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EFFICACY OF ORALLY ADMINISTERED ONDANSETRON IN THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING: A DOSE RANGING STUDY

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SUMMARY

In a placebo-controlled, double-blind study, we have compared the efficacy of ondansetron 16 mg, 8 mg and 1 mg administered 8-hourly for prevention of postoperative nausea and vomiting. We studied 995 patients undergoing major gynaecological surgery; 982 were included in the analysis. Study medication was administered 1 h before induction of anaesthesia and second and third doses were given 8 and 16 h after the first. The treatment groups were similar for patient characteristics, surgical procedures, anaesthetics administered and opioids given. The frequency of nausea was 75%, 70%, 56% and 55% after placebo and ondansetron 1 mg, 8 mg and 16 mg, respectively; the corrresponding frequencies of vomiting were 60%, 55%, 37% and 37%. Ondansetron 8 mg was as effective as 16 mg and both resulted in significant reductions in nausea and vomiting compared with placebo and ondansetron 1 mg (P < 0.001).

KEY WORDS

Antagonists, 5-hydroxytryptamine: ondansetron. Surgery: gynaecological. Vomiting: postoperative.

Postoperative nausea and vomiting are distressing and frequent adverse events after general anaesthesia and surgery [1]. Patients who undergo gynaecological surgery may be especially at risk, with 60% experiencing emetic effects [2]. Ondansetron is a 5-hydroxytryptamine (5-HT) antagonist with selectivity for 5-HT_3 receptors [3]; it has been reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs and radiotherapy [4, 5]. In addition, it has been reported recently that it was effective in the prevention of postoperative nausea and vomiting [6]. The effectiveness of various doses of ondansetron in the prevention of chemotherapy-induced emesis has been reviewed extensively [7, 8].

The present study was undertaken to compare the efficacy of ondansetron 16 mg, 8 mg and 1 mg administered 8-hourly in the prevention of postoperative nausea and vomiting. The 8-hourly doses of ondansetron 8 mg and 16 mg chosen for this study were based on the recommended oral dose for cancer chemotherapy and radiotherapy pertaining at the time. Ondansetron 1 mg three times daily was selected as a minimally effective dose [7, 8].

PATIENTS AND METHODS

This international, placebo-controlled double-blind study was carried out in 31 hospitals in the U.K., The Netherlands, Germany and Norway and was conducted with the approval of the Ethics Committees of those hospitals involved in the study. The study was explained to each patient and written informed consent was obtained. We studied patients aged 18–65 yr and weighing 45–90 kg, undergoing gynaecological surgery requiring a laparotomy or vaginal hysterectomy under general anaesthesia. Patients who were classed as ASA IV or V or who had vomited during the 24 h before administration of the study drug were excluded, as were patients who were pregnant or breast feeding. Additional exclusions included the use of antiemetics in the 24 h preceding administration of the study drug and the use of intragastric tubes after operation. Patients were allocated randomly to treatment with orally administered ondansetron 16 mg, 8 mg or 1 mg or matching placebo. The first dose of the study medication was administered approximately 1 h before induction of anaesthesia and the second and third identical doses 8 and 16 h after the first.

Premedication was administered to more than 98% of patients and all received diazepam or temazepam, apart from one patient in the placebo group who received lorazepam. The premedication was administered together with the study medication. Anaesthesia was induced using thiopentone

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TABLE I. *Patient characteristics (mean (range or SD))*

	Placebo ($n = 249$)	Ondansetron 1 mg ($n = 241$)	Ondansetron 8 mg ($n = 245$)	Ondansetron 16 mg ($n = 247$)
Age (yr)	41.6 (20–67)	41.9 (21–66)	41.9 (18–64)	43.3 (18–65)
Weight (kg)	65.4 (9.7)	65.7 (9.6)	65.8 (10.6)	66.8 (10.8)

except for four patients in the ondansetron 8 mg group, three of whom received etomidate and one who received propofol. Neuromuscular blocking agents were used as required. If necessary, atropine and neostigmine were given to antagonize neuromuscular block, although a small proportion of patients in each treatment group received glycopyrronium. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with enflurane or isoflurane as required, although five patients received halothane and one had anaesthesia maintained with midazolam after failure of the anaesthetic machine. More than 96% of patients received fentanyl for intraoperative analgesia. Two patients received morphine in place of fentanyl. The duration of anaesthetic administration and the time to recovery from anaesthesia were noted. Patients were considered to have recovered from anaesthesia when they obeyed spoken commands. Postoperative analgesia was provided with morphine as necessary and prochlorperazine or metoclopramide was used as rescue antiemetic treatment if required.

