

Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures

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Background: **The safety and antiemetic efficacy of CP-122,721, a novel neurokinin-1 antagonist, was evaluated when administered alone or in combination with ondansetron.**

Methods: **Using a randomized, double-blind, placebo-controlled study design, CP-122,721 was initially compared with placebo and subsequently to ondansetron alone and in combination for prophylaxis against postoperative nausea and vomiting in 243 women undergoing abdominal hysterectomy. In the dose-ranging studies (n = 86), patients received either CP-122,721 100 mg (vs. placebo) or 200 mg (*vs.* placebo) orally 60–90 min before induction of anesthesia. In the interaction study (n = 157), patients received CP-122,721 200 mg or placebo 60–90 min before induction of anesthesia, and ondansetron 4 mg or saline 2 ml intravenously 15–30 min before the end of surgery. Patients assessed their level of nausea and pain on arrival in the postanesthesia care unit and at 0.5-, 1-, 1.5-, 2-, 4-, 8-, 12-, and 24-h intervals postoperatively. Emetic episodes, need for rescue antiemetic–antinausea medication, postoperative complications, and patient satisfaction were recorded.**

Results: **In the initial dose-ranging study, only 10% of the patients experienced emesis within the first 8 h after surgery with CP-122,721 200 mg compared with 50% in the placebo group. CP-122,721 200 mg also decreased the need for rescue medication (25% *vs.* 48%). CP-122,721 100 mg was less effective than 200 mg in decreasing the incidence of repeated episodes of emesis. In the interaction study, 6% of the patients receiving CP-122,721 200 mg orally experienced emesis less than 2 h after surgery compared with 17% with ondansetron alone. With combined therapy, only 2% experienced emesis. In addition, the median times for 75% of patients to remain free from postoperative nausea and vomiting were 82, 75, and 362 min in the ondansetron, CP-122,721, and combination groups, respectively.**

Conclusions: **Oral CP-122,721 200 mg decreased emetic episodes compared with ondansetron (4 mg intravenously) during the first 24 h after gynecologic surgery; however, there was no difference in patient satisfaction. (Key words: Drug interactions; emesis; ondansetron.)**

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DESPITE the availability of newer serotonin (5-HT) subtype-3 antagonists, postoperative nausea and vomiting (PONV) remains the most common complication after major gynecologic procedures.[1,2] Several factors contribute to the high incidence of PONV, including gender, timing of the menstrual cycle, use of opioid analgesics, and the surgical procedure itself. It has been suggested that prophylactic administration of antiemetic drugs is particularly useful in high-risk gynecologic patients.[3,4]

In addition to the 5-HT_3 antagonists, a wide variety of prophylactic antiemetics have been used for the prevention of PONV.[1] However, many of the traditional antiemetics produce undesirable side effects.[5] Even the prototypic 5-HT_3 antagonist, ondansetron, has recently been reported to produce clinically significant side effects when used for routine prophylaxis.[6] Given the limited efficacy and well-known side effects associated with the available antiemetic drugs, the search for more efficacious compounds without side effects has continued.

The natural ligand of the neurokinin-1 (NK-1) receptor, substance P, has been identified in the nucleus tractus solitarius and the area postrema of the central nervous system, as well as in the peripheral nervous system.[7] It has been suggested that NK-1 receptor antagonists might be effective in the prevention of postoperative emesis because of their ability to block input from emetic stimuli in the central nervous system.[8,9] CP-122,721, a nonpeptide antagonist of the NK-1 receptor,[8] is the first NK-1 antagonist to be approved for clinical testing in North America.

Therefore, studies were designed to determine the safety and efficacy of CP-122,721 (*vs.* placebo) in the prevention of PONV, and to compare this novel compound with ondansetron when administered alone or in combination with the 5-HT_3 antagonist for prophylaxis in a high-risk gynecologic surgery population.

Materials and Methods

A total of 243 healthy, consenting American Society of Anesthesiologists physical status I or II, nonpregnant women presenting for total abdominal hysterectomy procedures were successfully enrolled in these sequential, multi-institutional review board–approved, randomized, double-blind studies. The dose-ranging studies (n = 86) were designed to compare CP-122,721 100 or 200 mg orally with placebo. In the interaction study (n =

157), the incidence of postoperative emesis was evaluated in women treated with CP-122,721 200 mg orally, ondansetron 4 mg intravenously, or a combination of both. In the dose-ranging studies, patients were enrolled at three sites, whereas five sites were used for the interaction study.

