A single iv dose of ondansetron 8 mg prior to induction of anaesthesia reduces postoperative nausea and vomiting in gynaecological patients

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The effect of a single intravenous dose of ondansetron in preventing postoperative nausea and emesis (retching and vomiting) (PONV) was investigated in a randomized, double-blind, placebo-controlled, multicentre, international study. Women of ASA class I–III, requiring gynaecological laparotomy, vaginal hysterectomy, or major vaginal surgery were selected for study. Two hundred and thirty-five received placebo, 231 received 1 mg ondansetron, 228 received 8 mg ondansetron and 229 received 16 mg ondansetron, as an infusion over five minutes before the induction of anaesthesia. A standardized balanced anaesthetic technique was employed. This consisted of premedication with either diazepam or temazepam, thiopentone induction, maintenance with nitrous oxide in oxygen supplemented with enflurane or isoflurane, intraoperative analgesia with fentanyl, neuromuscular blockade with any choice of agent and reversal

with neostigmine and atropine. Postoperative analgesia was achieved with morphine, and prochlorperazine or metoclopramide were given if a rescue antiemetic was required. A greater percentage of patients in the 8 mg and 16 mg ondansetron groups experienced no postoperative emesis (44% and 39% respectively) than in the placebo and 1 mg ondansetron groups (29% and 28% respectively) for the first 24 hr postoperative period (8 mg vs placebo and 1 mg: $P \leq 0.001$; 16 mg vs placebo: $P < 0.05$; 16 mg vs 1 mg: $P < 0.05$). Similarly, the percentage of patients who did not experience postoperative nausea were 20%, 26%, 31% and 28% for the placebo, 1 mg, 8 mg and 16 mg ondansetron treatment groups, respectively (8 mg and 16 mg vs placebo $P < 0.05$). Overall, the incidences of adverse events in the ondansetron and placebo groups were similar. It is concluded that intravenous ondansetron, at doses of 8 mg and 16 mg, is both well tolerated and effective in preventing postoperative nausea and emesis, and no greater benefit was observed with the 16 mg dose in comparison with the 8 mg dose.

Key words

COMPLICATIONS: nausea, vomiting;

VOMITING: anti-emetics, ondansetron, nausea.

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L'efficacité d'une dose unique d'ondansetron pour prévenir le phénomène émétique (haut-le-cœur et vomissement) est évaluée lors d'une étude multicentrique internationale, randomisée, à double insu et contrôlée avec placebo. Des patientes de classe ASA I–III soumises à une laparotomie gynécologique, hystérectomie vaginale ou chirurgie vaginale majeure sont sélectionnées. Parmi celles-ci, 235 reçoivent un placebo, 231 ondansetron 1 mg, 228 ondansetron 8 mg, et 229 ondansetron 16 mg. La préparation est perfusée pendant les 5 min qui précèdent l'anesthésie. On utilise une technique d'anesthésie équilibrée. La prémédication consiste en du diazépam ou du témazépam. L'induction est réalisée avec du thiopental, le maintien avec du protoxyde d'azote en oxygène avec ajout de fentanyl pour l'analgesie peropératoire, et la relaxation musculaire avec un choix de plusieurs agents. La relaxation est renversée par de l'atropine et de la néostigmine. A la période postopératoire, l'analgesie est obtenue avec de la morphine. Comme antiéméti-

que, les patientes reçoivent de la prochlorpérazine ou de la métoclopramide lorsque nécessaire. Dans les groupes ondansetron 8 et 16 mg, les patientes présentent moins de phénomènes émetiques (44 et 39% respectivement, que dans les groupes placebo et ondansetron 1 mg (29 et 28% respectivement dans les premières 24 hr postopératoires (8 mg vs placebo et 1 mg: $P \leq 0,001$; 16 mg vs placebo: $P < 0,05$; 16 mg vs 1 mg: $P < 0,05$). Le pourcentage de patientes qui n'ont pas souffert de nausées, est de 20%, 26%, 31% et 28% respectivement, pour les groupes placebo, ondansetron 1 mg, 8 mg et 16 mg (8 mg et 16 mg vs placebo: $P < 0,05$). Le nombre d'événements indésirables est le même dans les groupes ondansetron que dans le groupe placebo. En conclusion, aux doses de 8 et 16 mg, l'ondansetron est à la fois bien toléré et efficace pour la prévention des nausées et vomissements postopératoires, et la dose de 16 mg ne présente pas d'avantages sur celle de 8 mg.

