relief. The study was designed to maximize the likelihood that nausea and emesis were caused by opioid administration and minimize the likelihood of PONV through standardization of the anaesthetic regimen and restriction of the allowable surgical procedures. The study is referenced by Glaxo Wellcome Research and Development as S3AB3010.

Methods

This multinational, double-blind randomized, parallel-group study was conducted in 112 hospitals across 16 countries. Adult patients undergoing defined low emetogenic surgical procedures (e.g. orthopaedic surgery) using standardized general or regional anaesthetic procedures and who required post-surgical opioids for pain control were selected for entry into the study. Highly emetogenic surgical procedures (e.g. intra-abdominal and major gynaecological surgery) were excluded. Standardized general anaesthesia was achieved using the following protocol. Induction by propofol, maintenance with N_2O/O_2 and supplemented by an inhalational anaesthetic (e.g. isoflurane) and intra-operative analgesia by fentanyl. Standardized regional anaesthesia was achieved using the following protocol: Sedation by benzodiazepines (except lorazepam), maintenance with conduction anaesthesia and intra-operative analgesia with fentanyl. Patients were excluded from entry into the study if they had experienced any nausea or emesis during the 24 h prior to surgery. Patients who were receiving anti-emetics, or those with any medical condition that could confound the efficacy evaluations during the 24 h prior to surgery and throughout the duration of the study were also excluded.

Following recovery from surgery, all patients were randomized to receive a single i.v. dose of either ondansetron 8 mg, ondansetron 16 mg or metoclopramide 10 mg using a randomization code which was generated for the study. Each centre received medication for equal numbers of patients in each treatment group. Patient treatment numbers were assigned in consecutive order starting with the lowest number available. The study drug was administered only to those randomized patients who experienced opioid induced emesis within 6 h of receiving their initial dose of post-operative opioid.

The primary efficacy endpoint was 'complete control of emesis', which was assessed using the proportion of patients experiencing no emetic episodes and who were not rescued or withdrawn over the 24 h following study drug administration. Secondary assessments of response during the 24 h study period included the following: 'Complete control of nausea' (assessed using the proportion of patients experiencing no nausea and who were not rescued or withdrawn); the proportion of patients who required rescue anti-emetic medication; the number of emetic episodes; nausea scores; pain scores; patient satisfaction with study medication. Any licensed anti-emetic (except ondansetron) was allowed for rescue of patients who received study drug. The need for rescue or withdrawal from the study was determined either by the investigator or by the patient at their request.

Nausea, emesis, pain and patient's satisfaction with their anti-emetic medication were assessed throughout the 24 h following study drug administration using a patient diary card. The time of each emetic episode was recorded over this 24-h period, whilst nausea and pain were assessed separately on a linear scale (0 = no nausea/pain; 10 = nausea/pain as bad as it could be) at base-line (just prior to study drug administration) and at 15 min, 1 h, 2 h, 4 h, 6 h and 24 h after study drug administration. Patient satisfaction was assessed either at the end of the 24 h study period, or at the time of rescue or withdrawal from the study, whichever came first. This was assessed by asking patients to rate their level of satisfaction using a 5-point scale (very satisfied, satisfied, neutral, dissatisfied, very dissatisfied) in terms of: time to onset; duration of effect; overall satisfaction and whether they would consider receiving the study medication again.

The primary treatment group comparisons were between ondansetron 8 mg i.v. and metoclopramide and between ondansetron 16 mg i.v. and metoclopramide. The comparison between the two doses of ondansetron was secondary. Study group size was

determined from power calculations based on previous experience of ondansetron in OIE in a phase II study (Rung *et al*.[12]). For this study, it was estimated that the percentage of patients expected to experience no emesis in the 24-h period following treatment of OIE with ondansetron 16 mg i.v., ondansetron 8 mg i.v. and metoclopramide 10 mg i.v. were 50%, 40% and 30%, respectively. For the analysis of the primary endpoint, the overall Type I error for the two primary treatment comparisons was no greater than 5% and this was achieved using the procedure proposed by Hochberg [13]. Assuming 450 patients in each treatment group, the study had powers of more than 80% to detect differences between metoclopramide and each of the doses of ondansetron for the primary endpoint. It was anticipated from previous studies that one third of patients recruited would experience OIE, therefore it was planned to enrol 4050 patients to ensure 1350 (3×450) patients would receive randomized study medication.