Patients were excluded from participating in these studies if they had received any antiemetic medications within 24 h before induction of anesthesia, had received an investigational drug within the past 30 days, had vomited or retched within the preceding 24-h period, or were more than 60% above their ideal body weight. All patients provided a detailed medical history, including history of previous PONV, motion sickness, or dizziness, alcohol or drug consumption, as well as the date of their last menstrual period.

In the dose-ranging studies, either (1) a placebo or CP-122,721 100 mg or (2) a placebo or CP-122,721 200 mg was administered orally 60–90 min before induction of general anesthesia according to a randomized, double-blind protocol with two separate placebo groups. All study medications were prepared by the manufacturer (Pfizer, Inc., Groton, CT) in identical capsules. The general endotracheal anesthetic technique was standardized and included thiopental 3–5 mg/kg, fentanyl 2–4 μg/kg, isoflurane 0.6–1.2%, morphine 0.05–0.15 mg/kg, muscle relaxants and reversal drugs, as well as nitrous oxide. Morphine, 1–2 mg intravenously, was also administered for postoperative pain control using a patient-controlled analgesia (PCA) delivery system. The PCA morphine was initiated in the postanesthesia care unit when the patient first requested pain medication.

In the interaction study, patients were randomly assigned to one of three treatment groups using a computer-generated random number table. Each group received either CP-122,721 200 mg or placebo orally 60–90 min before induction of anesthesia, and either ondansetron 4 mg or saline 2 ml intravenously 15–30 min before the end of the surgical procedure under a standardized general anesthetic technique. Group 1 (ondansetron) received oral placebo and intravenous ondansetron, group 2 (CP-122,721) received oral CP-122,721 and intravenous saline, and group 3 (combination) received oral CP-122,721 and intravenous ondansetron. The oral study drug was supplied by Pfizer Inc. in blinded containers, whereas the parenteral (intravenous) solution was prepared by a local pharmacist who was not otherwise involved in the conduct of the study. The patients, anesthesiologists, and observers were all blinded to the study medications being administered.

The length of surgery (from skin incision to placement of the last suture) and anesthesia (from induction to discontinuation of nitrous oxide), as well as recovery times (from the end of surgery to eye opening and orientation to person and place, and discharge from the postanesthesia care unit) were also recorded. The degree of nausea and pain was assessed on arrival to the postanesthesia care unit and at 0.5-, 1-, 1.5-, 2-, 4-, 8-, 12-, and 24-h intervals after surgery using 100-mm linear visual analog scales (VAS; 0 = none, 100 = most severe). In the interaction study, patient satisfaction with the management of their emetic symptoms was also evaluated at 72 h postoperatively. The assessment involved asking the patients if they were "highly satisfied" with the management of their PONV symptoms. In addition, the occurrence of all clinically significant postoperative side effects (including changes in electrolytes and liver function tests), emetic episodes, and the need for rescue medications were recorded during the entire 72-h study period.

An emetic episode was defined as a single occurrence of vomiting or retching, and repeat episodes had to be separated by at least 2 min. In the postanesthesia care unit, a rescue medication (droperidol) was administered if the patient complained of persistent nausea (with a VAS nausea score $>$ 40 for at least 10 min) or experienced at least two emetic episodes. If the patient required antiemetic (or antinausea) drug therapy during the 72-h study period, they were considered a treatment failure. All rescue antiemetic (or antinausea) medications, PCA morphine requirements, and other postoperative medications were documented. The sample size calculation for the initial placebo-controlled, dose-ranging study was based on a power analysis assuming a $>$ 30% overall occurrence of postoperative emesis and the hypothesis that CP-122,721 would reduce the incidence by 50%. For the second interaction study, a minimum sample size of 40 patients for each group was determined by an *a priori* power analysis based on the assumptions that (1) the incidence of PONV in this patient population would be $\geq$ 30 %,[10,11] (2) a 10% reduction in PONV would be clinically relevant, and (3) $\alpha = 0.05$ and $\beta = 0.2$.

