Treatment of Postoperative Emetic Symptoms with Granisetron in Women Undergoing Abdominal Hysterectomy: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study

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ABSTRACT

Background: Postoperative emetic symptoms (nausea, retching, and vomiting) frequently occur in women undergoing general anesthesia for abdominal hysterectomy. In a previous report by us, granisetron, a selective serotonin receptor antagonist, was more effective than the traditional antiemetics, droperidol and metoclopramide, for the treatment of postoperative emetic symptoms in this population.

Objective: The aim of this study was to determine the optimal dose of granisetron for the treatment of emetic symptoms following abdominal hysterectomy.

Methods: This randomized, double-blind, placebo-controlled, dose-ranging study was conducted at Toride Kyodo General Hospital (Toride, Japan). Female patients aged 33 to 66 years experiencing postoperative emetic symptoms after abdominal hysterectomy were eligible for the study. Patients received IV granisetron at 1 of 4 doses (10, 20, 40, or 100 µg/kg) or placebo; they were then observed for 24 hours. Emetic symptoms and the need for a rescue antiemetic were recorded by nursing staff, who were blinded to treatment assignment.

Results: A total of 100 patients (mean [SD] age, 45 [7] years [range, 33–66 years]) were enrolled (n = 20 in each group). No significant differences in patient demographic characteristics were observed between the groups. The number of patients in whom complete control of postoperative emetic symptoms, defined as being free of emetic symptoms and not needing rescue antiemetic medication for 24 hours after study drug administration, was established was significantly greater in 3 of the granisetron groups than in the placebo group (6 patients [30%]: granisetron 10 µg/kg, 7 patients (35%; $P = \text{NS}$); granisetron 20 µg/kg, 17 patients (85%; $P = 0.001$); granisetron 40 µg/kg, 17 pa-

tients (85%; $P = 0.001$); and granisetron 100 $\mu\text{g/kg}$, 16 patients (80%; $P = 0.002$). No clinically significant adverse events attributable to the study drug were observed in any group.

Conclusion: In this study of patients who experienced emetic symptoms after undergoing general anesthesia for abdominal hysterectomy, granisetron at doses $\geq 20 \mu\text{g/kg}$ was effective in the treatment of established postoperative emetic symptoms. (*Curr Ther Res Clin Exp.* 2004;65:321–329) Copyright © 2004 Excerpta Medica, Inc.

Key words: nausea, retching, vomiting, antiemetics, selective serotonin receptor antagonist, granisetron, hysterectomy.

INTRODUCTION

Emetic symptoms (nausea, vomiting, and retching) are distressing adverse events (AEs) that frequently occur after general anesthesia and surgery, with female patients being particularly susceptible.¹ The reported incidence of these emetic symptoms is as high as 80% in women undergoing abdominal hysterectomy when no prophylactic antiemetic regimen is given.^{2,3} Pharmacologic approaches (eg, antihistamines, butyrophenones, dopamine receptor antagonist) have been investigated for the prevention and treatment of postoperative emetic symptoms, but undesirable AEs (eg, excessive sedation, restlessness, dystonic reactions, extrapyramidal signs) have been noted.¹

Ondansetron, a selective serotonin receptor antagonist (SSRA), is effective for the prevention of postoperative emetic symptoms⁴ and for the treatment of these established symptoms.⁵ Another SSRA, granisetron, has more potent and longer-lasting activity against chemotherapy-induced emesis than does ondansetron.⁶ In a previous study by us,⁷ granisetron was more effective than the traditional antiemetics, droperidol and metoclopramide, in the treatment of postoperative emetic symptoms in women undergoing general anesthesia for gynecologic surgery.

The primary objective of this study was to determine the optimal dose of granisetron for the control of established postoperative emetic symptoms. The secondary objective was to assess the safety profile of granisetron as an antiemetic. Therefore, we conducted a randomized, double-blind, placebo-controlled, dose-ranging study to assess the efficacy and tolerability of granisetron for the treatment of these established symptoms following general anesthesia for abdominal hysterectomy.

PATIENTS AND METHODS

A MEDLINE search was conducted for articles published from January 1990 to December 2001 using the following search terms: *complications, nausea, retching, vomiting, treatment, antiemetics, selective serotonin receptor antagonists, granisetron, and abdominal hysterectomy*. This search was performed to identify

the literature regarding the minimum effective dose of granisetron for the treatment of emetic symptoms following abdominal hysterectomy. No studies were found.