Statistical comparisons between proportions were made using Mantel–Haenszel χ^2-tests. Wilcoxon rank sum tests were used for comparisons of numbers of emetic episodes and levels of patient satisfaction. Non-parametric analysis of covariance [14] was used to assess treatment differences in nausea and pain scores, adjusting for base-line (pre-treatment) scores. All analyses were stratified according to country.

Results

Patient Demography

4511 patients were enrolled into the study, of whom 1366 experienced OIE post-surgically and received randomized treatment. Table 1 lists the patient background characteristics and their disposition across the three treatment groups. The three groups were well-balanced in terms of these factors. Seventy-seven percent of the patients were female, of whom, 48% were post-menopausal, 19% were surgically sterile and 33% were of child-bearing age. Ninety percent of the patients had experience of previous opioid use and only 17% had experienced OIE on a previous occasion. The majority (89%) of the patients received general anaesthesia during surgery and of these more than 99% received standardized anaesthesia and intra-operative analgesia as defined in the study protocol (see Methods). Orthopaedic surgical procedures were the most prevalent (41% of patients), with other patients receiving a range of surgical interventions (see Table 1). Morphine and pethidine were the most used opioids for post-operative pain, being used in 67% and 16% of patients, respectively.

Efficacy

During the 6 h post-treatment study period, ondansetron at both doses produced highly effective anti-emetic activity and these were significantly more effective than metoclopramide ($P < 0.001$, Fig. 1). The proportion of patients experiencing complete control of emesis was 63% and 61% for ondansetron 8 mg and ondansetron 16 mg, respectively, and 48% for metoclopramide. There was no significant difference between the anti-emetic effect of ondansetron at the two doses.

During the 24 h study period, ondansetron at either 8 mg or 16 mg was significantly more effective than metoclopramide in the complete control of emesis ($P< 0.004$) and nausea ($P< 0.017$) (Fig. 2). The proportion of patients experiencing complete control of emesis was 42% and 43% for ondansetron 8 mg and ondansetron 16 mg and 32% for metoclopramide 10 mg. The proportion of patients experiencing complete control of nausea was 22% and 21% for ondansetron 8 mg and ondansetron 16 mg and 15% for metoclopramide 10 mg. In addition, there was no significant difference between the two doses of ondansetron for complete control of emesis or nausea (Fig. 2).

A significantly greater proportion of patients given metoclopramide 10 mg received rescue anti-emetic medication in the 24 h study period compared with patients given either ondansetron 8 mg ($P=0.012$) or ondansetron 16 mg ($P=0.029$) The rates were 46% and 47% for ondansetron 8 mg and ondansetron 16 mg and 54% for metoclopramide 10 mg. There was no significant difference in the proportion of rescued patients between the two ondansetron groups.

The distributions of numbers of emetic episodes during the 24 h study period (Table 2) were significantly different between the metoclopramide 10 mg group and each of ondansetron 8 mg ($P=0.003$) and ondansetron 16 mg groups ($P=0.003$) and reflected the differences found between treatment

Table 1. Patient demography and background characteristics

	Ondansetron 8 mg i.v.	16 mg i.v.	Metoclopramide 10 mg i.v.	Total
Number of patients	456	461	449	1366
Age (years)				
Mean	50	51	49	50
Range	17–90	19–87	18–88	17–90
N	449	453	445	1347
Sex				
M	96 (21%)	116 (25%)	106 (24%)	318 (23%)
F	360 (79%)	345 (75%)	343 (76%)	1048 (77%)
Post-menopausal	168 (47%)	172 (50%)	159 (46%)	499 (48%)
Surgically sterile	75 (21%)	69 (20%)	56 (16%)	200 (19%)
Pre-menarche	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Child bearing potential	117 (33%)	103 (30%)	127 (37%)	347 (33%)
Previous opioid use	386 (88%)	395 (88%)	406 (93%)	1187 (90%)
With nausea/emesis	90 (20%)	62 (14%)	74 (17%)	226 (17%)
Without nausea/emesis	296 (67%)	333 (74%)	332 (76%)	961 (72%)
Type of anaesthesia				
General	408 (89%)	403 (87%)	409 (91%)	1220 (89%)
Regional	48 (11%)	58 (13%)	40(9%)	146 (11%)
Type of surgery*				
Orthopaedic	183 (40%)	193 (42%)	184 (41%)	560 (41%)
Vaginal hysterectomy	51 (11%)	50 (11%)	49 (11%)	150 (11%)
Plastic surgery	47 (10%)	50 (11%)	40 (9%)	137 (10%)
Other urogenital	36 (8%)	46 (10%)	46 (10%)	128 (9%)
Head and neck	47 (10%)	33 (7%)	46 (10%)	126 (9%)
Mastectomy	37 (8%)	36 (8%)	32 (7%)	105 (8%)
Other	33 (7%)	32 (7%)	34 (8%)	99 (7%)
Laminectomy	32 (7%)	28 (6%)	29 (6%)	89 (7%)
Thoracic	2 (< 1%)	4 (< 1%)	2 (< 1%)	8 (1%)