The major measure of efficacy was the number of patients who did not report nausea or vomiting during the first 24 h after recovery from anaesthesia compared with those who did. Requirement for rescue antiemetic medication was considered to be a treatment failure and those patients were scored as experiencing nausea and to have vomited. Data concerning nausea and vomiting were collected by direct questioning of the patient at 1, 4 and 24 h after recovery from anaesthesia. All observations were made without knowledge of which treatment the patient received. The frequencies of nausea and vomiting were noted, together with the grade of the worst nausea experienced within the 24-h period, using the grading system: no nausea = 0; mild nausea = 1; moderate = 2; severe nausea = 3. The number of episodes of vomiting and the time to onset of the first episode were recorded. Retching was not assessed as a separate entity.

Heart rate and arterial pressures were recorded immediately before administration of the study drug, at induction, during anaesthesia and recovery and 24 h after recovery from anaesthesia. Patients were questioned about any possible side effects of the study medication at 24 h after recovery from anaesthesia and again after 5–7 days, when blood and urine samples were obtained for laboratory screening before discharge of the patient. Laboratory tests included measurement of serum concentrations of sodium, potassium, calcium, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase. Blood samples were obtained for measurement of haemoglobin content, red blood cell count, PCV, mean cell volume, platelet count and total and differential white cell counts. Urine was analysed for the presence of protein and glucose.

Assuming a frequency of nausea and vomiting of 60% in the placebo group, the number of patients was selected to detect a 15% difference between the treatment groups at the 5% significance level with 80% power. Statistical analysis was performed on an Olivetti M380 using SAS version 6.04 (SAS Institute, Cary, NC, U.S.A.). Comparison of the frequencies and relative risks of nausea and vomiting and nausea grade were made using logistic regression techniques. The number of episodes of vomiting and the time to onset of the first episode of vomiting were compared using Wilcoxon rank sum tests, as was the time to recovery from anaesthesia. The differences in heart rates and arterial pressures between the preoperative value and the values recorded at induction, during anaesthesia, during recovery and at 24 h after recovery from anaesthesia were compared using analysis of variance techniques.

RESULTS

A total of 995 patients were entered into the study; 982 were evaluated for efficacy. Of the 13 patients who were not evaluated for efficacy, six had scheduled operations cancelled, four received antiemetics prophylactically or during the 24 h immediately preceding administration of the study drug, one patient had an intragastric tube *in situ* after operation, one patient was transferred to the intensive care unit after operation and one was withdrawn after a change in the planned operation resulted in her being extremely distressed after operation. The mean age and weight in each of the treatment groups were not significantly different (table I). Two older patients, one aged 66 yr and one aged 67 yr, were recruited, and both were included in the analysis. Five patients exceeded the recommended weight range by less than 5 kg and all were included in the analysis. There were no differences between the four groups for the mean doses or the numbers of patients who received temazepam or diazepam premedication.

The groups were well matched for types of operation performed (table II). A few patients in each group underwent either non-gynaecological surgery via laparotomy or laparoscopy, or unspecified gynaecological surgery, but all were included in the analysis of efficacy. The treatment groups were comparable in terms of the agents used for induction and maintenance of anaesthesia. Each of the treatment groups received similar amounts of opioid analgesia both during and after operation

TABLE II. *Types of operation performed*

	Placebo ($n = 249$)	Ondansetron 1 mg ($n = 241$)	Ondansetron 8 mg ($n = 245$)	Ondansetron 16 mg ($n = 247$)
Abdominal hysterectomy	153	158	135	156
Vaginal hysterectomy	37	27	41	40
Gynaecological laparotomy	50	52	61	48
Other	9	4	8	3

(table III). The duration of anaesthesia was similar for each of the groups and there were no significant differences in the times to recovery after anaesthesia (table IV).