Nausea and vomiting are common and distressing complications of surgery performed under anaesthesia,¹ and can occur in approximately 20% to 55% of patients.^{2,3} Such incidences have remained unchanged over the last few decades.³ A number of predisposing factors are thought to influence the incidence of postoperative nausea and vomiting (PONV). Such factors include sex, with women being two to three times more susceptible than men, which may be further related to the phase of the menstrual cycle, the anaesthetic technique employed, and also the type of surgery performed.^{2,3} It is known that women undergoing major gynaecological surgery with general anaesthesia experience a high incidence of PONV of approximately 60%.⁴ For this reason a similar group of patients was included in the present study.

Ondansetron is a selective 5-hydroxytryptamine subtype 3 (5-HT₃) receptor antagonist, which lacks effects at cholinergic, adrenergic, dopaminergic and histaminergic receptors.⁵ It has been shown to be effective in preventing nausea and vomiting associated with cancer chemotherapy and radiation therapy⁶⁻⁸ as well as that occurring postoperatively.^{9,10} This present study was designed to identify an optimum and safe single intravenous dose of ondansetron for the prophylaxis of postoperative nausea and emesis. The dose of 16 mg ondansetron was chosen because 16 mg of the oral preparation, when given before the operation and eight hours later, had been found previously to be effectively in preventing PONV.⁹ The other two doses of 1 mg and 8 mg ondansetron were also evaluated to try to establish a dose-response effect with this new anti-emetic.

Methods

This was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. All patients gave

written informed consent, after the nature of the study had been explained. Ethics committees concerned gave their approval before the study commenced.

Patient population

Patients of ASA grade I-III, aged between 18-65 yr, who were scheduled to undergo gynaecological laparotomy, vaginal hysterectomy or major vaginal surgery under general anaesthesia were selected for inclusion in the study. Patients were excluded if they had; evidence of uncontrolled clinically important neurological, renal, hepatic, cardiovascular, metabolic or endocrine dysfunction or clinically important abnormalities in laboratory screening tests; experienced vomiting or had received an anti-emetic 24 hr before administration of the study medication; or participated in a clinical study with an unregistered compound within a month of taking part in the study. In addition, patients were excluded from the study if they were scheduled to have a nasogastric tube *in situ* postoperatively, weighed <45 kg or >90 kg, or were pregnant or breast feeding.

Study medication

Study medication, 20 ml of either placebo (isotonic saline with citrate buffer), 1 mg, 8 mg or 16 mg ondansetron (as ondansetron hydrochloride dihydrate, all diluted to 20 ml in isotonic saline with citrate buffer), was administered as an infusion over five minutes immediately before the induction of anaesthesia.

Anaesthetic regimen

The drugs to be used for anaesthesia were defined for the study. However, clinicians were able to select the appropriate dose of each agent for individual patients.

Patients received premedication with diazepam or temazepam one hour before surgery. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen supplemented with enflurane or isoflurane. Analgesia at induction and during maintenance of anaesthesia was provided with fentanyl. Neuromuscular relaxants were given at the discretion of the investigator concerned and, if appropriate, reversal was achieved with atropine and neostigmine. Morphine was given for postoperative pain and either metoclopramide or prochlorperazine were prescribed as rescue anti-emetic.

Efficacy assessments

Trained nurses maintained a record of each emetic episode (retching or vomiting) during the 24 hr postoperative period. Episodes were considered separate if they were divided by an interval of one minute or greater. Nausea was assessed by direct questioning of the patient immediately before premedication and again at 1, 4 and

TABLE 1 Patient demography, duration of anaesthesia and time to recovery

	Placebo (n = 235)	Ondansetron		
		1 mg (n = 231)	8 mg (n = 228)	16 mg (n = 229)
Mean age (yr), (SD) Range = 18–65 yr	42.9 (8.5)	42.8 (8.3)	42.3 (8.4)	42.8 (8.8)
Mean weight (kg), (SD)	65.1 (10.2)	66.5 (10.0)	65.7 (10.0)	65.4 (11.0)
Mean height (cm), (SD)	161.1 (6.6)	162.9 (6.9)	161.8 (6.8)	162.3 (6.9)
Number of days since last menstrual cycle				
0–8 days	47	51	57	47
9–16 days	49	52	56	56
> 16 days	78	69	57	67
Post-menopausal	45	47	42	45
Not known	16	12	16	14
Mean duration of anaesthesia (min), (SD)	91 (42)	91 (41)	93 (39)	90 (35)
Mean time to recovery (min), (SD)	10 (8)	11 (8)	11 (9)	10 (8)

24 hr after recovery from anaesthesia. The patient graded the severity of nausea using a linear scale of 0 to 10 where zero represented "no nausea" and 10 was described as being "nausea as bad as it could possibly be."