The ethics committee of Toride Kyodo General Hospital (Toride, Japan) had approved clinical trials to assess the efficacy of antiemetics in patients undergoing elective surgery on June 30, 1995; this study was one of the approved trials.

Patients

Patients aged 33 to 66 years who were categorized as American Society of Anesthesiologists physical status I (no organic, physiologic, biochemical, or psychiatric disturbances) and were experiencing nausea lasting >10 minutes and/or retching or vomiting within 3 hours after recovery from anesthesia in the postanesthetic care unit for abdominal hysterectomy with or without salpingo-oophorectomy were eligible for inclusion in this study. Exclusion criteria were antiemetics given ≤ 24 hours before surgery, gastrointestinal disease, menstruation, and a history of motion sickness and/or postoperative emetic symptoms. Verbal consent was obtained from all eligible patients.

Methods

Preanesthetic medication was not given. Standard monitoring was used. An epidural catheter was inserted at the L2–3 or L3–4 level and was placed cephalad (~5 cm). Anesthesia was induced using IV thiopentone 5 mg/kg and fentanyl 2 $\mu\text{g/kg}$; vecuronium 0.2 mg/kg IV was used to facilitate tracheal intubation through the same catheter. After tracheal intubation, anesthesia was maintained using nitrous oxide 66% and isoflurane 1.0% to 3.0% (inspired concentration) in oxygen with controlled ventilation to maintain an end-tidal carbon dioxide concentration of 35 to 40 mm Hg. During surgery, 10 to 15 mL of lidocaine 1.5% was administered via the epidural catheter. Muscle relaxation was achieved using vecuronium, as required. A nasogastric tube was inserted, and suction was applied to empty the stomach of air and other contents. Before tracheal extubation, the nasogastric tube was again suctioned and then removed. At the end of the surgical procedure, nitrous oxide and isoflurane were discontinued, and IV atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were administered through the same catheter for reversal of muscle relaxation. The trachea was extubated after the patient awoke. Rectal temperature was monitored and maintained at 36.5°C to 37.5°C. Postoperative analgesia comprised a mixture of 100 mL of bupivacaine 0.125% and morphine 0.1 mg/kg administered epidurally at a rate of 2 mL/h using an infusion balloon catheter. Patients were also allowed to receive indomethacin 50 mg PR, if needed to control pain. Patients were randomly assigned, using a computer-generated random number table, to receive IV granisetron at 1 of 4 doses (10, 20, 40, or 100 $\mu\text{g/kg}$) or placebo (saline 5 mL).

Patients were observed for efficacy assessment for 24 hours after the study drug was administered. All episodes of emetic symptoms (nausea, vomiting, and retching) were recorded by nursing staff, who were blinded to treatment assignment. These nurses observed the patients at various intervals according to the normal ward routine. *Nausea* was defined as a subjectively unpleasant feeling associated with awareness of the urge to vomit; *vomiting* was defined as the forceful expulsion of gastric contents from the mouth; and *retching* was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents.¹ *Complete control of established postoperative emetic symptoms* was defined as being emesis-free (no nausea, vomiting, or retching) and not needing rescue antiemetic medication for 24 hours after study drug administration. If >2 emetic episodes occurred during the 24 hours after study drug administration, rescue antiemetic (IV metoclopramide 10 mg) was given. The severity of nausea was graded by the patient on an 11-point scale⁷ (0 = none to 10 = severe). The details of any other AEs were recorded by the nurses using patient interview.