There were significant differences between the treatment groups in the frequencies of nausea during the 24-h period after recovery from anaesthesia (table V). Ondansetron 8 mg and 16 mg resulted in a significant reduction in the frequency of nausea compared with both the 1-mg dose ($P = 0.001$) and placebo ($P < 0.001$). There was no statistical difference between ondansetron 8 mg and 16 mg or between the 1-mg dose and placebo.

The worst nausea grades experienced over the 24 h after recovery from anaesthesia in the placebo, ondansetron 1 mg, 8 mg and 16 mg treatment groups were 1.6, 1.4, 1.1 and 1.0 (mean) and 2, 1, 1 and 1 (median), respectively. Both ondansetron 8 mg and 16 mg significantly decreased the worst nausea grade compared with the 1-mg dose and placebo (8 mg *vs* 1 mg: $P = 0.005$; 16 mg *vs* 1 mg: $P = 0.001$; 8 mg and 16 mg *vs* placebo: $P < 0.001$). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

There was a significant reduction in the number of patients who experienced vomiting during the first 24-h period after recovery from anaesthesia for those treated with ondansetron 8 mg and 16 mg compared with patients who received 1 mg ($P < 0.001$) or placebo ($P < 0.001$) (table V). There were no significant differences between ondansetron 8 mg and 16 mg or between the 1-mg dose and placebo.

The median times to the first episode of vomiting were significantly longer for patients who received ondansetron 8 mg and 16 mg compared with those given the 1-mg dose and placebo ($P < 0.001$ for all comparisons) (table VI). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

Both ondansetron 8 mg and 16 mg resulted in significant reductions in the number of episodes of vomiting compared with the 1-mg dose and placebo ($P < 0.001$ for all comparisons) (table VII). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

When the relative risks of experiencing nausea and vomiting were calculated, patients were found to be approximately 40% as likely to experience these symptoms after ondansetron 8 mg or 16 mg treatment as after placebo (table VIII).

TABLE IV. *Duration and recovery from anaesthesia (median (range))*

	Placebo ($n = 249$)	Ondansetron 1 mg ($n = 241$)	Ondansetron 8 mg ($n = 245$)	Ondansetron 16 mg ($n = 247$)
Anaesthetic duration (min)	85 (35–297)	90 (26–257)	90 (32–276)	95 (20–272)
Recovery time (min)	7 (0–60)	7 (0–85)	7 (0–185)	8 (0–155)

TABLE V. *Percentages of patients in each treatment group who experienced nausea or vomiting in the first 24 h after recovery from anaesthesia*

	Placebo ($n = 247$)	Ondansetron 1 mg ($n = 238$)	Ondansetron 8 mg ($n = 243$)	Ondansetron 16 mg ($n = 245$)
Patients experiencing nausea (%)	75	70	56	55
Patients experiencing vomiting (%)	60	55	37	37

TABLE VI. *Median time to first episode of vomiting (h) (data unadjusted for rescue antiemetics)*

	Placebo	Ondansetron 1 mg	Ondansetron 8 mg	Ondansetron 16 mg
Patients who vomited	3.5	4.0	5.4	6.5
n	133	117	81	76
All patients	15.8	> 24.0	> 24.0	> 24.0
n	247	238	243	245

TABLE III. *Opioid analgesics used during and after operation (mean (range))*

Opioid administered	Placebo ($n = 249$)	Ondansetron 1 mg ($n = 241$)	Ondansetron 8 mg ($n = 245$)	Ondansetron 16 mg ($n = 247$)
During operation				
Fentanyl (μg)	302 (25–800)	315 (25–800)	313 (10–750)	309 (25–650)
n	243	236	242	242
After operation (0–24 h)				
Morphine mean dose per patient (mg)	39.8	40.1	38.9	39.5
n	244	234	234	243

TABLE VII. *Number of episodes of vomiting (data unadjusted for rescue antiemetics)*

