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Rolapitant for the Prevention of Postoperative Nausea and Vomiting: A Prospective, Double-Blinded, Placebo-Controlled Randomized Trial

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BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after surgery. Neurokinin-1 (NK_1) receptor antagonists have been shown to be safe and effective for the prevention and treatment of PONV in humans. Rolapitant is a potent, selective NK1 receptor antagonist that is rapidly absorbed, has a remarkably long half-life (up to180 hours), and appears to have a low potential for drug–drug interactions. We evaluated the dose response for rolapitant for the prevention of PONV in subjects at high risk for this condition, and rolapitant's effects on preventing delayed PONV were explored up to 5 days after surgery.

METHODS: A randomized, multicenter, double-blind, dose-ranging study of rolapitant was conducted with placebo and active control groups. Six hundred nineteen adult women undergoing open abdominal surgery were randomly assigned in equal ratios to 1 of 6 study arms: oral rolapitant in 5-mg, 20-mg, 70-mg, or 200-mg doses; IV ondansetron 4 mg; or placebo, stratified by history of PONV or motion sickness. The primary study endpoint was absence of emetic episodes, regardless of use of rescue medication, at 24 hours after extubation.

RESULTS: Groups assigned to rolapitant 20-mg, 70-mg, and 200-mg had a higher incidence of no emesis in comparison with placebo at 24 hours after surgery. A linear relationship between rolapitant dose and primary outcome was seen. The probability of an emetic episode was significantly lower in the rolapitant 70-mg and 200-mg groups in comparison with placebo ($P \leq 0.001$ based on the log-rank test). No significant differences were noted between rolapitant and the active control (ondansetron) at 24 hours after surgery, but there was a higher incidence of no emesis (regardless of rescue medication use) in the rolapitant 200- and 70-mg groups at 72 and 120 hours, respectively.

CONCLUSION: Rolapitant is superior to placebo in reducing emetic episodes after surgery and reduces the incidence of vomiting in a dose-dependent manner. No differences in side effect profile were observed between rolapitant and placebo. (Anesth Analg 2011;112:804–12)

Substance P is a regulatory peptide found in the gastrointestinal tract (vagal afferants) and regions of the central nervous system (the *nucleus tractus solitarii* and *area postrema*) implicated in the vomiting reflex.[1,2] Substance P is the preferred endogenous ligand at neurokinin-1 (NK_1) receptors. NK_1 receptor antagonists have demonstrated activity against both peripheral and central emetic stimuli in animal models.[3] Aprepitant, a highly selective, brain-penetrating NK_1 antagonist with a long half-life (9 to 12 hours), was approved in 2006 by the United States (U.S.) Food and Drug Administration for the management of postoperative nausea and vomiting (PONV).[4]

Rolapitant (rolapitant hydrochloride; Schering-Plough SCH619734)[a] is a potent, selective competitive NK_1 receptor antagonist with several advantages when compared with other drugs in this class. It has an exceptionally long half-life of 180 hours (>7 days), is rapidly absorbed after oral dosing, and in vitro studies showed that rolapitant did not inhibit CYP 2C9, 2C19, 2D6, and 3A4 enzymes or p-glycoprotein, meaning that there is a low risk of drug–drug interactions with rolapitant.[b] Oral doses of up to 200 mg were well tolerated in healthy volunteers.

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[a]Rolapitant hydrochloride. USAN description. Available at: www.ama-assn.org/ama1/pub/upload/mm/365/rolapitant_hcl.pdf. Accessed March 17, 2009.

[b]Schering-Plough Research Institute. Investigator's brochure: Information for investigational product. Rolapitant capsule and tablet (SCH 619734). November 26, 2007. See Addendum.

We hypothesized that rolapitant is more effective than placebo in reducing the incidence of postoperative vomiting and, given its long half-life, might exhibit benefits beyond the immediate acute postoperative setting. An active control group treated with ondansetron 4 mg was also included in the study to help assess the validity of the trial if no dose response of rolapitant was identified. The primary study objective was to assess the effect of a range of rolapitant doses for the prevention of PONV, as measured by the prevention of emetic episodes at 24 hours after tracheal extubation. Hence, the primary endpoint was the response rate of subjects who did not experience any emetic episodes (regardless of rescue medication use) for 0 to 24 hours. Secondary objectives included comparing the effects of rolapitant and placebo on the following: no emetic episodes at other time points up to 120 hours; no emetic episodes and no rescue medication; no nausea; time to first rescue medication use; time to first emetic episode; and time to first significant nausea (see **Study Definitions** for details). Safety and tolerability of rolapitant versus placebo were also assessed.