Statistical Analysis

Sample-size calculation was performed before the study. Using a predicted complete control of established postoperative emetic symptoms in the placebo group of 30% as the primary outcome,^{2,3} 20 patients per group were calculated to be required to yield an improvement of 50% with a power ($1 - \beta$) of 0.8 ($\alpha = 0.05$). Patient demographic characteristics were analyzed using analysis of variance with the Bonferroni correction for multiple comparisons and the chi-square test. The numbers of patients with or without emetic symptoms and the incidence of AEs were compared using the Fisher exact test. The severity of nausea was analyzed using the Kruskal-Wallis test. $P < 0.05$ was considered significant. Values were expressed as mean (SD), number (%), or median (range). Analyses were performed using the Statistical Package for Social Sciences version 8.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 105 female patients were screened for the study. Five patients were excluded based on the exclusion criteria (antiemetic given ≤ 24 hours before surgery [1 patient], gastrointestinal disease [1], menstruation [1], a history of motion sickness and/or previous postoperative emesis [2]). One hundred patients (mean [SD] age, 45 [7] years [range, 33–66 years]; mean [SD] height, 155 [10] cm [range, 143–173 cm]; mean [SD] body weight, 56 [8] kg [range, 38–75 kg]) were enrolled. Patient demographic characteristics and information on surgery and anesthesia are shown in **Table I**. No significant differences in demographic characteristics were found between the groups.

The number of patients in whom complete control of established postoperative emetic symptoms was achieved was significantly greater in 3 of the

Table I. Baseline demographic and clinical characteristics of the study patients (n = 20 patients per group).*

Characteristic	Granisetron Dose, $\mu\text{g/kg}$				Placebo
	10	20	40	100	
Age, y					
Mean (SD)	43 (7)	44 (8)	43 (11)	44 (8)	44 (9)
Range	33–66	35–66	33–63	34–65	33–65
Body weight, kg					
Mean (SD)	55 (8)	54 (9)	55 (9)	55 (7)	54 (7)
Range	42–73	45–75	38–75	40–75	44–68
Height, cm					
Mean (SD)	154 (9)	155 (10)	155 (11)	155 (10)	154 (11)
Range	145–172	145–173	147–168	143–170	143–168
Duration of surgery, min					
Mean (SD)	76 (24)	77 (28)	72 (33)	76 (28)	74 (23)
Range	30–120	42–134	30–140	44–134	32–121
Duration of anesthesia, min					
Mean (SD)	96 (22)	100 (26)	96 (34)	99 (28)	94 (24)
Range	50–145	65–155	50–161	67–155	65–143
Analgesics used postoperatively					
Morphine, epidurally, mg					
Mean (SD)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
Range	4–7	4–7	4–7	4–7	4–7
Indomethacin, no. (%)	3 (15)	2 (10)	3 (15)	3 (15)	2 (10)

*No significant between-groups differences were found.

granisetron-treated groups than in the placebo group (6 patients [30%]): granisetron 10 $\mu\text{g/kg}$, 7 patients (35%; $P = \text{NS}$); granisetron 20 $\mu\text{g/kg}$, 17 patients (85%; $P = 0.001$); granisetron 40 $\mu\text{g/kg}$, 17 patients (85%; $P = 0.001$); and granisetron 100 $\mu\text{g/kg}$, 16 patients (80%; $P = 0.002$). Severity of nausea was significantly less in patients who had received granisetron 20, 40, or 100 $\mu\text{g/kg}$ than in those who had received placebo (all, $P = 0.038$); no significant difference was observed between patients who received granisetron 10 $\mu\text{g/kg}$ and those who received placebo (**Table II**).

The most frequent AE was headache, which was not serious. The incidence of headache (5%–10%) did not differ significantly between the groups.

DISCUSSION

Women undergoing abdominal hysterectomy have a high incidence of postoperative emetic symptoms.^{2,3} This problem is multifactorial in origin, including demographic characteristics, the nature of the underlying disease, the type of surgery, the anesthetic technique used, and postoperative care.¹ The main

Table II. Treatment efficacy (n = 20 patients per group). (Values are expressed as no. [%] of patients unless otherwise indicated.)

	Granisetron Dose, µg/kg								Placebo, No. (%)
	10		20		40		100		
	No. (%)	p*	No. (%)	p*	No. %	p*	No. (%)	p*	
Symptom									
None†	7 (35)	0.500	17 (85)	0.001	17 (85)	0.001	16 (80)	0.002	6 (30)
Nausea	7 (35)	1.000	2 (10)	0.064	2 (10)	0.064	2 (10)	0.064	7 (35)
Severity of nausea, median (range)‡	8 (6–10)	0.430	5 (4–6)	0.038	5 (4–6)	0.038	4.5 (4–5)	0.038	8 (7–10)
Vomiting	6 (30)	0.500	2 (10)	0.064	2 (10)	0.064	2 (10)	0.064	7 (35)
Retching	1 (5)	0.500	0 (0)	0.500	0 (0)	0.244	0 (0)	0.244	2 (10)
Rescue medication used, no. (%)	4 (20)	0.500	0 (0)	0.024	0 (0)	0.024	0 (0)	0.024	5 (25)

*Difference versus placebo.