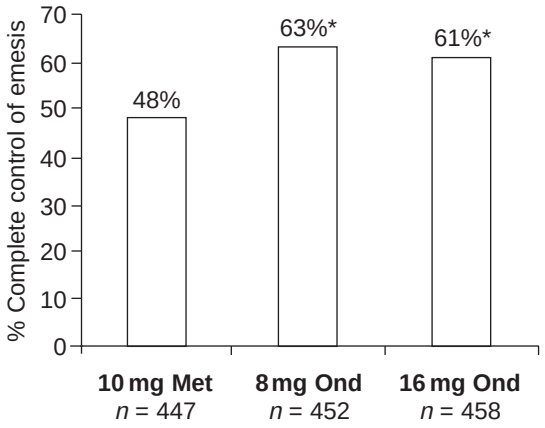
Values are number (%) of patients. *Patients may have undergone more than one surgical procedure.

groups for complete control of emesis and the use of rescue medication. There was again no significant difference between the two doses of ondansetron.

Table 3 shows nausea scores for the three groups at base-line (just before study drug administration) and throughout the 24 h study period. Mean nausea scores were comparable at base-line for the three groups and were lower following study drug administration. There were no significant differences between any of the three pairs of treatment groups.

Table 4 shows pain scores at base-line and over the 24 h study period. The scores were significantly lower for metoclopramide than for either ondansetron 8 mg i.v. ($P = 0.017$) and ondansetron 16 mg i.v. ($P = 0.022$). This may have reflected the trend that there was an increased use of opioids following rescue, and that more patients received rescue medication in the metoclopramide group than in both ondansetron groups. These differences were not considered to be clinically relevant.

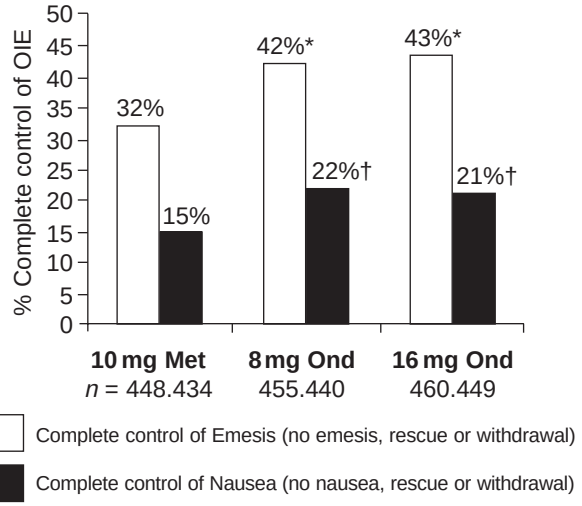
Table 5 shows patient satisfaction with their treatment. Patients who had received either dose of ondansetron were significantly more satisfied with their anti-emetic treatment than those who had received metoclopramide. Again there was no significant difference between the two doses of ondansetron.



*$P \leq 0.001$ vs. metoclopramide (Mantel–Haenszel χ^2-test)

Complete control of emesis is defined as the proportion of patients experiencing no emetic episodes and who were not rescued or withdrawn during the study period.

Fig. 1. Control of opioid-induced emesis by ondansetron (8 mg and 16 mg) and metoclopramide (10 mg) during the 6 h post-treatment study period.



*$P \leq 0.004$ vs. metoclopramide (Mantel–Haenszel χ^2-test)
†$P \leq 0.0017$ vs. metoclopramide (Mantel–Haenszel χ^2-test)

Fig. 2. Control of opioid-induced emesis and nausea by ondansetron (8 mg and 16 mg) and metoclopramide (10 mg) during the 24 h post-treatment study period