Categoric data were analyzed using the chi-square test and continuous data were analyzed with one way analysis of variance. For normally distributed data, the between-group comparisons were performed by analysis of covariance with baseline scores designated as the covariate. Non-normally distributed data were analyzed using a Kruskal-Wallis test followed by Kruskal-Wallis Z test for multiple comparisons. Time to first emetic event and to rescue medications were analyzed using log-rank test statistics. The curves of the time to when 25% of the patients in each group were judged to have failed the prophylactic antiemetic therapy (*i.e.*, had their first episode of emesis–retching or required rescue antiemetic therapy for nausea) were determined by the Kaplan-Meier method. Summary statistics included mean values ± SD, median values and ranges, and percentages and numbers. A P value < 0.05 was considered statistically significant. All statistical tests were performed us-

Table 1. Demographic and Antiemetic Effectiveness Data for the Four Groups in the First Dose-ranging Study

	Placebo (n = 21)	CP-122,721 100 mg (n = 21)	Placebo (n = 24)	CP-122,721 200 mg (n = 20)
Age (yr)	43 ± 7	43 ± 11	43 ± 7	42 ± 8
Weight (kg)	63 ± 7	69 ± 12	74 ± 18	78 ± 11
Surgery time (min)	97 ± 46	95 ± 48	81 ± 34	108 ± 64
Postoperative pain assessment				
Maximum pain score (mm)†	75 ± 7	62 ± 7	63 ± 8	42 ± 8
24-h PCA morphine usage (mg)	50 ± 26	53 ± 23	47 ± 22	45 ± 24
Postoperative emetic symptoms				
Maximum nausea score (mm)†	37 ± 4	18 ± 3	27 ± 4	16 ± 2
Vomiting or retching				
< 8 h (%)	12 (57)	7 (33)	12 (50)	2 (10)*
< 72 h (%)	14 (67)	9 (43)	22 (92)	10 (50)
≤ 2 episodes (%)	14 (67)	20 (95)*	17 (71)	20 (100)*
Antiemetic medication required				
< 8 h (%)	12 (57)	7 (33)	11 (46)	5 (25)*
< 72 h (%)	17 (81)	16 (76)	19 (79)	8 (40)*

Values are mean ± SD or (%).

* Significantly different from the placebo group; *P* value < 0.05. † Visual analog scale (VAS) score; 0 = none, 100 = most severe.

PCA = patient-controlled analgesia.

ing the Number Cruncher Statistical Systems version 6.0 program (NCSS Corp., Kaysville, UT).

Results

Of the 277 patients enrolled in the two studies, 34 were withdrawn because of protocol violations (*e.g.*, inadvertent administration of a drug with antiemetic properties during surgery), failure to receive the study medication at the appropriate time, or cancellation of the surgical procedure. In both the dose-ranging (n = 86) and interaction (n = 157) studies, the treatment groups were comparable with respect to age, weight, height, history of PONV and motion sickness, day of menstrual cycle, duration of surgery, and PCA morphine usage during the first 72 h postoperatively (tables 1 and 2).

In the dose-ranging studies, both CP-122,721 100- and 200-mg oral doses were found to decrease emetic symptoms compared with placebo treatments (table 1). In addition, the 200-mg dose of CP-122,721 delayed the onset of emesis compared with the placebo treatments (fig. 1). Although the maximum nausea VAS scores were lower in both CP-122,721 groups compared with placebo treatments, these differences did not achieve statistical significance. In the early postoperative period, pain VAS scores were similar in patients treated with CP-122,721 100 or 200 mg orally compared with the placebo treatments. There was no significant difference between the PCA morphine requirement in the CP-122,721 and placebo groups during the initial 24-h postoperative period.

Table 2. Demographic Data for the Three Antiemetic Treatment Groups in the Second Study

	Ondansetron (n = 52)	CP-122,721 (n = 52)	Combination (n = 53)
Age (yr)	43 ± 7	44 ± 7	43 ± 7
Weight (kg)	74 ± 15	71 ± 14	75 ± 16
History of PONV (%)	4 (18)	4 (18)	5 (20)
Postmenopausal (%)	36 (69)	37 (71)	37 (70)
Baseline VAS scores			
Nausea (mm)	4 ± 4	3 ± 2	2 ± 2
Pain (mm)	7 ± 5	5 ± 3	7 ± 6
Surgery time (min)	162 ± 62	146 ± 53	139 ± 53
Anesthesia time (min)	196 ± 75	177 ± 55	171 ± 55

Values are mean ± SD or (%).

