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Treatment of Postoperative Nausea and Vomiting after Outpatient Surgery with the 5-HT_3 Antagonist Ondansetron

Phillip Scuderi, M.D., Bernard Wetchler, M.D.,† Yung-Fong Sung, M.D.,‡ Melinda Mingus, M.D.,§ Stuart DuPen, M.D.,‖ Louis Claybon, M.D.,# John Leslie, M.D.,¶ Pekka Talke, M.D.,** Jeffrey Apfelbaum, M.D.,†† Said Sharifi-Azad, M.D.,‡‡ Melissa F. Williams, Pharm.D.§§*

Background: **Postoperative nausea and vomiting following outpatient surgery can significantly delay discharge. This study evaluates the safety and efficacy of ondansetron (a new 5-HT_3 antagonist) in the treatment of postoperative nausea and vomiting in patients following outpatient surgery.**

Methods: **Five hundred outpatient surgical patients (53 male and 447 female), receiving general endotracheal anesthesia, were studied at ten centers. Patients were stratified by gender and received, in a randomized, double-blind manner, 1, 4, or 8 mg ondansetron or placebo in response to nausea and/or vomiting postoperatively. Episodes of vomiting, nausea scores, adverse events, vital signs, and laboratory values were evaluated before and during the 24 h after study drug administration.**

Results: **Complete response to study medication (no vomiting and/or retching, and no rescue antiemetic over the initial 0–2-h period) was more frequent in the ondansetron groups (1 mg 57%, 4 mg 61%, and 8 mg 57%) than in the placebo group (30%, $P < .001$). For the 0–24-h study a complete response occurred in only 15% of the placebo group compared to 41%, 47%, and 47% of the 1-, 4-, and 8-mg ondansetron groups, respectively ($P < .001$ for all comparisons with placebo). Median nausea scores (range 0–10) during the initial observation period (0–2 h) were significantly lower for all doses of ondansetron (1.3, 0.8, 1.8 for 1, 4, and 8 mg, respectively) as compared with placebo (2.3). No significant differences occurred in hemodynamic stability, incidence of adverse events, or changes in laboratory values in the ondansetron groups compared to the placebo group.**

Conclusions: **Ondansetron, in doses less than 8 mg, is a safe, effective antiemetic for treating postoperative nausea and vomiting. (Key words: Antagonists, serotonin: ondansetron. Receptors, 5-HT_3: serotonin. Complications, postoperative: nausea; vomiting.)**

OF the 22 million surgical procedures performed annually in the United States, approximately 50% take place in outpatient settings.[1] Postoperative nausea and

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* Associate Professor, Department of Anesthesia, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

† Director, Departments of Anesthesia and Ambulatory Surgery, The Methodist Medical Center of Illinois, Peoria, Illinois.

† Associate Professor, Department of Anesthesiology, Emory School of Medicine, Atlanta, Georgia.

§ Assistant Professor, Department of Anesthesiology, Mt. Sinai School of Medicine, New York, New York.

‖ Director, Pain Consultation Service, Department of Anesthesia, Swedish Hospital Medical Center, Seattle, Washington.

Chairman, Department of Anesthesia, Mercy Hospital Anderson, Cincinnati, Ohio.

¶ Assistant Professor, Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina.

** Assistant Professor of Anesthesiology and Surgery, Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas.

†† Associate Professor and Vice Chairman of Clinical Affairs, Department of Anesthesia and Critical Care, University of Chicago Hospital, Chicago, Illinois.

‡‡ Clinical Associate Professor, Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania.

§§ Senior Clinical Research Scientist, Department of Clinical Research, Glaxo Inc., Research Triangle Park, North Carolina.