†Defined as being free of emetic symptoms and not needing rescue antiemetics.

‡Scale: 0 = none to 10 = severe.

patient-related factors are age, sex, obesity, menstruation, and a history of motion sickness and/or previous postoperative emesis.¹ In the present study, however, these factors were well balanced among the groups. Also, patients with a history of motion sickness and/or previous postoperative emesis and those who were menstruating were excluded from the study because they had a high risk for postoperative emetic symptoms.^{1,8} Therefore, the difference in the rate of complete control of established postoperative emetic symptoms can be attributed to the study drug.

Granisetron is effective for the treatment of emesis in patients receiving cytotoxic drugs.⁹ In our previous study,⁷ granisetron increased the rate of complete control of postoperative emetic symptoms in patients undergoing general anesthesia for elective gynecologic surgery. The present study showed that the antiemetic efficacy of granisetron 20, 40, and 100 $\mu\text{g}/\text{kg}$ was superior to that of placebo for the treatment of postoperative emetic symptoms following anesthesia for abdominal hysterectomy, but there was no significant difference in complete control of symptoms between the granisetron 10- $\mu\text{g}/\text{kg}$ and placebo groups. These findings suggest that granisetron 20 $\mu\text{g}/\text{kg}$ can be regarded as the optimal dose for the treatment of established emetic symptoms in women undergoing abdominal hysterectomy. The exact mechanism of action of granisetron for the treatment of these symptoms is unknown, but it has been suggested that granisetron may act on sites containing serotonin receptors with demonstrated antiemetic effects.¹⁰

Granisetron lacks the sedative, dysphoric, and extrapyramidal signs that are associated with the traditional antiemetics, droperidol and metoclopramide.^{1,11} In our study, the most common drug-related AE was headache, which was not serious. There were no significant differences in the incidence of headache among the groups. Thus, no clinically significant AEs attributable to the study drug were observed in any group.

Based on our MEDLINE search, this was the first study of the appropriate dose of granisetron for the control of postoperative emetic symptoms following abdominal hysterectomy. We found that granisetron 20 $\mu\text{g}/\text{kg}$ is the optimal dose for increasing the rate of complete control of emetic symptoms for 24 hours after drug administration. However, in a previous study,¹² prophylactic antiemetic therapy with granisetron 40 $\mu\text{g}/\text{kg}$ was as effective as 60 $\mu\text{g}/\text{kg}$, and 20 $\mu\text{g}/\text{kg}$ was ineffective for the prevention of postoperative emetic symptoms in women undergoing gynecologic surgery. Consequently, granisetron 40 $\mu\text{g}/\text{kg}$ was found to be the appropriate dose for preventing these symptoms in that population.¹² The reason for this difference is not known, but it may be attributed to the difference in the use of granisetron as an antiemetic (prophylaxis vs treatment).

The results of the present study are important because of the potential cost reduction of therapy. In Japan, the pharmacy pays US \$33.40 for granisetron 1 mg, which is much more expensive than traditional antiemetics—\$1.80 for droperidol 1.25 mg and \$0.60 for metoclopramide 10 mg. This may delay the

widespread use of granisetron as an antiemetic. However, the use of droperidol and metoclopramide has been limited because these drugs occasionally cause extrapyramidal symptoms.¹ The US Food and Drug Administration recently issued an AE warning about droperidol because of its dysrhythmogenic activity (eg, prolonged QT syndrome).¹³ In our previous study,⁷ granisetron was more effective than these traditional antiemetics for the treatment of established postoperative emetic symptoms in women undergoing abdominal hysterectomy. Therefore, a decision about antiemetics should not be limited to these costs but should also consider patient outcome and the overall cost if patients are not treated. Further research is needed to perform the cost-effectiveness analysis.

CONCLUSION

In this study of patients who experienced emetic symptoms after undergoing general anesthesia for abdominal hysterectomy, granisetron at doses ≥ 20 $\mu\text{g}/\text{kg}$ was effective in the treatment of established postoperative emetic symptoms.

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