METHODS

Study Subjects

Forty-five centers in the U.S. and Canada participated in this study (P04937AM1, study sponsor SPRI); of these, 37 enrolled subjects. The protocol was registered with ClinicalTrials.gov (NCT00539721) and was approved by each center's ethics board/IRB. All subjects provided written informed consent before beginning participation in the trial.

Adult women with an ASA physical status 1 to 3 scheduled to undergo elective open abdominal surgery under general anesthesia who were expected to be hospitalized for at least 24 hours and to require postoperative IV patient-controlled analgesia (PCA) were eligible for the study. Patients with clinically significant or unstable cardiac, respiratory, hepatic, or renal disease, allergies to study medications, retching/vomiting or moderate to severe nausea 24 hours before anesthesia, or chronic nausea or vomiting were not eligible for the study. Other exclusion criteria included antiemetic treatment within the previous 5 days; need for opioid adjuncts during study period; a body mass index >40; any condition requiring daily opioid use within 7 days before surgery; and expected need for placement of a nasogastric tube for gastric suction (a nasogastric tube could be inserted at the end of surgery for decompression only).

Randomization and Study Intervention

Study subjects were randomly allocated in a double-blind fashion and equal ratio to 1 of 6 study arms: oral rolapitant 5 mg, 20 mg, 70 mg, and 200 mg, placebo, and active control with IV ondansetron 4 mg (Fig. 1). Randomization was performed before surgery according to a computer-generated randomization schedule, and stratified on the basis of history of PONV or motion sickness. Blinding was ensured with matching placebo capsules. Intravenous ondansetron (2 mL) and saline placebo (2 mL) were prepared by the pharmacists in a blinded 3-mL syringe. Oral rolapitant or placebo was administered no later than 30 minutes before induction of anesthesia. Intravenous ondansetron or placebo was administered immediately before the induction of anesthesia as directed in the ondansetron package insert.

Other Study Treatment

Benzodiazepines were given as a preanesthetic medication. Propofol was used for induction (but not maintenance) of anesthesia. The choice of drugs used for neuromuscular blockade was at the discretion of the individual investigator; reversal of neuromuscular blockade with neostigmine and glycopyrrolate was recommended. Anesthesia was maintained by sevoflurane, desflurane, or isoflurane in oxygen. Nitrous oxide was allowed in concentrations up to 50%. Choice of intraoperative opioids was left to the investigator's discretion; however, opioid adjunct medications including nonsteroidal anti-inflammatory drugs, gabapentin, pregabalin, dexmedetomidine, ketamine, or clonidine were prohibited. Postoperatively, IV morphine PCA was initiated in the postanesthesia care unit when the subject was responsive and could follow instructions on its use. If the subject was allergic to morphine, alternatives such as fentanyl, hydromorphone, or meperidine PCA were allowed instead.

During the 24 hours after tracheal extubation, IV ondansetron 4 mg was used as the initial antiemetic rescue medication. If the subject did not have IV access, oral ondansetron up to 8 mg was used. Initial rescue medication was administered upon subject request or investigator recommendation. Rescue medication was offered for complaints of nausea with a severity of ≥4 measured on an 11-point verbal response scale (see below). For nausea scores <4, rescue medication was administered upon the subject's request. After the initial dose of rescue medication was administered, additional choice of rescue therapy was at the investigator's discretion.

Study Definitions

Nausea was defined as feeling of sickness in the stomach characterized by the urge to vomit. *Vomiting* was defined as expulsion of stomach contents through the mouth. *Retching* was an attempt to expel stomach contents through the mouth that was not productive. An e*metic episode* was defined as a single vomit or retch, or multiple vomits/retches separated by <1 minute. *Significant nausea* was defined as a subject reporting a nausea score ≥4 on a verbal rating scale of 0 to 10.

Data collected included patient demographic information, the risk factors for PONV, duration of anesthesia, postanesthesia care unit and hospital stay, the number and time of emetic episodes, time and indication for use of rescue medication, and time and severity of subject complaints of nausea (rated on a verbal rating scale of 0 to 10, where 0 represents no nausea and 10 represents the worst nausea imaginable), as well as the subject's self-report of her most severe nausea and her contemporaneous nausea in that observation period. After the 24-hour evaluation, study staff visited the subject daily throughout the hospitalization to collect data on nausea, vomiting, concomitant medication use, and adverse events (AEs); after discharge, subjects were contacted daily by telephone to collect this