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Address reprint requests to Dr. Scuderi: Department of Anesthesia, Bowman Gray School of Medicine, Wake Forest University Medical Center, Medical Center Boulevard, Winston-Salem, North Carolina 27157-1009.

vomiting are two of the primary causes of morbidity in patients undergoing outpatient surgical procedures. These factors not only cause patient discomfort in the hospital and at home, but also prolong recovery room stays and even result in overnight hospital admission.[2,3]

Available antiemetic agents include the antihistamines (*e.g.*, hydroxyzine, promethazine), butyrophenones (*e.g.*, droperidol), and dopamine antagonists (*e.g.*, metoclopramide). While these drugs are considered effective in the treatment of postoperative nausea and vomiting, only a few have been proved effective as single-drug therapy in cases where no prophylactic antiemetic was administered preoperatively.[4–7] These drugs also have undesirable side effects, including excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal reactions, all of which may compound patient morbidity.[8–11]

Ondansetron, one of the new class of 5-hydroxytryptamine subtype 3 (5-HT_3) receptor antagonists, has been shown to be effective in the prevention of nausea and vomiting associated with highly emetic cancer chemotherapy.[12] Studies in the postoperative setting have shown ondansetron (8 mg iv) to be effective in prevention[13] and treatment[14,15] of postoperative nausea and vomiting. The objective of this multicenter trial was to determine whether smaller doses of ondansetron are effective compared with placebo in the treatment of postoperative nausea and vomiting. The safety and efficacy of three intravenous doses of ondansetron (1, 4, and 8 mg) were each compared to placebo in the treatment of postoperative nausea and vomiting in male and female patients who underwent outpatient surgical procedures after receiving general endotracheal anesthesia.

Methods and Materials

Written informed consent was obtained from 1,346 patients at ten institutions after approval by each institution's Human Subjects Committee. Patients were ASA physical status I or II between the ages of 17 and 70 yr who were scheduled to undergo outpatient surgical procedures with general endotracheal anesthesia. The subset of patients (500 total) who subsequently experienced postoperative nausea or vomiting within 2 h of admission to the post anesthesia care unit (PACU) were entered into the treatment groups.

Patients were ineligible for the study if they had received any other antiemetic agent within 24 h before the study began, had vomited or retched within 24 h, had prestudy serum alanine amino transaminase (ALT) concentrations greater than twice the upper limit of the normal range, had a serum creatinine > 2.0 mg/dl, were more than 100% over ideal body weight, had a liver or peritoneal biopsy performed during the surgical procedure, were breastfeeding, or had continuous gastric suction *via* an intragastric tube during surgery. All women were required to have a negative pregnancy test before enrollment in the study.

General endotracheal anesthesia included an induction agent (thiopental, thiamylal, or methohexital), an opioid analgesic (fentanyl, morphine sulfate, or alfentanil), and nitrous oxide-oxygen. Isoflurane was administered as necessary to maintain hemodynamic stability. Neuromuscular blocking agents included succinylcholine, d-tubocurarine, pancuronium, atracurium, and vecuronium. Reversal of neuromuscular blockade was achieved with neostigmine or edrophonium, with glycopyrrolate or atropine administration as needed. Premedication was limited to midazolam, fentanyl, or alfentanil.

After complaint of nausea or vomiting in the PACU, patients were randomized to receive 1, 4, or 8 mg ondansetron (administered as ondansetron hydrochloride dihydrate), or placebo intravenously over 2–5 min. Ondansetron for injection (2 mg/ml) and matching placebo supplies were provided by Glaxo Inc. (Research Triangle Park, NC). Placebo was a sterile isotonic solution containing citric acid monohydrate, sodium citrate, sodium chloride, and water for injection buffered to *p*H 3.5. All ondansetron doses were diluted with placebo to a volume of 8 ml and then with normal saline (0.9% NaCl) to a total volume of 20 ml to maintain the blinded design of the study. The placebo dose was 8 ml diluted with normal saline to 20 ml. The study continued for 24 h after study drug infusion.