Safety

Ondansetron was well tolerated at either i.v. dose of 8 mg or 16 mg. The incidence of adverse events occurring post-treatment was similar across all three treatment groups (17% in the ondansetron 8 mg group, 16% in the ondansetron 16 mg group, and 14% in the metoclopramide 10 mg group). The incidence of drug-related adverse events (those assessed by the investigator as causally related to study medication) was low in all three groups (5% in the ondansetron 8 mg group, 6% in the ondansetron 16 mg group and 4% in the metoclopramide 10 mg group). The most commonly reported adverse events (i.e. occurring in more than 2% of patients in any treatment group), were pruritus (6% in the ondansetron 8 mg group, 4% in the ondansetron 16 mg group, 3% in the metoclopramide 10 mg group), headache (3% in the ondansetron 8 mg group, 5% in the ondansetron 16 mg group, 1% in the metoclopramide 10 mg group) and dizziness (2% in the ondansetron 8 mg group, 2% in the ondansetron 16 mg group and 1% of the metoclopramide group). All other adverse events occurred in less than 2% of patients in all treatment groups.

Serious adverse events occurring in the post-treatment period were reported in five patients. In one case (near anaphylactic shock – rash on face and bronchospasm), the event was considered by the investigator to be causally related to study medication. This patient received metoclopramide. There was one death reported during the study in a patient who had not received any study medication. The death occurred after the end of the study.

Discussion

Opioids are widely used for pain management in many situations from chronic conditions such as arthritis and cancer, to acute pain crisis management associated with conditions including sickle-cell anaemia, trauma and post-surgical recovery. Although opioids are highly effective analgesics, pain management using opioids can be suboptimal [15,16]. Inadequate dosing resulting in suboptimal pain control often occurs as a result of patients choosing to suffer pain rather than the unpleasant side effects of nausea and emesis/vomiting associated with these drugs [17].

Opioid-induced emesis in the post-surgical setting is well documented. Studies have shown the incidence to range between 10% and 50%, with no clear indication as to the causes of this variability [18–24]. In addition to the OIE element, many factors could

Table 2. Number of emetic episodes during the 24 h study period

	Ondansetron 8 mg	16 mg	Metoclopramide 10 mg
Number of subjects	456	461	449
Number of emetic episodes			
0	191 (42%)	199 (43%)	144 (32%)
1	39 (9%)	33 (7%)	29 (6%)
2	9 (2%)	5 (1%)	17 (4%)
3	1 (< 1%)	1 (< 1%)	9 (2%)
> 3	2 (< 1%)	0	3 (< 1%)
Rescued	211 (47%)	218 (47%)	244 (54%)
Withdrawn (not rescued)	0	4 (< 1%)	2 (1%)
Not recorded	3	1	1

Values are number (%) of emetic episodes. Percentages are based on the number of subjects with evaluable data.

Table 3. Nausea scores during the 24 h study period

8 mg	Ondansetron 16 mg	Ondansetron 10 mg	Metoclopramide
n	453	460	447
Base-line	5.7	5.9	5.9
15 min	1.8	1.9	1.6
15min – 1 h	1.4	1.5	1.1
1 h–2 h	1.2	1.3	1.4
2 h–4 h	1.5	1.5	1.8
4 h–6 h	1.6	1.6	1.9
6 h–24 h	1.6	1.7	1.9

Scores are mean values.
There were no significant differences for comparisons between any pair of treatments.
A score of 0 = no nausea; a score of 10 = nausea as bad as can be.

Table 4. Pain scores during the 24 h study period

	Ondansetron 8 mg	Ondansetron 16 mg	Metoclopramide 10 mg
n	453	460	446
Base-line	4.8	5.0	4.8
15 min	4.1	4.1	3.7
15min – 1 h	3.5	3.5	3.1
1 h–2 h	3.2	3.3	2.7
2 h–4 h	3.0	3.1	2.7
4 h–6 h	2.8	2.8	2.6
6 h–24 h	3.2	3.1	3.1

Scores are mean values.
The pain scores for the metoclopramide group were significantly lower when compared with ondansetron 8 mg ($P = 0.017$) and ondansetron 16 mg ($P = 0.022$), but there was no significant difference between the ondansetron groups.
A score of 0 = no pain; a score of 10 = pain as bad as can be.

potentially contribute to the incidence of emesis in these studies, including type of surgery, anaesthetic regimen, age and gender of the patient. The present study design attempts to maximize the likelihood that nausea and emesis are due to the opioids and minimize the likelihood that nausea and emesis are reflective of PONV. In the present study, recruitment was restricted to patients undergoing inherently low emetogenic surgical procedures. Furthermore the anaesthetic regime was strictly controlled to minimize PONV. Patients who experienced any nausea or emesis prior to receipt of their first post-surgical opioid were excluded from the treatment phase of the study. These measures give confidence that the present study investigates the control of OIE and not PONV.