PONV = postoperative nausea and vomiting; VAS = visual analog scale.

The VAS nausea scores did not differ among the ondansetron, CP-122,721, and the combination groups (table 3). Although the percentage of patients complaining of nausea (VAS score > 40) and the time to and requirements for rescue antiemetic drugs were similar in all three groups (fig. 2), the incidence of the emetic episodes was significantly lower after CP-122,721 200 mg alone or in combination with ondansetron 4 mg compared with ondansetron 4 mg alone (table 4). In addition, the Kaplan-Meier plot shows that the median time interval for 75% of the patients to remain completely free from any emetic episodes was significantly longer after the combination of CP-122,721 200 mg and ondansetron 4 mg than with either drug alone (fig. 3). Analogous to the findings in the placebo-controlled study, CP-122,721 was not associated with apparent analgesic- or opioid-sparing activity compared with ondansetron (table 4).

Compared with the placebo treatments, the only clinically significant adverse event attributed to CP-122,721 during the 72-h follow-up period was an increased incidence of headaches. Of 41 patients in the two CP-122,721 groups in the dose-ranging studies, 9 pa-

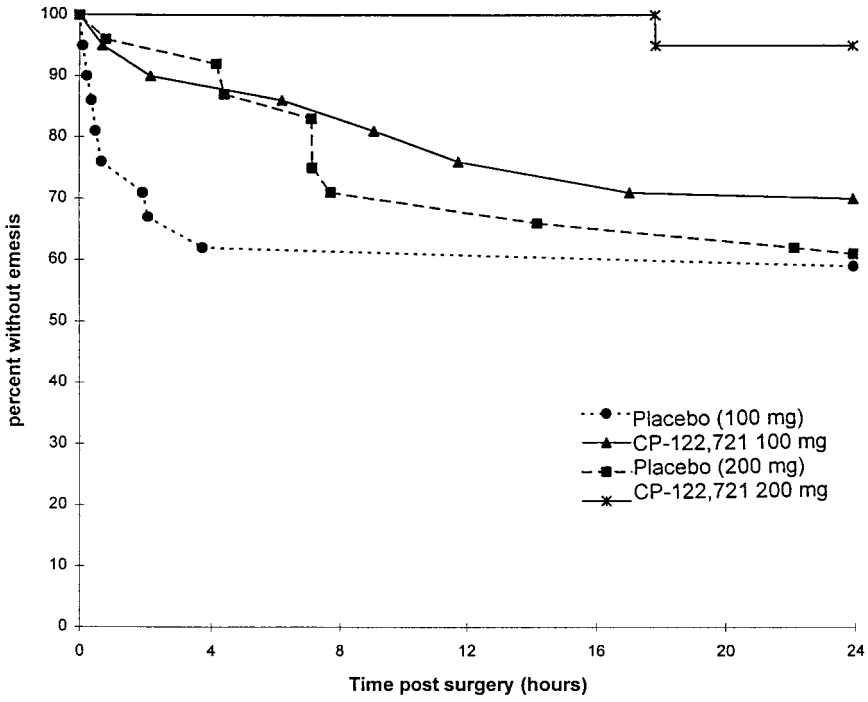

Fig. 1. Kaplan-Meier plot of the fraction of patients in the dose-ranging studies who remained free of emetic symptoms during the first 24 h after surgery. Because the study was performed sequentially at doses of 100 mg (*vs.* placebo) followed by 200 mg (*vs.* placebo), four separate curves are shown for placebo (*vs.* 100 mg), placebo (*vs.* 200 mg), CP-122,721 100 mg, and CP-122,721 200 mg. The delay in time to emesis and the proportion of patients with emesis were significantly different ($P < 0.01$) in patients receiving 200 mg *versus* placebo.

tients (22%) complained of postoperative headaches compared with only one patient (2%) in the placebo groups ($P < 0.05$). All of the headaches were either of mild (60%) or moderate (40%) severity. In the interaction study, there was a similar incidence of headaches in the ondansetron, CP-122,721, and combination groups: 1 (2%), 5 (10%), and 3 (6%), respectively. There were no differences in other side effects among the three groups in the second study. Finally, patient satisfaction with the management of their PONV symptoms was similar with CP-122,721 and ondansetron (table 3).