Before study drug administration in the PACU, patients were asked to assess their nausea using a whole number linear numeric scale of 0–10, with 0 described as "no nausea" and 10 described as "nausea as bad as it could possibly be."[14] For 2 h after study drug administration, patients continued to assess their nausea at 30-min intervals. Additionally, the number of emetic episodes (vomiting and retching) was recorded. Vital signs (blood pressure, heart rate, and respiratory rate) were collected before and at 2, 4, 6, 8, 10, 20, 30, 60, and 120 min after study drug administration. Blood samples for laboratory tests were collected before study drug administration, before PACU discharge, and at the end of the 24-h study. Complete blood counts with

differentials and serum chemistries including liver enzymes were performed on all samples.

All patients receiving the study drug were observed for a minimum of 2 h then discharged from the PACU when standard discharge criteria were met. Before discharge, patients were given a diary card to be completed at the end of the 24-h study. Patients were to record all medications taken (including antiemetic medications), all vomiting or retching episodes, any adverse events, and an overall assessment of their nausea, from the time they left the hospital until the end of the 24-h study. Patients also were contacted by telephone to verify all data recorded on the diary card.

Nausea and/or vomiting that persisted after study drug administration was treated by the principal investigator at each study site according to the standards of care at each institution. Choice of antiemetic therapy was left to the discretion of the individual investigators.

Before randomization, patients were stratified by gender to ensure equal distribution of doses within each strata. The Mantel-Haenszel test was used to compare each of the three doses to placebo across strata. The primary efficacy variable was the number of emetic episodes the patient experienced. The number of emetic episodes (vomiting or retching) was grouped to create treatment response variables. A complete response was defined as no emetic episodes. If a patient experienced more than one emetic episode or required rescue antiemetic therapy following study drug administration, patients were considered treatment failures. All tests were two-tailed and were considered significant at $P \leq .05$.

Nausea scores were the secondary efficacy variable. Median nausea scores were calculated at each time point for each treatment group. If a patient required rescue antiemetic therapy for nausea or vomiting, the last nausea score before rescue was carried over to the remaining time point(s) to calculate a median overall nausea score for the 0–2-h study. Wilcoxon's rank-sum test was used to compare each of the ondansetron treatment groups to placebo with respect to changes in nausea scores from the baseline nausea score. No correction was made for multiple comparisons. For vital sign and laboratory means analysis, the mean of the difference from baseline for each ondansetron group was compared with that of the placebo group, using the two-sample t test at a significance level of 0.05.

Results

Patient demographic data are presented in table 1. No significant differences existed among the 1 mg, 4

Table 1. Patient Characteristics

Characteristic	Placebo (n = 129)	Ondansetron 1 mg (n = 130)	Ondansetron 4 mg (n = 119)	Ondansetron 8 mg (n = 122)
Sex (%)				
Female	90	88	90	89
Male	10	12	10	11
Ethnic origin (%)				
Caucasian	84	82	76	80
Asian	2	0	<1	<1
African American	9	12	22	13
Other	5	7	2	6
Age* (yr)	33.6 ± 0.8	33.5 ± 0.8	31.6 ± 0.7	33.3 ± 0.8
Weight* (kg)	66.8 ± 1.3	66.8 ± 1.3	69.3 ± 1.5	69.6 ± 1.4
Duration of anesthesia* (min)	64.4 ± 3.1	64.5 ± 3.0	68.8 ± 4.2	65.3 ± 3.1
Opioid in PACU (%)	57	63	61	64
Surgery type (%)				
Gynecologic	78	72	71	71
Orthopedic	8	11	17	12
Peripheral	7	8	5	5
ENT/oral	5	7	3	8
Eye	2	2	2	2
Abdominal	1	0	3	1

* Values are mean ± SE.

mg, 8 mg, or placebo groups with respect to gender distribution, weight, height, number of days since last menstrual cycle, alcohol consumption, and previous anesthetic experience. The 4-mg group was significantly different from placebo with respect to age and ethnic origin distribution. Neither of these characteristics nor their interaction with treatment were significant. Treatment groups were also similar with respect to surgery type and duration of anesthesia. Between 71% and 78% of the patients in each group had gynecologic surgery. The mean duration of anesthesia in each group was approximately 1 h. All patients received an opioid intraoperatively. Similar percentages of patients in each treatment group received opioids in the PACU. During the 22 h after discharge, 57% of placebo patients and 56–60% of ondansetron patients received opioids. Data collected from the time of discharge from PACU to 24 h after study drug administration was available for 497 of the 500 patients enrolled.