Safety assessments

A physical examination was carried out and blood and urine samples were taken before the day of operation and 5–7 days after. Details of menstrual status were recorded, where possible. Status was recorded as post-menopausal or the start of the last menstrual cycle as 0–8 days, 9–16 days, or >16 days before the day of operation. Blood samples were assessed as an indicator of renal, hepatic and haematological function. Urine samples were analysed for the presence of protein and glucose, and pH. If data postoperatively were outside the normal range they were followed up until normal. Patients were encouraged to mention any possible side effects 24 hr after the operation and again 5–7 days later at the time of the physical examination. Vital signs, including heart rate and non-invasive arterial blood pressure, were recorded at the time of the first visit, premedication, arrival in the operating room, induction of anaesthesia and every 15 min thereafter until one hour after recovery, and again 24 hr after recovery.

The duration of anaesthesia and the time required for patients to recover from the anaesthetic agents (defined as the first response to a spoken command) were assessed.

Statistical and analytical aspects

The sample size chosen was designed to detect a decrease in nausea and emesis from 60% after placebo to 45% after ondansetron with a power of 80% assuming two-sided tests at the 5% significance level. The proportions of patients who did not experience emesis and nausea during the 0–24 hr after recovery from anaesthesia were compared among treatments for the total population. The

comparisons were made using logistic regression analysis and were repeated taking into account any possible influencing effects of one country over another. The total number of emetic episodes during each time period and the time to the first emetic episode were compared among treatments for the total population using Wilcoxon rank sum tests. These analyses were repeated taking into account any influencing effects of any one country, using the van Elteren method. Since some centres recruited only a small number of patients, centres were combined into countries for the purpose of analysis. All analyses adjusted for country gave similar results to the unadjusted analyses.

Results

Study population

Of the 923 patients who entered the study, only seven were completely excluded from the analysis. These were excluded because of protocol violations; either incorrect surgery was performed, a gastric-tube was used post-operatively or patients were given other prophylactic antiemetics in addition to the study medication. Demographic data and mean duration of anaesthesia (90–93 min) and mean time to recovery (10–11 min) are listed in Table I. All variables are well matched. The groups were comparable with regard to the type of surgery performed (Table II) and the dosage of intraoperative anaesthetic and analgesic agents used, together with the postoperative dosage of morphine (Table III).

Efficacy

A greater number of patients in the 8 mg and 16 mg ondansetron groups did not experience emesis than in the placebo and the 1 mg ondansetron groups during the 24 hr post-recovery period (Table IV). Nausea was also experienced by fewer patients in the 8 mg and 16

TABLE II Types of surgery performed

Surgery	Placebo (n = 235)	Ondansetron		
		1 mg (n = 231)	8 mg (n = 228)	16 mg (n = 229)
Abdominal hysterectomy (%)	156 (66.4)	149 (64.5)	162 (71.1)	148 (64.6)
Vaginal hysterectomy (%)	26 (11.1)	33 (14.3)	16 (7.0)	34 (14.8)
Gynaecological laparotomy (%)	33 (14.0)	31 (13.4)	39 (17.1)	32 (14.0)
Other major gynaecological surgery (%)	17 (7.2)	14 (6.1)	8 (3.5)	11 (4.8)
Other surgery (%)	3 (1.3)	4 (1.7)	3 (1.3)	4 (1.8)