Table 3. Visual Analog Scale (VAS) Scores for Assessment of Nausea and Patient Satisfaction in the Second Study

	Ondansetron (n = 52)	CP-122,721 (n = 52)	Combination (n = 53)
Nausea VAS score (mm)*			
Baseline before surgery	4 ± 13	3 ± 12	2 ± 6
Upon arrival to PACU	21 ± 28	17 ± 16	15 ± 28
Maximum nausea VAS score (mm)			
None (%)	0 (0)	2 (4)	1 (2)
1–20 (%)	0 (0)	2 (4)	1 (2)
21–40 (%)	1 (2)	2 (4)	2 (4)
41–70 (%)	4 (8)	4 (9)	6 (12)
> 70 (%)	45 (90)	37 (79)	40 (80)
Nausea ≤ 8 h (%)	76	80	80
≤ 24 h (%)	98	96	98
Highly satisfied with PONV management	81	75	80

Values are mean ± SD or (%). No statistically significant differences.

* Nausea VAS scores: 0 = none, 100 = most severe.

PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting.

Discussion

Gynecologic surgical procedures are associated with a high incidence of PONV.[11,12] The incidence of PONV after lower abdominal gynecologic procedures without prophylactic antiemetic treatment varies from 40% to 80%.[1] Ondansetron has been shown to decrease the incidence of PONV after gynecologic surgery,[12,13] and recent studies have suggested that it is more effective when administered near the end of the surgical procedure.[4,10] Therefore, in our second study, ondansetron was administered 15–30 min before the end of the operation in an effort to optimize its antiemetic efficacy in this high-risk gynecologic surgery population. Although the meta-analysis by Tramer *et al.*[6] suggested that an 8-mg dose of ondansetron provided more effective prophylaxis against PONV than a 4-mg dose, this finding has been questioned because of the many inherent problems with meta-analysis,[14] including a lack of standardization of the timing of drug administration, as well as differences in the anesthetic techniques and types of surgical procedures.[15] A more recent dose-ranging study involving the use of ondansetron for PONV prophylaxis found that 4 mg administered intravenously was equivalent to 8 mg administered intravenously.[16] Despite optimization of the antiemetic dosage regimen, up to 20% of patients undergoing high-risk gynecologic procedures will continue to experience emesis with ondansetron, consistent with our experience in the interaction study.

The vomiting reflex can be triggered by activation of both mechanoreceptors in the gastrointestinal tract as well as *via* central mechanism during the perioperative period. A drug that can block this reflex arc should be