Postoperatively, within the first 2 h after study drug administration, significantly fewer patients receiving placebo had no emetic episodes (complete response) than either 1, 4, or 8 mg ondansetron patients ($P < .001$ all ondansetron groups compared to placebo, fig. 1). Similarly, over the entire 24 h following study drug administration, significantly fewer patients receiving placebo were complete responders compared to any of the ondansetron treated groups (fig. 1). In the 0–2 h and the 0–24 h after study drug administration, significantly more patients receiving placebo had more than one emetic episode, received rescue medication, or were withdrawn (treatment failures) than did patients in the ondansetron treatment groups (fig. 2). The percentage of patients with a complete response over the 24-h study is shown in table 2. Ondansetron, in addition to providing acute relief from nausea and vomiting, provides protection against nausea or vomiting during the 24 h following drug administration. Median, first and third quartiles, and range of nausea scores for all treatment groups over the 0–2-h study are shown in figure 3. There were significant differences in median nausea scores for each ondansetron group compared with placebo. When the data are split by strata, similar results are seen. Among female patients, 15% of placebo-treated patients were complete responders compared to 38% (1 mg), 47% (4 mg), and 46% (8 mg) of the ondansetron-treated patients over the 0–24-h study.

There was no significant difference in the incidence of adverse events between placebo and each of the on-

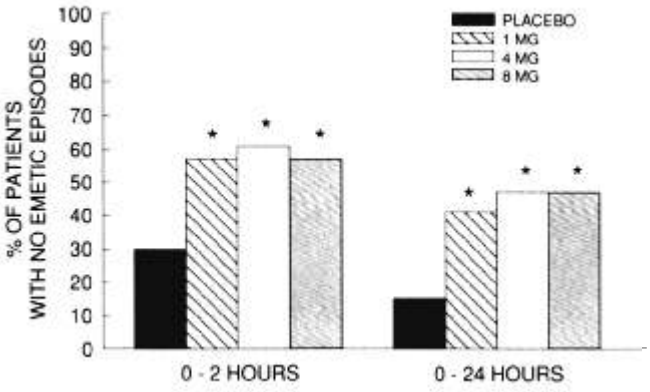

Fig. 1. The percentage of patients in each study group having no emetic episodes during the initial observation period (0–2 h) and during the follow-up period (0–24 h). * = $P < .001$ compared to placebo.

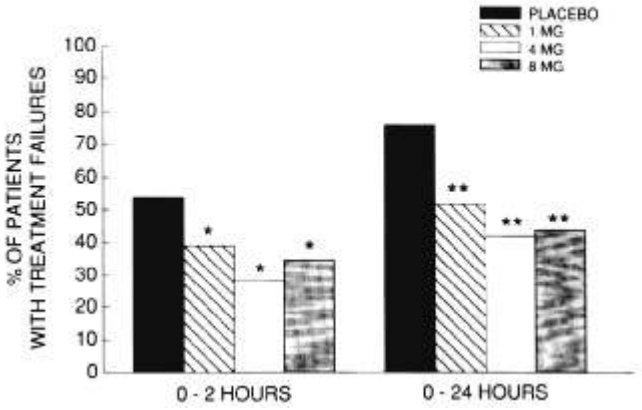

Fig. 2. The percentage of patients in the placebo group *versus* the three ondansetron treatment groups classified as treatment failures (more than one emetic episode or administration of a rescue antiemetic) during the initial observation period (0–2 h) and during the follow-up period (0–24 h). * = $P < .05$ compared to placebo; ** = $P < .001$ compared to placebo.