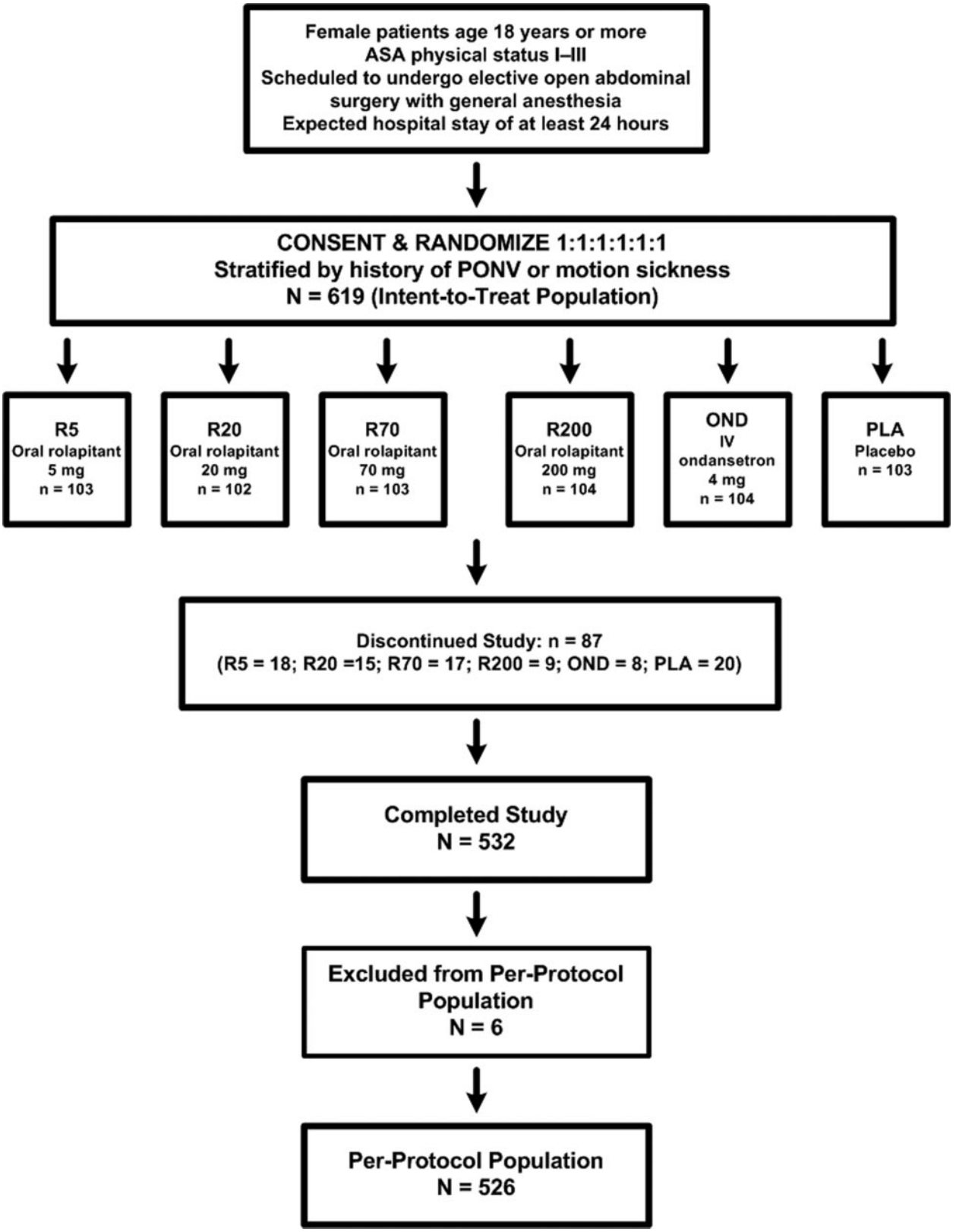

Figure 1. Study flow (intent-to-treat and per-protocol populations). PONV = postoperative nausea and vomiting; PLA = placebo; OND = ondansetron; R5, R20, R70, R200 = rolapitant 5 mg, 20 mg, 70 mg, 200 mg.

information. Final safety follow-up assessment occurred between 30 and 60 days after surgery.

Safety and tolerability were assessed by physical examination and laboratory analysis, electrocardiograms (ECG), and collection of AEs. Laboratory safety analysis and a 12-lead ECG were performed at baseline, 24 hours after tracheal extubation and at the final follow-up visit between 30 and 60 days after surgery. AEs were recorded throughout the study period. Additional safety assessments included duration of recovery from anesthesia and measurement of vital signs at baseline, 24 hours after tracheal extubation, and at a follow-up visit (30 to 60 days after surgery).

