The Efficacy of RS-25259, a Long-Acting Selective 5-HT_3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures

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We evaluated the safety and efficacy of RS-25259, a potent and long-acting selective 5-HT_3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) in women undergoing hysterectomy procedures. In this randomized, double-blind, placebo controlled, dose-ranging study, 218 healthy, consenting women were assigned to one of the six treatment groups: placebo or RS-25259 0.1, 0.3, 1.0, 3.0, or 30 μg/kg. All patients underwent a standardized general anesthetic technique. The study medication was administered IV 20–30 min before the end of surgery. During the initial 24-h period after surgery, the incidence of vomiting, the need for rescue antiemetics, the time to the first episode of emesis, and administration of rescue antiemetic medication, as well as a nausea visual analog scale and verbal categorical scale scores were recorded. In addition, recovery times from the end of anesthesia and the incidences of perioperative side effects were noted. Only 30 μg/kg RS-25259 significantly decreased the incidence of vomiting and the requirement for rescue antiemetics. The largest dose of RS-25259 also delayed the time to the first emetic episode and reduced the number of treatment failures. However, no differences were found in the severity of postoperative nausea (versus saline), and postoperative headaches were more common after the administration of RS-25259 0.3–30 μg/kg IV. In conclusion, RS-25259 30 μg/kg IV was effective in reducing the incidence of PONV after major gynecologic surgery, but the occurrence of headaches with the larger doses of RS-25259 is a concern. **Implications:** RS-25259, a long-acting 5-HT_3 antagonist, was effective in reducing postoperative vomiting only at the largest dose studied (30 μg/kg). However, RS-25259 had no antinausea activity, and the larger doses were associated with an increased incidence of headaches in the postoperative period.

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Nausea, retching, and vomiting are common complications after major gynecologic surgery (1–3). Dehydration, electrolyte imbalance, excessive tension on suture lines, venous hypertension, and increased hematoma formation are secondary problems related to persistent or intractable postoperative emesis (4). Several different classes of prophylactic antiemetics have been administered in an attempt to decrease the incidence of postoperative nausea and vomiting (PONV). However, many of the commonly used antiemetics are associated with undesirable side effects (5,6).

Ondansetron, the first 5-HT_3 receptor antagonist, possesses antiemetic activity in women who develop intractable PONV after gynecologic surgery (7). Studies have confirmed the efficacy of ondansetron in both the treatment and prevention of PONV (8,9). However, a meta-analysis suggested that the use of ondansetron is associated with an increased incidence of headaches and transient elevations in liver enzymes (10).

RS-25259 is a potent and highly selective 5-HT_3 receptor antagonist (11) that is more effective than ondansetron in preventing chemotherapy-induced emesis in animals (12). In this preliminary, double-blind, dose-ranging study, the efficacy and safety of RS-25259 were evaluated when administered prophylactically to women undergoing major gynecologic surgical procedures.

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Methods

This randomized, double-blind, placebo-controlled study was performed at two medical centers (University of Texas Southwestern Medical Center in Dallas, TX and Wake Forest University Baptist Medical Center in Winston-Salem, NC). After obtaining institutional review board approval at both medical centers, 218 ASA physical status I or II consenting women undergoing an abdominal or vaginal hysterectomy with a standardized general anesthetic technique were enrolled in the study. Exclusion criteria included pregnancy, body weight >100% of the calculated ideal body weight, hypersensitivity to 5-HT_3 antagonists, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before the operation, a recent history of narcotic or alcohol abuse, and preexisting abnormalities involving the renal, hepatic, cardiovascular, metabolic, or endocrine systems. Patients were asked to provide a detailed medical history and demographic information (including age, weight, height, alcohol or drug consumption, last menstrual period, any history of PONV or motion sickness).

Because a history of PONV is associated with an increased risk of PONV after a subsequent operation (1), patients were assigned to one of two strata based on their history of PONV after general anesthesia. Within each strata, patients were randomized to one of six prophylactic treatment groups: placebo (saline) or 0.1, 0.3, 1.0, 3.0, or 30 μg/kg RS-25259. Each dose of study medication was prepared by the hospital pharmacy in a total volume of 15 mL of isotonic sodium chloride solution and was administered IV over 30 s approximately 20–30 min before the end of surgery.