Table 2. Duration of Antiemetic Effect

Time after Administration	Placebo (n = 129)	% of Patients without Emeis or Rescue Antiemetic		
		1 mg* (n = 130)	4 mg* (n = 119)	8 mg* (n = 122)
30 min	68	78	85	87
60 min	48	65	74	70
90 min	38	60	66	63
120 min	30	57	62	58
24 h	15	41	49	47

* $P < .005$, each treatment group *versus* placebo.

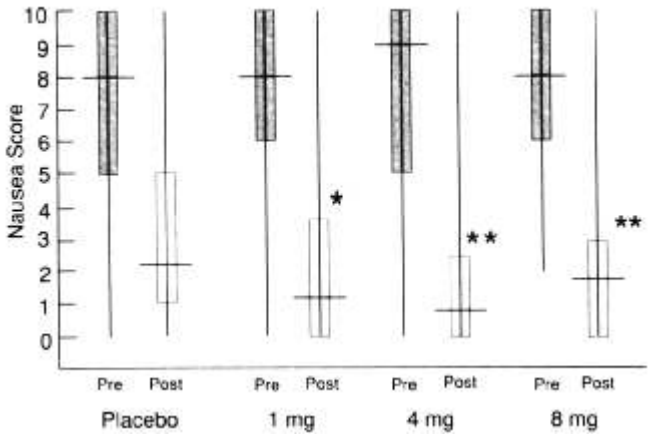

Fig. 3. The median (horizontal line), first and third quartiles (box), and range (vertical line) of nausea scores for patients before (Pre) and after (Post) study drug administration. Post represents overall scores for the initial observation period (0–2 h). * = $P < .05$ compared to placebo; ** = $P < .005$ compared to placebo.

dansetron groups (table 3). All adverse events that occurred at a frequency of 5% or greater in any group are listed. The most frequently reported events were headache, dizziness, musculoskeletal pain, drowsiness/sedation, and nonspecific chest pain.

Mean vital signs were similar among all four treatment groups throughout the 0–2-h study. Means of laboratory tests, adjusted for baseline for the ondansetron groups and for multiple comparisons, were not significantly different compared to the placebo group at 2 and 24 h after study drug administration. One patient who received placebo and one patient who received 4 mg ondansetron experienced increases in hepatic transaminases that resolved spontaneously. A third patient who received placebo had a transient elevation in total bilirubin at the 24-h assessment.

Discussion

It is generally accepted that outpatient surgical procedures are a cost-effective and efficient method of patient care. Nausea and vomiting after surgery can negate the benefits of outpatient surgery by increasing recovery time, intensity of nursing care, and patient morbidity. In addition, nausea and vomiting can persist after the patient is discharged from the PACU and can be exacerbated by ambulation. An effective antiemetic that could be used to treat nausea and vomiting when they occurred, without extending recovery time, and which would remain effective for the 24 h following treatment would be a significant asset to the anesthesiologists' armamentarium of drugs.

Previous studies have proved the effectiveness of 8 mg ondansetron in the prevention and treatment of postoperative nausea and vomiting.[14,15] The objective of this trial was to determine whether smaller doses are effective compared to placebo. In this trial 1-, 4-, or 8-mg intravenous doses of ondansetron were all significantly more effective in treating established nausea or vomiting than placebo. Each ondansetron dose also resulted in significantly lower nausea scores during the 2-h initial observation period as compared with placebo. There was also a significantly lower rate of treatment failure in the ondansetron groups as compared with placebo during the initial observation period and during the remainder of the 24-h study.

While available antiemetics are generally considered effective in the treatment of postoperative nausea and vomiting, few have been tested as single doses against placebo in patients with established nausea and/or emesis. The side-effect profile, particularly sedation, may limit the usefulness of these agents in the outpatient surgery population, especially when administered late in the recovery period.

In this study, headache, dizziness, and drowsiness or sedation were not significantly different in the ondansetron-treated patients compared with placebo. Therefore, it does not appear that ondansetron affects mental status. Additionally, ondansetron does not affect cardiovascular or respiratory status, as indicated by similar mean vital signs across all treatment groups, nor does it affect laboratory values.