The overall incidence of OIE reported in this study was 30%. The three treatment groups were well balanced in terms of demographic factors including gender, age, ethnic origin, type of anaesthesia, surgery type, history of OIE and opioid type. It is notable that approximately 75% of the patients were female in each of the treatment groups.

None of the currently marketed anti-emetic medications is indicated specifically to treat OIE. The present study was designed as a comparative study in the

Table 5. Patient Satisfaction with Study Medication during Study Period

	Ondansetron 8 mg	Ondansetron 16 mg	Metoclopramide 10 mg
Speed of onset	355/443 (80%)	345/450 (77%)	315/439 (72%)
Duration of effect	317/442 (72%)	306/450 (68%)	268/440 (61%)
Control of emesis	318/443 (72%)	326/449 (73%)	279/440 (63%)
Use medication again?			
Yes	293/443 (66%)	294/452 (65%)	243/442 (55%)
Not sure	87/435 (20%)	94/448 (21%)	116/446 (26%)
No	65/433 (15%)	62/443 (14%)	81/450 (18%)

Values show proportion and percentage of patients who were very satisfied and satisfied with study medication in terms of speed of onset, duration of effect, control of emesis and also their willingness to use the study medication again.
In all cases, there was a highly significant difference between ondansetron 8 mg and metoclopramide 10 mg ($P < 0.005$) and between ondansetron 16 mg and metoclopramide 10 mg ($P < 0.043$) in terms of grade of satisfaction or willingness to use medication again. There were no significant differences in response between the two doses of ondansetron.

treatment of established OIE in post-surgical patients. A dose-ranging study [12] has shown that ondansetron 4 mg and 16 mg i.v. were significantly more effective than placebo for complete control of emesis (the proportion of patients experiencing complete control of emesis: placebo 16%, ondansetron 4 mg 38% and ondansetron 16 mg 50%, $n = 28$–32 [12]). In addition, whilst this study demonstrated that ondansetron 16 mg i.v. in post-surgical patients was more effective than ondansetron 4 mg i.v., it did not establish the dose for maximal effect. Therefore, the present study included both an 8-mg and a 16-mg treatment group, and compared these with metoclopramide 10 mg i.v. Although metoclopramide is not licensed for use for OIE, 10 mg i.v. is commonly used to treat postsurgical patients suffering nausea and emesis and so it was included as comparator in the present study.

The present study has shown that during the 24 h following treatment for OIE, ondansetron and metoclopramide were effective. In addition, patients receiving ondansetron 8 mg i.v. or ondansetron 16 mg i.v., as a single dose, were significantly better controlled for both emesis and nausea than those receiving metoclopramide 10 mg i.v. Furthermore, a significantly smaller proportion of patients receiving either dose of ondansetron required rescue anti-emetic medication during the 24 h than those who received metoclopramide 10 mg i.v. This study also demonstrated that there was no significant difference in efficacy between the two doses of ondansetron, and therefore that 8 mg i.v. is the optimal dose in this setting.

In support of the present study, previous studies in volunteers [25], post-surgical patients [12] and non-surgical patients [26] have also shown ondansetron to be effective in controlling OIE in a wide range of clinical settings.

Nausea and emesis in the post-surgical setting are well known to affect patients' quality of life [27,28]. This study has shown that patients who had received ondansetron for the treatment of OIE were more satisfied with their anti-emetic medication than those who had received metoclopramide. This suggests ondansetron can improve the patients' quality of life and play an important role in facilitating optimum pain management through the use of opioids by minimizing nausea and emesis.

Conclusions

This study demonstrated that both ondansetron 8 mg i.v. and ondansetron 16 mg i.v., given as single doses, are significantly more effective in the treatment of established OIE in post-surgical adult patients than a single dose of metoclopramide 10 mg i.v. There is no significant difference in anti-emetic efficacy between the two doses of ondansetron, and both are well tolerated. In this study ondansetron 8 mg i.v. was

found to be the optimum dose for treating OIE. Ondansetron is the first anti-emetic for which efficacy in OIE has been formally assessed.