Statistical Analysis

Primary and secondary study endpoints. The primary study endpoint was the response rate of subjects who did not experience any emetic episodes regardless of use of rescue medication for 24 hours after tracheal extubation. Secondary endpoints included the following: response rates of subjects who did not experience any emetic episodes (regardless of rescue medication use) for 0 to 2 hours, 0 to 6 hours, 0 to 48 hours, 0 to 72 hours, 0 to 96 hours, and 0 to 120 hours; complete response (no emetic episodes and no use of rescue medication) and absence of nausea at the same time points; as well as time to first rescue medication use, first emetic episode, and first significant nausea.

Analysis and sample size justification. Treatment comparisons for binary efficacy endpoints were made using logistic regression models that included terms of treatment and the covariate of history of PONV or motion sickness. For each of the time-to-event secondary efficacy endpoints, the Kaplan–Meier estimates of the survival function were presented in graphical form for the placebo and the rolapitant treatment groups. A log-rank test was performed to assess the statistical significance of observed treatment differences in the time-to-event distributions between placebo and rolapitant groups. A P value of <0.05 (2-sided) was considered statistically significant.

For the primary efficacy analysis, the intent-to-treat population (all randomized patients) was considered primary and the per-protocol population (all randomized patients who had open abdominal surgery, received a dose of study medication, and provided 24-hour efficacy assessment) was considered secondary. Secondary efficacy analyses, sensitivity analyses, exploratory analyses, and safety analyses were performed only on the intent-to-treat population, unless otherwise specified.

With a sample size of 100 evaluable subjects per treatment, the study had at least 80% power for detecting an odds ratio (OR) of 2.33 for the primary endpoint of rolapitant versus placebo at a significance level of 5% (2-sided), assuming 50% response rate in the placebo arm and 70% response rate in a rolapitant arm. An active-control arm (ondansetron) was included for assay sensitivity. Sample size calculations were performed on the basis of a logistic regression model adjusting for history of PONV or motion sickness using East® software, version 4 (Cytel Statistical and Software Services, Inc., Cambridge, MA). SAS statistical analysis software (version 8.2, SAS Institute, Cary, NC) was used to conduct the statistical analysis.

For the primary analysis and the sensitivity analyses, a step-down method was conducted with the assumption that the drug would show increasing efficacy with increasing dose. By using a step-down method, we can preserve familywise error rate at a 5% significance level without adjustment of multiplicity.[5] That is, under the condition of showing statistical significance at an α level of 0.05, a set of sequentially conducted hypotheses were tested for efficacy in the following order: (a) rolapitant 200 mg versus placebo; (b) rolapitant 70 mg versus placebo; (c) rolapitant 20 mg versus placebo; and (d) rolapitant 5 mg versus placebo. This testing procedure would be stopped once a null hypothesis failed to be rejected.

RESULTS

Intent-to-Treat (Randomized) and per-Protocol Populations

Six hundred nineteen subjects were randomized from 37 centers; of these, 532 subjects completed the trial through 30- to 60-day follow-up (Fig. 1). Of the 87 patients who did not complete the study, 30 were lost to follow-up, 26 withdrew for reasons unrelated to study medication, 12 discontinued the study because of protocol ineligibility, 11 were discontinued because of noncompliance with the protocol, 4 were discontinued because of administrative reasons, 3 were discontinued because of AEs, and 1 was discontinued because of incisional pain. There were no differences in the distribution of the discontinued patients among the groups. Demographic data and patient characteristics were no different among groups (Table 1).

Primary Endpoint

Groups that received rolapitant 20 mg, 70 mg, and 200 mg had a significantly higher incidence of no emetic episodes in comparison with the placebo group at 24 hours after tracheal extubation (Table 2, Fig. 2A). The groups receiving rolapitant 70 mg and 200 mg showed a significantly greater incidence of no emetic episodes at all time points up to 120 hours after surgery (Table 2, Figs. 2B and 3). A linear relationship between rolapitant dose and the primary outcome was observed. The ORs of rolapitant 70 mg and 200 mg to placebo for the primary outcome were 2.87 ($P < 0.001$, 95% confidence interval [CI] 1.54 to 5.35) and 4.73 ($P < 0.001$, 95% CI 2.37 to 9.42), respectively.

Secondary Endpoints

Two groups treated with rolapitant (70 and 200 mg) had a higher incidence of complete response (no emesis or use of rescue antiemetic) at 72 hours, 96 hours, and 120 hours after surgery in comparison with placebo ($P < 0.05$), whereas ondansetron showed no significant difference in comparison with placebo at these time points. The rolapitant 200-mg group also had a significantly higher complete response rate at 48 hours (Table 2). The dose response for these endpoints was observed to be related to dose of rolapitant in a linear fashion.