While it is difficult to compare this study to others in the literature because of differences in methodology,

Table 3. Adverse Events

Events	Placebo (n = 129)	Ondansetron 1 mg (n = 130)	Ondansetron 4 mg (n = 119)	Ondansetron 8 mg (n = 122)
Any adverse event	64	55	57	63
Headache	18	11	20	21
Dizziness	15	13	10	16
Musculoskeletal pain	12	2	9	14
Drowsiness/ sedation	7	7	6	8
Nonspecific chest pain	5	4	2	4

Values are percentages.

ondansetron appears to be as efficacious as available antiemetics. In a comparison study, Loeser *et al.* showed that droperidol (5 mg im) had 33% fewer and prochlorperazine (10 mg im) 37% fewer patients experiencing vomiting at 4 h post treatment than did the placebo group.[7] Only droperidol continued to have significantly fewer patients with vomiting (31%) at 24 h compared to placebo. A direct comparison of ondansetron with these agents is needed.

Ondansetron appears to be an effective antiemetic when used to treat nausea and vomiting in outpatients. All doses tested (1, 4, and 8 mg) were significantly better than placebo in treating postoperative nausea and vomiting and preventing its recurrence. All ondansetron doses were well tolerated with an incidence of side effects no greater than placebo, making this drug an attractive choice as an antiemetic in the outpatient surgery setting.

References

1. Henderson JA: Ambulatory surgery: Past, present, and future. Anesthesia for Ambulatory Surgery. Edited by Wetchler BV. Philadelphia, JB Lippincott, 1991, pp 1–27

2. Gold B, Kitz D, Lecky JH, Neuhaus JM: Unanticipated admission to the hospital following ambulatory surgery. JAMA 262:3008–3010, 1989

3. Isenberg SJ, Apt L, Yamada S: Overnight admission of outpatient strabismus patients. Ophthalmic Surg 21:540–543, 1990

4. Barton MD, Libonati M, Cohen PJ: The use of haloperidol for treatment of postoperative nausea and vomiting—a double-blind placebo-controlled trial. ANESTHESIOLOGY 42:508–512, 1975

5. Van Leeuwen L, Helmers JH: The efficacy of Domperidone (R33812) in the treatment of postoperative vomiting: A double-blind study with a placebo. Anaesthesist 29:490–493, 1980

6. Fragen RJ, Caldwell N: A new benzimidazole antiemetic, domperidone, for the treatment of postoperative nausea and vomiting. ANESTHESIOLOGY 49:289–290, 1978

7. Loeser EA, Bennett G, Stanley TH, Machin R: Comparison of droperidol, haloperidol and prochlorperazine as postoperative antiemetics. Can Anaesth Soc J 26:125–127, 1979

8. Korttila K, Linnoila M: Skills related to driving after intravenous diazepam, flunitrazepam or droperidol. Br J Anaesth 46:961–969, 1974

9. Lee CM, Yeakel AE: Patient refusal of surgery following Innovar premedication. Anesth Analg 54:224–226, 1975

10. DeGrandi T, Simon JE: Promethazine-induced dystonic reaction. Pediatr Emerg Care 3:91–92, 1987

11. Melnick BM: Extrapyramidal reactions to low-dose droperidol. ANESTHESIOLOGY 69:424–426, 1988

12. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL: Efficacy of ondansetron (GR38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 322:810–816, 1990

13. McKenzie R, Odell S, Rudy T, Joslyn A: Ondansetron, a selective serotonin type 3 ($5\text{-}HT_3$) antagonist, reduces nausea and vomiting in females following major gynecologic surgery (abstract). ANESTHESIOLOGY 73:A739, 1990

14. Bodner M, White PF: Antiemetic efficacy of ondansetron after outpatient laparoscopy. Anesth Analg 73:250–254, 1991

15. Larijani GE, Gratz I, Afshar M, Minassian S: Treatment of postoperative nausea and vomiting with ondansetron: A randomized, double-blind comparison with placebo. Anesth Analg 73:246–249, 1991