		Ondansetron		
	Placebo ($n = 247$)	1 mg ($n = 238$)	8 mg ($n = 243$)	16 mg ($n = 245$)
No. patients who vomited	133	177	81	76
No. episodes				
Mean	1.6	1.6	0.9	0.9
Median	1	0	0	0
Range	0–13	0–20	0–10	0–10

Side effects were recorded for all patients, regardless of possible cause. The frequency of reporting was similar for all groups (36% of patients in the placebo group and 37% of patients who received ondansetron). The majority of side effects reported were those that might be expected in surgical patients and there were no important differences between treatment groups. Increases in aminotransferase activities (ALT and AST) to greater than the reference ranges were common in all treatment groups, with a slightly greater incidence in patients treated with ondansetron (ALT 19%; AST 17%) compared with placebo (ALT 14%; AST 15%).

There were no significant differences in heart rates or diastolic arterial pressures between the groups. There were increases in systolic pressure during the period between induction and recovery and during the period immediately following recovery in the ondansetron 16 mg group compared with the placebo group. The treatment difference was statistically significant, but did not exceed 5 mm Hg.

DISCUSSION

This study was designed to identify the optimum dose and side effects of ondansetron 1 mg, 8 mg and 16 mg given orally three times a day, for prevention of postoperative nausea and vomiting after gynaecological surgery. The treatment groups were similar in terms of the type of patient and their characteristics, surgical procedure, types of anaesthetics used and opioid analgesics administered. The frequencies of nausea (75%) and vomiting (60%) observed in the placebo group were comparable to those reported previously [2]. Ondansetron reduced the frequency of nausea and vomiting in a dose-dependent manner compared with placebo and was equally effective against both symptoms. Not only was the frequency of nausea decreased but, in addition, the severity of nausea experienced was reduced as assessed by the worst nausea grade recorded for each patient. The 8-mg and 16-mg doses consistently provided significant improvement compared with the 1-mg dose, but there were no significant differences in efficacy between placebo and the 1-mg dose or between the 8-mg and 16-mg doses.

There were no significant differences in the overall frequency of side effects with ondansetron compared with placebo. Transient asymptomatic increases in alanine and aspartate aminotransferase activities were common in the placebo group. There were small increases in transaminase activities in the ondansetron-treated patients compared with the placebo treatment group, but the differences were unlikely to be of clinical significance. Asymptomatic increases in transaminases have been reported during the use of ondansetron for the treatment of nausea and vomiting during cytotoxic therapy and are included in existing prescribing information for this indication.

The increase in systolic arterial pressure after treatment with ondansetron 16 mg was of small magnitude and had no clinical relevance in the population studied. It remains to be investigated if this effect is more evident in patients who suffer from pre-existing hypertension. No other significant effects were observed on the cardiovascular system.

There was no effect of ondansetron on recovery time after anaesthesia. This is an important consideration for the treatment of patients undergoing day-case surgery, in whom major requirements are a rapid recovery from anaesthesia followed by minimal postoperative nausea and vomiting.

In conclusion, we found that three doses of ondansetron administered orally at 8-hourly intervals significantly reduced the frequency and severity of postoperative nausea and the frequency and number of episodes of vomiting. Both ondansetron 8 mg and 16 mg were more effective than 1 mg and placebo. An earlier study [6] has reported the efficacy of ondansetron 16 mg, administered orally 1 h before anaesthesia and again 8 h later, in preventing postoperative nausea and vomiting. The present study suggests that ondansetron 16 mg is no more effective than 8 mg when given three times a day. Ondansetron appeared to be well tolerated and effective in the prevention of postoperative nausea and vomiting.

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TABLE VIII. *Relative risk (95% confidence interval) of experiencing nausea or vomiting during the first 24 h after recovery from anaesthesia for ondansetron compared with placebo*

	Ondansetron 1 mg	Ondansetron 8 mg	Ondansetron 16 mg
Nausea	0.77 (0.52–1.15)	0.42 (0.29–0.61)	0.40 (0.28–0.59)
Vomiting	0.82 (0.57–1.17)	0.40 (0.28–0.58)	0.40 (0.28–0.58)

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