The probability of an emetic episode was significantly lower in the rolapitant 70-mg and 200-mg groups than in the placebo group ($P \leq 0.001$ based on the log-rank test; Fig. 3). Among the subjects who had emetic episodes,

Table 1. Demographics and Baseline Characteristics of Intent-to-Treat Population (*N* = 619)

	Placebo (*n* = 103)	Rolapitant 5 mg (*n* = 103)	Rolapitant 20 mg (*n* = 102)	Rolapitant 70 mg (*n* = 103)	Rolapitant 200 mg (*n* = 104)	Ondansetron 4 mg (*n* = 104)	Total (*n* = 619)
Age, years	45.8 (10.1)	44.6 (10.1)	47.1 (12.6)	44.1 (10.1)	47.4 (10.9)	47.9 (12.6)	46.1 (11.2)
Weight, kg	76.1 (15.4)	76.4 (17.4)	75.6 (16.4)	79.1 (17.3)	77.7 (15.4)	79.3 (16.2)	77.4 (16.4)
Height, cm	163.1 (6.2)	163.5 (7.0)	163.9 (7.5)	163.3 (8.5)	162.9 (7.2)	164.0 (6.5)	163.5 (7.2)
Race—White, *n* (%)	72 (70)	81 (79)	83 (81)	71 (69)	77 (74)	83 (80)	467 (75)
BMI, kg/m^2	28.5 (5.2)	28.5 (6.1)	28.1 (5.8)	29.6 (5.9)	29.2 (5.3)	29.4 (5.6)	28.9 (5.7)
PONV risk factors							
History of PONV and motion sickness, *n* (%)	50 (49)	50 (49)	51 (50)	53 (51)	53 (51)	51 (49)	308 (50)
History of PONV, *n* (%)	31 (30)	38 (37)	33 (32)	38 (37)	40 (38)	35 (34)	215 (35)
History of motion sickness, *n* (%)	33 (32)	25 (24)	33 (32)	31 (30)	34 (33)	28 (27)	184 (30)
History of smoking, *n* (%)	30 (29)	37 (36)	28 (27)	36 (35)	31 (30)	40 (38)	202 (33)
Intraoperative morphine equivalent dose, mg	37 (20)	33 (27)	33 (25)	32 (22)	29 (19)	33 (21)	33 (23)
IV PCA morphine equivalent dose, mg	67 (78)	69 (61)	78 (96)	69 (59)	61 (62)	74 (96)	70 (77)
Duration of anesthesia, hours	2.2 (1.0)	2.2 (1.0)	2.2 (1.1)	2.1 (0.9)	2.0 (0.9)	2.3 (1.1)	2.2 (1.0)
Duration of PACU stay, hours	1.9 (1.0)	1.8 (1.0)	1.9 (0.9)	2.0 (1.3)	2.0 (2.8)	1.8 (0.9)	1.9 (1.5)
Duration of hospital stay, days	4.0 (1.5)	4.0 (2.1)	4.6 (2.6)	4.1 (2.2)	4.1 (1.8)	4.4 (3.2)	4.2 (2.3)

All values are given as mean (SD) unless otherwise noted. BMI = body mass index; PONV = postoperative nausea and vomiting; PCA = patient-controlled analgesia; PACU = postanesthesia care unit.

Table 2. Incidence of Primary and Secondary Outcomes, Intent-to-Treat Population (*N* = 619)

	Placebo (*n* = 103)	Rolapitant 5 mg (*n* = 103)	Rolapitant 20 mg (*n* = 102)	Rolapitant 70 mg (*n* = 103)	Rolapitant 200 mg (*n* = 104)	Ondansetron 4 mg (*n* = 104)
Freedom from emesis						
0–24 hours, *n* (%)	60 (58)	72 (70)	74 (73)*	82 (80)†	90 (87)†	81 (78)*
0–48 hours, *n* (%)	58 (56)	65 (63)	69 (68)	77 (76)*	88 (85)†	77 (74)*
0–72 hours, *n* (%)	53 (52)	62 (61)	66 (65)	77 (76)	83 (81)‡	70 (67)
0–120 hours, *n* (%)	48 (47)	54 (52)	58 (57)	78 (76)†‡	76 (73)†	64 (62)*
Complete response						
0–24 hours, *n* (%)	27 (27)	34 (33)	33 (32)	38 (37)	40 (39)	38 (37)
0–48 hours, *n* (%)	23 (22)	31 (30)	28 (28)	34 (33)	38 (37)*	33 (32)
0–72 hours, *n* (%)	21 (20)	27 (27)	27 (27)	33 (32)*	36 (35)*	31 (30)
0–120 hours, *n* (%)	18 (18)	24 (23)	24 (24)	34 (33)*	32 (31)*	27 (26)
Incidence of no nausea						
0–24 hours, *n* (%)	15 (15)	23 (22)	21 (21)	25 (24)	19 (18)	22 (21)
0–48 hours, *n* (%)	13 (13)	22 (21)	15 (15)	22 (21)	17 (16)	20 (19)
0–72 hours, *n* (%)	12 (12)	20 (20)	12 (12)	21 (21)	14 (14)	19 (19)
0–120 hours, *n* (%)	10 (10)	17 (17)	10 (10)	21 (20)*	13 (13)	17 (16)
Incidence of no PONV						
0–24 hours, *n* (%)	14 (14)	23 (22)	21 (21)	25 (24)*	19 (18)	22 (21)
Time to first emetic episode, mean hours (SD)	14.9 (22.0)	20.0 (28.9)	17.7 (24.0)	11.7 (15.9)*	28.3 (33.5)†	27.4 (28.5)
Time to first rescue medication, mean hours (SD)	7.1 (9.6)	8.4 (15.2)	9.8 (15.3)	6.1 (8.0)	10.4 (20.5)	11.9 (19.8)
Time to significant nausea, mean hours (SD)	7.5 (11.3)	9.8 (19.8)	11.7 (18.3)	6.2 (8.3)	11.3 (19.9)	12.8 (20.5)