In the preoperative holding area, patients completed a baseline 100-mm visual analog scale (VAS) for nausea (0 = no nausea to 100 = maximal nausea) and a verbal categorical scale (VCS) (1 = no nausea, 2 = mild nausea, 3 = moderate nausea, or 4 = severe nausea). Midazolam 2 mg IV was used to premedicate all patients. On arrival in the operating room, routine monitoring devices consisting of a noninvasive blood pressure cuff, pulse oximeter probe, and electrocardiogram were placed. General anesthesia was induced with thiopental and an opioid analgesic (either fentanyl or sulfentanil) and was maintained with isoflurane, nitrous oxide (N_2O) in oxygen, and a nondepolarizing neuromuscular blocking drug. Residual neuromuscular block was antagonized with neostigmine and glycopyrrolate. After tracheal extubation, the patients were transported to the postanesthesia care unit (PACU) where morphine or meperidine was administered as needed for postoperative analgesia.

The anesthetic time (from induction of anesthesia to discontinuation of N_2O) and the operating time (from surgical incision to completion of the last suture) were recorded. The times at which patients were able to follow commands (e.g., squeeze the investigator's hand) and were discharged from the PACU were also noted. Episodes of PONV and administration of rescue antiemetics were recorded during the first 24-h period after surgery. An emetic episode was defined as a single vomiting or retching event or any combination of these events separated by less than 1 min.

Rescue antiemetic medication was administered after a repeat emetic episode or at the request of the patient. In addition, the time interval to first experiencing an emetic episode or to receiving a rescue antiemetic, as well as treatment failures (defined as a situation in which the patient experienced a single emetic episode or required rescue antiemetic medication), were noted. On arrival in the PACU and 1, 2, 4, 8, 12, 16, 20, and 24 h after the end of anesthesia, patients were asked to assess their degree of nausea using the VAS and VCS. At the end of the 24-h observation period, a VCS was also used to evaluate the overall degree of nausea during the postoperative period. Overall patient satisfaction with the control of their PONV was assessed using a VCS (1 = very good, 2 = good, 3 = fair, and 4 = poor). Finally, all patients were contacted 24 h, 3 days, and 14 days after the operation and asked the nonspecific question, "Is anything bothering you?"

The statistical analysis consisted of a one-way analysis of variance (ANOVA) to compare the continuous variables among the six treatment groups. If a significant difference was noted, Scheffé's multiple comparison test was performed to determine intergroup differences. A two-way ANOVA was used to analyze the repeated measures. Categorical variables were analyzed by using the χ^2 test or Fisher's exact test as appropriate. All tests were two-sided, and a P value <0.05 was considered statistically significant. Data are presented as mean values ±SD, numbers, or percentages.

Results

The demographic data for the six treatment groups are summarized in Table 1. The six groups were comparable with respect to age, weight, height, number of days since the start of their last menstrual cycle, percentage of patients with a history of PONV and motion sickness, and type of hysterectomy procedure (i.e., transabdominal versus vaginal). The dosages of anesthetic and analgesic drugs administered during the intraoperative and postoperative period, the duration of anesthesia and surgery, and the time to following verbal commands, and the duration of the PACU stay were also similar among all six groups.

Within the first 2 h after surgery, the incidence of vomiting was significantly reduced in patients receiving RS-25259 30 μg/kg IV compared with the groups