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References

1 Philip BK. Opioids in outpatient anesthesia. *Anesthesiol Rev* 1991; **8** (Suppl.1): 4–8.
2 Comroe JH, Dripps RD. Reactions to morphine in ambulatory and bed patients. *Surgery, Gynecol Obstetrics* 1948; **87**: 221–224.
3 Watcha M, White P. Post-surgical nausea and vomiting: its etiology, treatment and prevention. *Anesthesiology* 1992; **77**: 162–184.
4 Andersen R, Krohg K. Pain as a major cause of post-surgical nausea. *Canadian Anaesthetists' Soc J* 1976; **23**: 366–369.
5 Sharma SK, Davies MW. Patient-controlled analgesia with a mixture of morphine and droperidol. *Br J Anaesthesia* 1993; **71**: 435–436.
6 Williams OA, Clarke FL, Harris RW, Smith P, Peacock JE. Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting. *Anaesthesia* 1993; **48**: 881–884.
7 Barrow PM, Hughes DG, Redfern N, Urie J. Influence of droperidol on nausea and vomiting during patient-controlled analgesia. *Br J Anaesthesia* 1994; **72**: 460–461.
8 Gan TJ, Alexander R, Fennelly M, Rubin AP. Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of post-surgical nausea and vomiting. *Anesth Analg* 1995; **80**: 81–85.
9 Roberts CJ, Millar JM, Goat VA. The anti-emetic effectiveness of droperidol during morphine patient-controlled analgesia. *Anaesthesia* 1995; **50**: 559–562.
10 Walder AD, Aitkenhead AR. A comparison of droperidol and cyclizine in the prevention of post-surgical nausea and vomiting associated with patient-controlled analgesia. *Anaesthesia* 1995; **50**: 654–656.
11 Alexander R, Lovell AT, Jones RM. Comparison of ondansetron and droperidol in reducing post-surgical nausea and vomiting associated with patient-controlled analgesia. *Anaesthesia* 1995; **50**: 1086–1088.
12 Rung GW, Claybon L, Hord A *et al.* Intravenous ondansetron for postsurgical opioid-induced nausea and vomiting. *Anesth Analg* 1997; **84**: 832–838.
13 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988; **75**: 800–802.
14 Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. In: Berry Da, ed. *Statistical Methodology in the Pharmaceutical Sciences.* New York: Marcel Dekker Inc., 1990: 423–426, 453–455.
15 Ward SE, Goldberg N, Miller-McCauley V *et al.* Patient–related barriers to management of cancer pain. *Pain* 1993; **52**: 319–324.
16 Ashburn MA, Lipman AG. Management of pain in cancer patients. *Anesth Analg* 1993; **76**: 402–416.
17 Kantor TG, Hopper M, Laksa E. Adverse effects of commonly ordered oral narcotics. *J Clin Pharmacology* 1981; **21**: 1–8.
18 Stenseth R, Sellevold O, Breivik H. Epidural morphine for post-surgical pain: experience with 1085 patients. *Acta Anaesthesiol Scandinavia* 1985; **29**: 148–156.
19 Wheatley RG, Madej TH, Jackson IJB, Hunter D. The first year's experience of an acute pain service. *Br J Anaesthesia* 1991; **67**: 353–359.
20 Benzon HT, Wong HY, Belavic AM *et al.* A randomised double-blind comparison of epidural fentanyl injection

versus patient controlled analgesia with morphine for postthorocotomy pain. *Anesthesia Analgesia* 1993; **76**: 316–322.

21 Dottrens M, Rifat K, Morel DR. Comparison of extradural administration of sufentanil, morphine and sufentanil-morphine combination after ceasarian section. *Br J Anaesthesia* 1992; **69**: 9–12.

22 Freedman G, Kreitzer J. Addition of droperidol to PCA morphine sulphate reduced nausea and vomiting and potentiates analgesia. *Anesthesiology* 1991; **75** (3A): A668.

23 Harmer M, Slattery PJ, Rosen M, Vickers MD. Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine and meptazinol. *Br Med J* 1983; **286**: 680–682.

24 Robinson SL, Fell D. Nausea and vomiting with use of a patient-controlled analgesia system. *Anaesthesia* 1991; **46**: 580–582.

25 Koch JTL, Xu L, Bingaman S *et al.* Effect of ondansetron on morphine-induced nausea, vasopressin, and gastric myoelectric activity in healthy humans. *Gastroenterology* 1993; **104**: A535.

26 Sussman G, Shurman J, Creed MR *et al.* Intravenous ondansetron for the treatment of opioid-induced nausea and vomiting. *Clinical Therapeutics* 1999. (in press.)

27 Kenny GNC. Risk factors for post-surgical nausea and vomiting. *Anaesthesia* 1994; **49** (Suppl.): 6–10.

28 Polazzo MGA, Strunin L. Anaesthesia and emesis I: etiology. *Can Anaesthesia Soc J* 1984; **31**: 178–187.