TABLE III Anaesthetic and analgesic agents used

	Ondansetron			
Drug	Placebo (n = 235)	1 mg (n = 231)	8 mg (n = 228)	16 mg (n = 229)
<i>Premedication</i>				
Temazepam – mtd (range), mg	19.7 (10–30)	20.3 (10–30)	19.7 (10–30)	20.3 (10–30)
Diazepam, oral – mtd (range), mg	10.9 (5–20)	11.0 (5–20)	10.7 (5–20)	10.8 (2.5–20)
Diazepam, rectal – mtd (range), mg	14.0 (10–20)	13.7 (10–15)	15.6 (10–20)	13.8 (10–20)
<i>Anaesthesia</i>				
Thiopentone – mtd (range), mg	312.2 (150–500)	318.5 (125–500)	305.9 (150–500)	305.7 (125–600)
N ₂ O/Enflurane – mean range, %	62.1–64.9/0.6–1.4	61.6–64.6/0.6–1.4	61.8–64.6/0.6–1.3	61.2–64.4/0.6–1.4
N ₂ O/Isoflurane – mean range, %	63.2–66.5/0.5–1.4	63.4–66.7/0.4–1.2	63.2–66.4/0.5–1.4	63.2–66.0/0.4–1.2
Vecuronium – mtd (range), mg	7.8 (2–19)	7.9 (2–15)	7.8 (4–18)	7.6 (4–16)
Pancuronium – mtd (range), mg	6.4 (3–14)	6.3 (0.5–12)	6.2 (1–10)	5.8 (1–9)
Succinylcholine – mtd (range), mg	90.2 (50–100)	86.9 (50–100)	85.4 (50–100)	87.1 (50–100)
Atracurium – mtd (range), mg	39.6 (15–70)	40.7 (20–70)	35.5 (1–63)	41.3 (15–100)
Alcuronium – mtd (range), mg	17.4 (7.5–30)	17.2 (10–25)	17.7 (12–25)	17.7 (12.5–25)
Fentanyl – mtd (range), µg	258.4 (25–950)	262.9 (15–900)	256.5 (25–800)	262.7 (25–1000)
Atropine – mtd (range), mg	1.1 (0.5–2)	1.1 (0.5–2.5)	1.1 (0.5–2)	1.1 (0.5–2.5)
Neostigmine – mtd (range), mg	2.5 (1.3–6)	2.6 (1–5)	2.6 (1–5)	2.5 (0.5–5)
Glycopyrronium – mtd (range), mg	0.7 (0.5–1)	0.6 (0.6–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.6)
<i>Postoperative analgesia</i>				
Morphine – mtd*, mg	37	35.4	35.6	39.2

mtd = mean total dose. *Range not available.

TABLE IV Percentage of patients who did not experience nausea and emesis 0–24 hours after recovery from anaesthesia

	Placebo (n = 235)	Ondansetron		
		1 mg (n = 231)	8 mg (n = 228)	16 mg (n = 229)
Nausea	20%	26%	31%*	28%*
Emesis	29%	28%	44%†	39%*

Analyses were performed using logistic regression techniques.

*Different from placebo $P < 0.05$.

†Different from placebo and 1 mg ondansetron $P \leq 0.001$.

mg ondansetron groups than in the placebo group ($P < 0.05$).

Both the 8 mg and 16 mg of ondansetron were found to delay the time to the first emetic episode, and to reduce

the median number of emetic episodes, compared with placebo group (Table V).

Menstrual cycle

The stage of the menstrual cycle was recorded for a total of 865 patients (Table I). The incidences of emesis and nausea for the different phases of the menstrual cycle in all treatment groups were between 62–66% and 73–75%, respectively. As the differences in the ranges for these incidences were small (emesis: 4%, nausea 2%) it is clear that one phase of the menstrual cycle did not exhibit any clinically relevant increase in PONV over any other. Additionally, the overall incidences of PONV for all phases of the menstrual cycle did not differ greatly from the overall study incidences (emesis: 56–71%, nausea: 69–80%). Thus, menstrual cycle was not found to

TABLE V The time to first emetic episode and number of emetic episodes during the 0–24 hr post-recovery period

	Placebo (<i>n</i> = 235)	Ondansetron		
		1 mg (<i>n</i> = 231)	8 mg (<i>n</i> = 228)	16 mg (<i>n</i> = 229)
Mean time to first episode for patients who experienced emesis (hr)	5.5	6.4	8.0*	8.1*
Median number of emetic episodes	>4	>4	1.0*	2.0†

**P* ≤ 0.001 vs placebo.†*P* = 0.021 vs placebo.

TABLE VI Adverse events

Adverse events	Placebo	Ondansetron		
		1 mg	8 mg	16 mg
Number of patients randomized	235	231	228	229
Number of patients with adverse events	49%	53%	53%	49%
Bradycardia	8%	9%	10%	7%
Constipation	10%	13%	9%	10%
Headache	8%	8%	6%	7%

be an important influence on the incidence of PONV in this study.

Safety

Constipation, bradycardia and headache were the most frequently reported adverse events and the incidence of these adverse events was similar in all groups (Table VI). The following adverse events were reported by approximately 2% of the patients in the ondansetron and placebo groups, anaemia, musculoskeletal pain, dizziness, anxiety, agitation, sleep disturbances, cough, pruritus, urinary tract infection, pyrexia and haemorrhage. The incidence of these adverse effects was similar in all treatment groups. No clinically important changes in blood pressure, heart rate, blood haematology or biochemistry were noted during the study.