PONV = postoperative nausea and vomiting; complete response = no emetic episodes and no use of rescue medication; no PONV = no nausea and no emetic episodes.

* $P < 0.05$, treatment versus placebo.

† $P < 0.001$, treatment versus placebo.

‡ $P < 0.05$, treatment versus ondansetron.

median time to first emetic episode was longer in the rolapitant 200-mg group ($P < 0.001$) than in the placebo group, and was significantly different for rolapitant versus placebo overall ($P < 0.001$); however, median time to first emetic episode was significantly shorter for rolapitant 70 mg than for placebo ($P = 0.001$).

No overall difference in incidence of nausea was observed among the groups, although the incidence of no nausea was significantly higher in the rolapitant 70-mg group at 96 hours and 120 hours after surgery (Table 2). On the basis of the log-rank statistic, the probability of significant nausea was lower in the rolapitant 200-mg group than in the placebo group ($P = 0.05$). No differences were noted among rolapitant groups and placebo in time to first rescue medication usage.

In addition to primary and secondary analyses that compared rolapitant with placebo, exploratory analyses were also performed comparing the rolapitant arms with the active control (ondansetron 4 mg) in the selected primary and secondary efficacy endpoints of *no emetic episodes* and *complete response*. The rolapitant 200-mg group

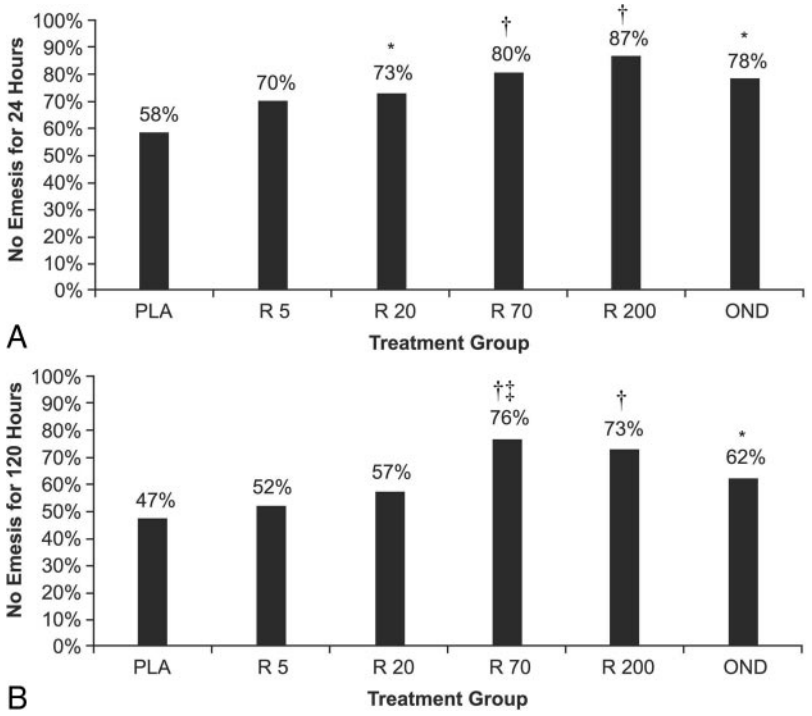

Figure 2. A, Incidence of no emesis for 24 hours. Groups that received rolapitant (R20, R70, R200 = rolapitant 20 mg, 70 mg, 200 mg) and ondansetron (OND) had a significantly higher incidence of no emetic episodes in comparison with the placebo group (PLA) at 24 hours after tracheal extubation. B, Incidence of no emesis for 120 hours. The groups receiving rolapitant 70 mg and 200 mg showed a significantly greater incidence of no emetic episodes at all time points up to 120 hours after surgery in comparison with the other groups (where $*P < 0.05$, treatment versus placebo, $\dagger P < 0.001$, treatment versus placebo, $\ddagger P < 0.05$, treatment versus ondansetron.