Table 1. Demographic Characteristics and Surgical and Recovery Times

		RS-25259 (μg/kg)				
	Saline	0.1	0.3	1.0	3.0	30
n	36	27	41	35	40	39
Age (yr)	41 ± 8	43 ± 9	39 ± 7	39 ± 9	42 ± 8	42 ± 8
Weight (kg)	70 ± 14	76 ± 18	70 ± 16	74 ± 17	73 ± 14	71 ± 13
Height (cm)	162 ± 10	164 ± 7	163 ± 7	164 ± 9	164 ± 7	162 ± 7
Last menstrual period						
0–8 d	7	7	12	12	10	11
9–16 d	4	5	6	5	8	8
>16 d	24	14	23	16	21	20
Unknown	1	1	0	2	1	0
Previous PONV	14	12	14	13	15	12
Previous motion sickness	5	4	3	6	5	2
Intraoperative opioid analgesics (μg)						
Fentanyl	271 ± 140	304 ± 129	305 ± 92	262 ± 94	242 ± 103	277 ± 113
Sufentanil	89 ± 30	88 ± 27	86 ± 29	78 ± 27	92 ± 33	86 ± 32
Postoperative opioid analgesics (mg)						
Morphine	47 ± 35	56 ± 31	46 ± 21	59 ± 25	60 ± 31	56 ± 26
Meperidine	283 ± 173	273 ± 102	243 ± 151	221 ± 180	217 ± 152	334 ± 118
Anesthetic time (min)	132 ± 46	147 ± 73	148 ± 64	146 ± 76	138 ± 57	148 ± 71
Operative time (min)	108 ± 39	121 ± 61	122 ± 57	122 ± 72	117 ± 53	120 ± 66
Respond to commands (min)	10 ± 7	11 ± 6	11 ± 11	12 ± 10	11 ± 6	9 ± 6
Duration of PACU stay (min)	102 ± 34	101 ± 30	102 ± 33	101 ± 40	106 ± 33	87 ± 38

Values are means ± SD or *n*.
PONV = postoperative nausea and vomiting, PACU = postanesthesia care unit.

receiving saline or RS-25259 0.1 or 1.0 μg/kg IV (Table 2). Similarly, RS-25259 30 μg/kg IV was significantly more effective in preventing vomiting within the first 12 h after surgery than either the saline or RS-25259 0.1 μg/kg IV. RS-25259 30 μg/kg IV also marginally decreased the number of emetic episodes within the first 24 h postoperatively compared with placebo treatment ($P = 0.05$). Although the need for rescue antiemetics within the first 2 h was similar among all groups, RS-25259 1.0, 3.0, and 30 μg/kg IV significantly decreased the antiemetic requirement compared with saline within the first 12 h after surgery. Within the first 24 h after surgery, only the 30 μg/kg IV dose of RS-25259 significantly reduced the antiemetic requirement compared with the saline group. In addition, the time to the first emetic episode was significantly shorter in patients receiving saline or RS-25259 0.1 μg/kg IV compared with those receiving 30 μg/kg IV RS-25259. Similarly, the mean time to the first episode of vomiting was significantly shorter in the patients receiving RS-25259 0.1 μg/kg IV than in those receiving RS-25259 0.3 μg/kg IV. The percentage of treatment failures was significantly higher in the saline group than in the RS-25259 30 μg/kg IV group during the first 24 h after surgery (Table 2).

Among patients with a history of PONV, there were no differences in the incidence of vomiting or in the need for rescue antiemetic medication among the six groups (Table 3). However, among patients with no history of PONV, RS-25259 30 μg/kg IV was significantly more effective in the prevention of emetic episodes within the first 2, 12, and 24 h after surgery, and it decreased the need for rescue antiemetic therapy within 12 and 24 h after surgery compared with saline. RS-25259 1.0 μg/kg IV was also effective in reducing the number of emetic episodes and the need for antiemetic rescue medication within 12 h compared with saline (Table 4). Of interest, the VAS and VCS scores for nausea did not differ among the six groups (data not shown). The overall satisfaction with the control of PONV in the first 24 h after surgery was also similar (data not presented).

Finally, the overall incidences of adverse side effects were similar among all treatment groups (Table 5). However, more postoperative headaches were noted in patients who received larger doses of RS-25259 (0.3–30 μg/kg) compared with those who received saline and the smallest dose of RS-25259 (0.1 μg/kg) ($P < 0.02$).