Three patients, aged between 41 and 57 yr, died 15 to 21 days after they received study medication. One patient, who had a medical history of non-insulin dependent diabetes, pyelonephritis and pulmonary tuberculosis, received 1 mg ondansetron and was discharged from hospital. This patient was subsequently re-admitted to the hospital 13 days after the operation suffering with diabetic hyperglycaemia coma and died 21 days after surgery. The investigator considered the event almost certainly related to the patient's underlying condition and unrelated to the study drug. Two other patients, who had received 8 mg and 16 mg of ondansetron, died 15 and 21 days later due to severe intra-abdominal sepsis and septicaemia. The investigator considered these events unlikely to be related to the study medication.

A 57-yr old patient with a past history of hypertension, hay fever, asthma and allergy to penicillin, experienced an anaphylactic reaction of moderate severity (bronchospasm occurred and systolic blood pressure decreased to 75 mmHg) 21 min after receiving 16 mg ondansetron. Following treatment with adrenaline the symptoms resolved within ten minutes. The investigator considered it unlikely that the event was caused by the study medication and commented that the premedicant, acebutolol, contributed to the worsening of the bronchospasm and collapse.

Discussion

The study was designed to evaluate the safety and efficacy of an optimum dose of intravenous ondansetron for the prevention of postoperative nausea and emesis in patients undergoing general anaesthesia for gynaecological surgery. Patients receiving general anaesthesia for gynaecological surgery were chosen for the study as previous studies have shown that these procedures are associated with a high incidence of emesis and nausea.⁴ In addition, a variety of other factors has been shown to affect the incidence of postoperative nausea and emesis.^{2,3} These factors include types of gynaecological surgery performed, patient age, duration of anaesthesia and doses of narcotic analgesic medication administered. In this study all of these factors were well balanced between the treatment groups.

The phase of the menstrual cycle at which a gynaecological operation takes place has also been reported to influence postoperative emesis and nausea. Honka-

vaara *et al.*¹¹ found the greatest incidence of postoperative nausea and vomiting following gynaecological laparoscopies carried out during the luteal phase of the cycle 20 to 24 days after menstruation. The results of the present study failed to confirm these findings as there were no differences in the incidences of emesis and nausea for patients who were post-menopausal or for patients who were undergoing gynaecological operations 0 to 8 days, 9 to 16 days or greater than 16 days after the start of the last menstrual cycle. However, the differences in the results of these studies may be due to differences in the study population. Many patients in this study had irregular menstrual cycles whereas those in the Honka-vaara study were reported to be normal, also the days of the menstrual cycle were grouped differently.

It should be stressed that if patients complained, only once, of retching or vomiting, or if they experienced nausea grade 1, only once, they were considered to have had emesis and nausea in the analysis. Thus the criteria for assessing efficacy were very stringent. The overall incidence of emesis of 71% observed in the placebo group is comparable with that reported previously.^{9,12} This study showed clearly that both 8 mg and 16 mg of ondansetron, when compared with placebo, were capable of reducing postoperative emesis following gynaecological surgery during the whole 24 hr postoperative period by 15% and 10%, respectively. In addition, emesis was also better controlled with 8 mg and 16 mg of ondansetron than with 1 mg of ondansetron. Ondansetron 8 mg and 16 mg also reduced the incidence of nausea by 11% and 8%, respectively. There did not appear to be a difference in the efficacy of 8 mg and 16 mg ondansetron. Furthermore, the results of this study confirm those of other studies which have found both 8 mg intravenous ondansetron and 16 mg oral ondansetron to be effective in reducing the incidence of postoperative emesis and nausea in patients who had received major gynaecological surgery.^{9,12}

This study showed that intravenous ondansetron administered at induction of anaesthesia was safe and well tolerated. It has been noted previously that constipation and headache can occur following ondansetron administration in cancer patients. This was not reflected in this study as the incidence of these complaints did not differ between the placebo or ondansetron groups, this may be explained by the single-dose regimen of this study in comparison with the multi-dose regimen in most cancer patient studies. Although three patients died during the study all events were considered by the investigators to be unlikely to be related to the study medication. Similarly, for the patient who experienced an anaphylactic shock reaction, many other drugs had been given in addition to ondansetron and thus the relationship of the event to ondansetron was not clear. The investigator con-

sidered this event was unlikely to be due to the study medication.

In conclusion, patients undergoing gynaecological surgery are at high risk of experiencing postoperative emesis and nausea. The present study has shown that a greater proportion of these patients in both the 8 mg and 16 mg treatment groups experienced no emesis and no nausea than in the placebo group. In addition, the higher dose of ondansetron 16 mg, was not more effective than the 8 mg dose.

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