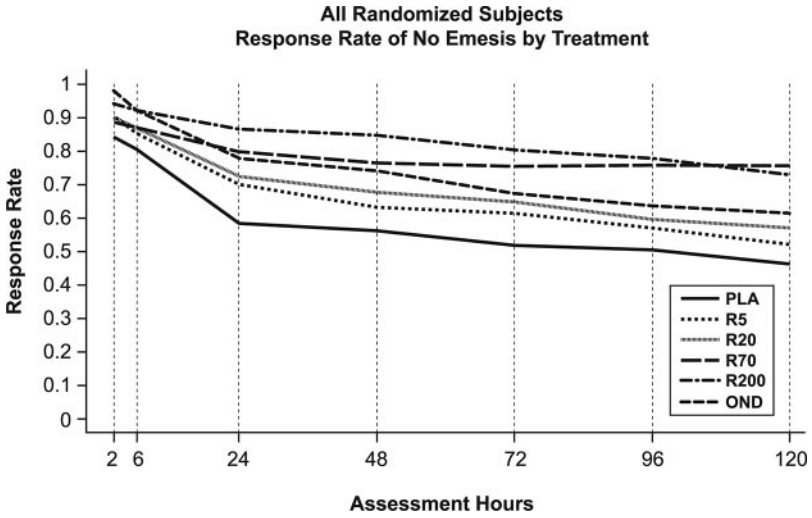

Figure 3. Cumulative percentages of absence of emesis over the duration of the study (120 hours). The probability of an emetic episode was significantly lower in the rolapitant 70 mg and 200 mg groups than in the placebo group ($P \leq 0.001$) on the basis of the log-rank test. PLA = placebo; OND = ondansetron; R5, R20, R70, R200 = rolapitant 5 mg, 20 mg, 70 mg, 200 mg.

showed a significantly higher incidence of no emetic episodes at 72 and 96 hours than did ondansetron ($P < 0.05$). In addition, the rolapitant 70-mg group showed a significantly higher incidence of no emetic episodes (regardless of rescue medication use) at 2 and 120 hours ($P < 0.05$) (Table 2). No other significant differences were observed between the rolapitant-treated groups and the ondansetron group. The incidence of emesis after rescue (with ondansetron) showed no difference in the ondansetron versus nonondansetron (placebo and rolapitant) groups. The rolapitant 70-mg group showed a significantly higher incidence of no PONV (no nausea and no emesis) in comparison with placebo at 24 hours ($P < 0.05$). When outcomes after 24 hours were examined for the time periods of 24 to 48 hours, 48 to 72 hours, and 72 to 120 hours, there was an increase in complete response ($P = 0.02$) and no nausea ($P = 0.03$) for the 48- to 72-hour period in the rolapitant 70-mg group. There was a similar decrease in the incidence of vomiting for the 24- to 48-hour and 48- to 72-hour periods ($P < 0.05$) and an increase in the incidence of complete response ($P = 0.02$) for the 48- to 72-hour period in the rolapitant 200-mg cohort.

The overall incidence of AEs was not clinically significant across all groups versus placebo. The most common AE was postoperative ileus, with an incidence that ranged from 0% to 4% among groups. No other AEs had an incidence of >2%. Laboratory findings including ECGs and vital sign measurements were also not significantly different when compared with placebo, and no safety concerns were noted. One patient on the active control (ondansetron) arm died because of a preexisting condition (neoplasm).

DISCUSSION

This dose–response study demonstrated that rolapitant reduces the incidence of emetic episodes at all assessment time points up to 120 hours after surgery in subjects at high risk for developing PONV. A linear dose–response relationship was observed up to 70 mg: rolapitant 70 mg and 200 mg were the most effective, prolonging the duration of no emetic episode and the time to need for rescue antiemetic. The difference in efficacy between rolapitant 70 mg or 200 mg and ondansetron did not attain statistical significance, because the study was not powered to compare rolapitant with ondansetron.