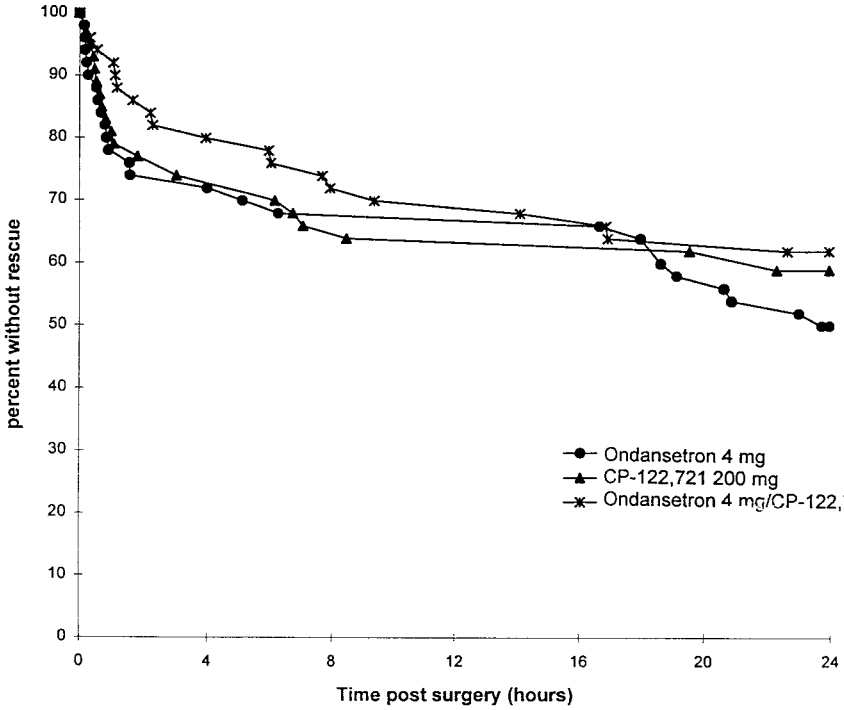

Fig. 2. Kaplan-Meier plot demonstrating the time to rescue for either nausea or emesis in the interaction study where patients received either ondansetron, CP-122,721, or a combination of both. Although there was a delay in the first 8 h after surgery in the number of subjects requiring rescue for nausea or emesis in the combination group, the overall need for rescue antiemetics was similar in all three treatment groups at 24 h.

useful in the prevention of nausea and vomiting.[1,2] Substance P, an endogenous ligand for the NK-1 receptor, evokes a wide variety of biological responses, including stimulation of gastrointestinal smooth muscle activity, exocrine gland secretion, afferent sensory responses to gastric distention, and other visceral afferent stimuli.[17,18] It is present in both vagal and sympathetic afferents and may potentiate "wind-up," as well as the activation of reflexes mediated, in part, by other neurotransmitter systems. Animal studies showed that selective NK-1 antagonists have a broad-spectrum antiemetic effect that is dependent on their ability to penetrate the central nervous system.[7,8,17,18] A preliminary study involving another NK-1 receptor antagonist (GR 205171) used postoperatively found that this investigational compound also provided better control of PONV than placebo in patients undergoing major gynecologic surgery procedures.[19]

Table 4. Postoperative Pain and Emetic Symptoms and the Need for "Rescue" Antiemetic Therapy in the Interaction Study

	Ondansetron (n = 52)	CP-122,721 (n = 52)	Combination (n = 53)
Emetic episodes < 24 h (%)			
0	76	94*	96*
1	14	2	1
2	8	4	2
≥ 3	2	0	1
Emesis < 24 h (%)	24	6*	4*
Median emesis-free time for 75% of patients (min)	82	75	362*
Treatment failure (%)	16	4	2*
Rescue antiemetic (%)	60	46	40
PCA morphine in 72 h (mg)	103 ± 61	82 ± 41	81 ± 38
Postoperative pain VAS scores (%)			
< 5 mm	0	4	2
5–20 mm	0	4	2
21–40 mm	2	9	12
41–70 mm	90	79	80
> 71 mm	8	4	4

Values are mean ± SD, numbers, or percentages.

* Significantly different from ondansetron alone; $P < 0.05$.

PCA = patient-controlled analgesia; VAS = visual analog scale: 0 = none, 100 = severe.

Because NK-1 antagonists do not have activity at the 5-HT_3 receptors,[7–9] we hypothesized that the combination of CP-122,721 and ondansetron would exert a more profound antiemetic effect because of their antagonistic activity at different central nervous system receptor sites. The current study suggests that the antiemetic activity of this NK-1 antagonist compares favorably with ondansetron. Furthermore, the prolongation of the emesis-free period in the group receiving the combination therapy would suggest that blockade of both NK-1 and 5-HT_3 receptors may result in enhanced antiemetic activity. Further investigations of this selective NK-1 antagonist alone and in combination with other commonly used antiemetic drugs are necessary to determine the optimal use of this novel compound in clinical practice.