Discussion

This clinical study demonstrated that the IV administration of RS-25259 30 μg/kg 20–30 min before the

Table 2. Patients Experiencing Vomiting, Receiving Antiemetic (Rescue) Medication, and Reported as Treatment Failures in the First 24 Hours After Surgery

		RS-25259 (μg/kg)				
	Saline	0.1	0.3	1.0	3.0	30
n	36	27	41	35	40	39
Vomiting (%)						
0–2 h	17	15	10	14	13	0*†‡
0–12 h	39	41	24	23	23	13*†
0–24 h	47	44	32	34	30	26
Rescue antiemetics (%)						
0–2 h	31	22	22	23	20	23
0–12 h	72	63	56	43*	43*	46*
0–24 h	75	67	61	54	53	49*
Time to first emesis (min)	339 ± 319	213 ± 189	637 ± 530†	428 ± 507	475 ± 544	795 ± 416*†
Time to rescue antiemetic (min)	234 ± 211	314 ± 308	326 ± 264	381 ± 447	430 ± 473	474 ± 330*
Treatment failures (%)	78	70	63	60	58	51*

Values are percentages or means ± SD.
* $P < 0.05$ versus saline.
† $P < 0.05$ versus RS-25259 0.1 μg/kg.
‡ $P < 0.05$ versus RS-25259 1.0 μg/kg.

Table 3. Patients with a History of PONV Who Experienced Vomiting or Required Rescue Antiemetic Therapy Within 24 Hours After Surgery

		RS-25259 (μg/kg)				
	Saline	0.1	0.3	1.0	3.0	30
n	14	12	14	13	15	12
Vomiting (%)						
2 h	14	25	14	31	20	0
12 h	36	50	43	46	27	25
24 h	43	58	50	54	33	42
Rescue antiemetics (%)						
2 h	29	33	29	46	20	33
12 h	79	75	79	62	47	67
24 h	79	75	86	62	67	67

PONV = postoperative nausea and vomiting.

Table 4. Patients with No History of PONV Who Experienced Emesis or Required Rescue Antiemetics Within 24 Hours After Surgery

		RS-25259 (μg/kg)				
	Saline	0.1	0.3	1.0	3.0	30
n	22	15	27	22	25	27
Vomiting (%)						
2 h	18	7	7	5	8	0*
12 h	41	33	15	9*	20	7*
24 h	50	33	22	23	28	19*
Rescue antiemetics (%)						
2 h	32	13	19	6	20	19
12 h	68	53	44	32*	40	37*
24 h	73	60	48	50	44	41*

PONV = postoperative nausea and vomiting.
* $P < 0.05$ versus saline.

end of surgery was effective in decreasing emesis in women undergoing major gynecologic surgery. However, analogous to the recent findings of Tramer et al. (10) with ondansetron, larger doses of RS-25250 were associated with more headaches. Although the length of stay in the PACU was slightly shorter in the large-dose RS-25259 group, this difference was not statistically significant. Moreover, the patients' overall satisfaction with the control of the PONV symptoms was not improved by the administration of RS-25259. Considering the more meaningful outcome measures (e.g., recovery times, patient satisfaction), RS-25259 seems to be of limited benefit in this high-risk patient population.

The 5-HT_3 receptor antagonists are effective in reducing emesis by acting on both the central and peripheral nervous systems (13). Ondansetron has been successfully used for both prophylaxis and treatment of PONV with few clinically significant adverse effects (7–9). Although apparently free of activity at histaminergic, dopaminergic, or cholinergic receptors (14), side effects such as chest pain, headaches, and extrapyramidal symptoms have been reported with ondansetron (15,16) and other 5-HT_3 antagonists. Granisetron and tropisetron, two more recently introduced 5-HT_3 receptor antagonists that have also been reported to decrease emesis after surgical procedures (17,18), possess longer elimination half-life values than ondansetron [9–11 h (19) and 6–7 h (20) versus 2.8 ± 0.6 h (21), respectively]. However, the long-lasting antiemetic activity associated with granisetron is allegedly due to its high affinity for the 5-HT_3 receptor (22,23). Of interest, Naguib et al. (24) reported that the prophylactic administration of ondansetron was as effective as granisetron and tropisetron in reducing the incidence of PONV during the first 24 h after laparoscopic cholecystectomy. Unfortunately, none of the currently

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