Although serotonin (5-HT_3) receptor antagonists have questionable efficacy against centrally induced emesis, nonpeptide NK_1 receptor antagonists have demonstrated activity against both peripheral and central emetic stimuli in animal models.[6–9] Evidence suggesting the potential efficacy of NK_1 receptor antagonists against PONV was obtained in clinical trials of a number of different drugs in this class, which were assessed in patients undergoing major and minor gynecologic surgery. In the first study, patients undergoing abdominal hysterectomy received antiemetic prophylaxis with either the NK_1 receptor antagonist CP-122,721 alone, a 5-HT_3 receptor antagonist alone, or both in combination.[10] The NK_1 antagonist, alone or in combination with the active control, was significantly superior to the active control in preventing emesis in the first 24 hours after surgery. This antiemetic has not been developed further. In a second study, the NK_1 antagonist casopitant was investigated in a dose–response study of patients undergoing laparoscopic procedures. The combination of ondansetron 4 mg with casopitant in all studied doses (50 mg, 100 mg, and 150 mg) was superior to ondansetron alone in the complete response rate (no emesis or use of rescue).[11]

Aprepitant is the first NK_1 receptor antagonist that has been approved for management of PONV. In a large study, oral aprepitant (40 mg or 125 mg) was superior to IV ondansetron 4 mg in reducing the incidence of emesis after abdominal hysterectomy.[12] The aprepitant 125-mg and 40-mg groups had an emesis-free incidence of 95% and 90%, respectively, in comparison with 74% in the ondansetron group. Another NK_1 receptor antagonist, GR-205,171 was investigated in patients with established PONV and found to be superior to placebo in controlling emesis.[13]

Our findings suggest that NK_1 receptor antagonists have increased efficacy when compared with placebo in preventing postoperative vomiting in high-risk subjects, although no difference in incidence of nausea was observed. Moreover, the observed increased efficacy of rolapitant at the doses studied in this trial seems to persist for up to 120 hours after surgery, an attribute that may be particularly relevant in light of the need for better management of the relatively high incidence of postdischarge nausea and vomiting among surgical patients. Rolapitant has a significantly longer half-life (180 hours)[c] when compared with other drugs in its class, although it is unclear whether the longer half-life translates into any clinical benefits.

Rolapitant was generally well tolerated at all dose levels studied in this trial. The incidence of AEs and serious AEs was not different among the rolapitant-, ondansetron-, and placebo-treated groups. For other laboratory assessments, including ECG findings, there were also no statistical differences among treatment groups at 24 hours after surgery. In exploratory analyses, we did not find a significant difference between the rolapitant and ondansetron groups other than a higher incidence of no emesis (regardless of rescue medication use) in the rolapitant 200-mg group at 72 hours and 0 to 96 hours, and in the rolapitant 70-mg group at 2 hours and 120 hours.

This study has a number of limitations. Rolapitant is available only in oral formulation and hence must be administered preoperatively. However, it is more rapidly absorbed and has a much longer half-life than do other antiemetics in its class. Our study recruited only women because they generally have a higher risk for developing PONV; hence, our results may not be extrapolated beyond this population and must be interpreted with caution. Nitrous oxide, which can increase PONV risk,[14] was allowed in this study because it was routinely used by several of the participating centers. Although there is a significant body of published literature supporting the use of combination antiemetics to improve efficacy and reduce side effects, this study, which is the first study of rolapitant for prevention of PONV in humans, assessed only single therapy. Thus, further studies aimed at elucidating optimal doses and combinations are needed. Similarly, propofol-maintained anesthesia is effective in reducing the incidence of PONV but is not widely practiced in the U.S. Finally, ondansetron was administered at induction of anesthesia in accordance with product-labeling instructions. However, a study by Sun et al.[15] suggests that ondansetron may in fact be more effective when administered toward the end of surgery. The redosing of ondansetron as the rescue antiemetic in the ondansetron group may have conferred less benefit in comparison with the other groups in which ondansetron had not been used as a prophylaxis. However, a further analysis comparing the incidence of emesis after rescue showed no difference in the ondansetron versus nonondansetron (placebo and rolapitant) groups. Additionally, the exploratory analyses were not originally planned, and the results should be interpreted with caution.

In summary, rolapitant reduced the incidence of postoperative vomiting in a dose-dependent manner and was superior to placebo at all doses studied, while exhibiting no difference in side effect profile to placebo. Furthermore, there was no statistically significant difference between rolapitant (at any of the studied doses) and ondansetron in terms of primary outcome variables. Additional larger studies are needed to characterize rolapitant's optimal dose range in terms of efficacy and safety and its clinical utility when used in combination with other antiemetics for the management of PONV, and to investigate its potential efficacy in the extended postdischarge setting.

APPENDIX. ROLAPITANT INVESTIGATORS GROUP

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[c]Schering-Plough Research Institute. Investigator's brochure: Information for investigational product. Rolapitant capsule and tablet (SCH 619734). November 26, 2007. See Addendum.

[d]Site activated but did not randomize patients.

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DISCLOSURES

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