Tramer *et al.*[6] reviewed 53 clinical trials that investigated the efficacy and safety of ondansetron for preventing PONV. These investigators concluded that patients receiving ondansetron for antiemetic prophylaxis were at risk for postoperative headaches. Although CP-122,721 was well tolerated and apparently safe when administered either alone or in combination with ondansetron, it was also

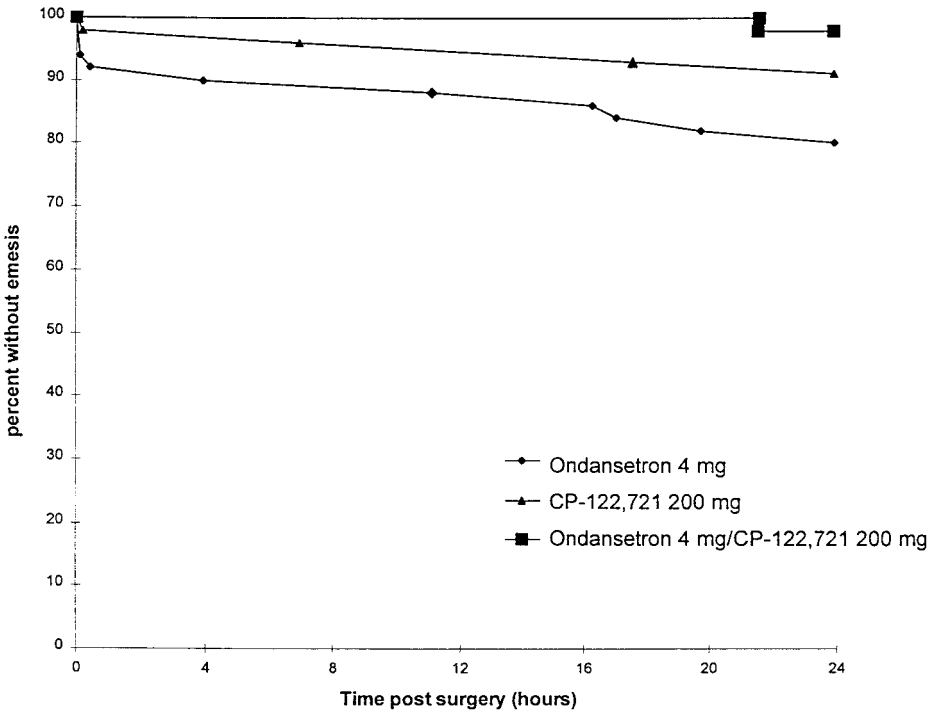

Fig. 3. Kaplan-Meier plot demonstrating the fraction of patients in the interaction study remaining free of emetic events during the first 24 h after surgery in the ondansetron (diamonds), CP-122,721 (triangles), and combination (squares) groups. The difference between the ondansetron-alone group and the two groups receiving CP-122,721, either alone or in combination with ondansetron, was significant ($P < 0.05$) with respect to the number of events and the time to occurrence of emesis.

associated with an increased incidence of postoperative headaches (22% *vs.* only 2% in the placebo groups).

In a cost-effectiveness analysis of ondansetron that examined both the direct and indirect costs, Watcha and Smith[20] concluded that routine prophylaxis with ondansetron was cost-effective if the expected incidence of PONV exceeded 30%. This estimate was based on the suboptimal efficacy obtained with existing dosing and timing regimens, and using the drug alone rather than in combination with other antiemetic agents. As pointed out by Fisher,[15] a major problem with many of the early PONV studies involving ondansetron (and other newer 5-HT_3 antagonist drugs) is that they focused exclusively on so-called surrogate end points. Of interest, more recent publications involving the use of ondansetron as a prophylactic antiemetic have provided data on clinically relevant outcome measures (*e.g.*, patient satisfaction, time needed to resume normal activities, and willingness to pay).[4,11] The failure to obtain recovery and outcome data represents serious deficiencies in the current study designs. The availability of these data in follow-up studies with CP-122,721 will make it possible to perform more meaningful comparative assessments of this novel antiemetic drug.

In conclusion, preoperative administration of the orally active NK-1 antagonist CP-122,721 (200 mg orally) was found to be similar to ondansetron (4 mg intravenously) in decreasing emetic symptoms after abdominal hysterectomy procedures. Patient satisfaction with the control of their PONV symptoms after CP-122,721 prophylaxis was also similar to ondansetron. The combination of CP-122,721 and ondansetron significantly prolonged the time to administration of the first rescue antiemetic drug compared with either drug alone, and almost completely prevented the occurrence of emesis. These preliminary data suggest that the combination of an NK-1 and 5-HT_3 receptor antagonist may be useful for antiemetic prophylaxis of surgical patients at high risk of developing PONV. NK-1 antagonists may represent a useful new class of antiemetic drugs.

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References

1. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. ANESTHESIOLOGY 1992; 1:62–84
2. Kenny GN: Risk factors for postoperative nausea and vomiting. Anaesthesia 1994; 49(Suppl):6–10
3. Eriksson H, Korttila H: Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. Anesth Analg 1996; 82:533–8
4. Tang J, Wang BG, White PF, Watcha MF, Qi J, Wender RH: Effect of timing of ondansetron administration on its efficacy, cost-effectiveness and cost-benefit as a prophylactic antiemetic in the ambulatory setting. Anesth Analg 1998; 86:274–82
5. Melnik B, Sawyer R, Karembelkar D, Phitayakorn P, Limuy N, Patel R: Delayed side effects of droperidol after ambulatory general anesthesia. Anesth Analg 1989; 69:748–5
6. Tramer M, Reynolds J, Moore R, McQuay H: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting. ANESTHESIOLOGY 1997; 87:1277–89
7. Gillis R, Helke C, Hamilton B, Norman W, Jackobowitz D: Evidence that substance-P is a neurotransmitter of baro- and chemoreceptor afferents in nucleus tractus solitarius. J Brain Res 1980; 181:476–81
8. McLean S, Ganong A, Seymour PA, Bryce DK, Crawford RT, Morrone J, Reynolds LS, Schmidt AW, Zorn S, Watson J, Fossa A, DePasquale M, Rosen T, Nagahisa A, Tsuchiya M, Heym J: Characterization of CP-122,721: A nonpeptide antagonist of the neurokinin NK-1 receptor. J Pharmacol Exp Ther 1996; 227: 900–8
9. Grunberg SM: Innovative approaches in the treatment of emesis. Support Care Cancer 1997; 5:9–11

10. Sun R, Klein KW, White PF: The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth Analg 1997; 84:331–6

11. Tang J, Watcha MF, White PF: A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 1996; 83:304–13

12. McKenzie R, Kovac A, O'Connor T, Duncalf D, Angel J, Gratz I, Tolpin E, McLeskey C, Joslyn A: Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. ANESTHESIOLOGY 1993; 78:21–8

13. Bodner M, White PF: Antiemetic efficacy of ondansetron after ambulatory surgery. Anesth Analg 1991; 73:250–4

14. White PF, Watcha MF: Has the use of meta-analysis enhanced our understanding of therapies for postoperative nausea and vomiting? Anesth Analg 1999; 88:1200–2

15. Fisher D: The "big little problem" of postoperative nausea and vomiting [editorial]. ANESTHESIOLOGY 1997; 87:1271–3

16. Dershwitz M, Conant JA, Chang YC, Rosow C, Connors P: A randomized, double-blind, dose-response study of ondansetron in the prevention of postoperative nausea and vomiting. J Clin Anesth 1998; 10:314–20

17. Sagan S, Josien H, Karoyan P, Brunissen A, Chassaing G, Lavielle S: Tachykinin NK-1 receptor probed with constrained analogues of substance P. Bioorg Med Chem 1996; 4:2167–78

18. Gonsalves S, Watson J, Ashton C: Broad spectrum antiemetic effects of CP-122,721, a tachykinin NK-1 receptor antagonist, in ferrets. Eur J Pharmacol 1996; 305:181–5

19. Diemunsch P, Schoeffler P, Bryssine B, Chelimuller LE, Lees J, McQuade B, Spragg C: Anti-emetic activity of the NK1 receptor antagonist GR 205171 in the treatment of established PONV following major gynecological surgery. Br J Anaesth 1999; 82:274–6

20. Watcha MF, Smith I: Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery. J Clin Anesth 1994; 6:370–7

Appendix

Number (n) of Patients Enrolled at Each Study Site

Dose-ranging Studies (Part I)	
Site #5011	n = 23
Site #5012	n = 40
Site #5013	n = 23
Total	86 patients

Interaction Study (Part II)	
Site #5012	n = 36
Site #5013	n = 20
Site #5017	n = 53
Site #5023	n = 16
Site #5056	n = 32
Total	157 patients