Anesthesiology
78:21–28, 1993

J. B. Lippincott Company, Philadelphia

Comparison of Ondansetron Versus *Placebo to Prevent Postoperative Nausea and Vomiting in Women Undergoing Ambulatory Gynecologic Surgery*

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Background: **Postoperative nausea and emesis, especially in ambulatory surgical patients, remains a troublesome problem. This study was performed to compare the incidence of nausea and emesis during the 24-h postoperative period in ondansetron-treated patients *versus* placebo-treated patients.**

Methods: **Using a randomized prospective double-blind study design, women between the ages of 18 and 70 yr undergoing gynecologic surgical procedures with general opioid anesthesia on an outpatient basis were enrolled. Ondansetron or placebo was administered prior to induction of anesthesia. Patients were stratified according to history of nausea and emesis during previous exposure to general anesthesia and randomized to dose received.**

Results: **Data from the 544 women showed that all doses of intravenous ondansetron tested (1, 4, and 8 mg) were significantly more effective (62%, 76%, and 77%, respectively) than placebo (46%) in reducing the incidence of emesis following surgery until 24 h after recovery room entry. All these doses were more effective than placebo in patients with no prior history of emesis following surgery and the 4- and 8-mg doses were more effective than placebo in patients with a prior history of emesis following surgery. All doses of ondansetron tested were generally well tolerated with adverse events, clinical laboratory tests, and recovery room vital signs similar to those of placebo. Serum aspartate transaminase (AST) was increased in five patients (1 mg, 2 patients; 4 mg, 1 patient; 8 mg, 2 patients). In the three patients in whom subsequent analysis were performed, the serum AST had decreased to preoperative levels.**

Conclusions: **Ondansetron given intravenously to prevent postoperative nausea and emesis was highly effective in the 4- and 8-mg doses in women having ambulatory gynecologic surgery. (Key words: Antagonists, serotonin: ondansetron. Complications, postoperative: nausea; vomiting.)**

IN recent years, the number of surgical procedures performed on an outpatient basis has increased, accounting for approximately one-half of the estimated 22 million surgeries performed in the United States each year.‡‡ As such, an important consideration for cost control is the management of the major causes of

This article is accompanied by an editorial. Please see: White PF, Watcha MF: Are new drugs cost-effective for patients undergoing ambulatory surgery? ANESTHESIOLOGY 78:2–5, 1993.

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Received from Magee-Womens Hospital, Pittsburgh, Pennsylvania; University of Kansas Medical Center, Kansas City, Kansas; Kenmore Mercy Hospital, Kenmore, New York; Albert Einstein College of Medicine, Bronx, New York; University of Tennessee, Memphis, Tennessee; Medical College of Pennsylvania, Philadelphia, Pennsylvania; Medical Center of Delaware, Wilmington, Delaware; University of Colorado Health Sciences Center, Denver, Colorado; and Glaxo Inc., Research Triangle Park, North Carolina. Accepted for publication September 26, 1992. Supported by Glaxo Inc., Research Triangle Park, North Carolina.

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‡‡ Henderson J: Surgery is a growth business. Health Industry Today 2:11–16, 1987.

morbidity in this patient population (pain, nausea, and vomiting) and to ensure that such complications will not prevent patients from returning home on the day of their surgery.

A variety of drugs are used for preventing postoperative nausea and vomiting. The most commonly used prophylactic antiemetics include those categorized as anticholinergics (*e.g.*, scopolamine, hyoscine), antihistamines (*e.g.*, hydroxyzine, promethazine), butyrophenones (*e.g.*, droperidol), dopamine receptor antagonists (*e.g.*, metoclopramide), and most recently, sympathomimetics (*e.g.*, ephedrine). Although these antiemetics are generally effective, they have undesirable side effects, including excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal reactions.§§[1-5] A preferred antiemetic would be effective and have minimal side effects, especially those that might be cause for hospital admission (*e.g.*, sedation).

Ondansetron, a selective serotonin 5-hydroxytryptamine type 3 receptor antagonist, has been approved by the Food and Drug Administration for the prevention of nausea and vomiting associated with the initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. In clinical trials to establish the use of ondansetron for these indications, the most commonly reported adverse events were headache, diarrhea, and transient increases in the levels of plasma aspartate aminotransferase, aspartate transaminase (AST), and alanine aminotransferase (ALT).[6]

Pilot studies have shown that 8 mg intravenous ondansetron is more effective than placebo in preventing postoperative nausea and vomiting.[7,8] This is the first large multicenter double-blind placebo controlled study designed to evaluate the safety and efficacy of prophylactic 1-, 4- and 8-mg doses of intravenous ondansetron in women undergoing elective ambulatory gynecologic procedures, a patient population with a high incidence of postoperative nausea and emesis.

Methods and Materials

After obtaining institutional review board approval and written informed consent from patients, eight separate centers enrolled nonpregnant, ASA physical status I or II women between 18 and 70 yr of age scheduled for gynecologic laparoscopies. Patients provided medical histories; demographic information including height, weight, age, alcohol consumption, last menstrual cycle, and ethnic origin; and a blood sample for laboratory safety studies. Patients were excluded from enrollment if they had received any prophylactic antiemetics preceding surgery, were more than 75% over their ideal body weight, were scheduled to have gastric suction during or after surgery, had abnormalities in clinical laboratory tests of liver function, were scheduled to undergo a liver biopsy during surgery, or were pregnant.

Because a history of nausea and vomiting after general anesthesia is believed to predict future response, patients were initially placed in strata based on previous experience with general anesthesia.[9] The two strata were: (1) nausea and vomiting following previous general anesthesia and (2) no previous general anesthesia or no nausea and vomiting following previous general anesthesia. Following strata assignment, patients were randomized within each center to receive either 1, 4, or 8 mg ondansetron (as ondansetron hydrochloride dihydrate) or placebo. Placebo (8 ml) or the appropriate volume of ondansetron (2 mg/ml) was admixed with normal saline to a final volume of 20 ml and administered intravenously in a double-blind fashion over a 2–5-min period immediately before induction of anesthesia. Vital signs (arterial blood pressure and heart and respiration rate) were monitored immediately before and after study drug administration and for the first 2 h after recovery room entry.

All patients underwent endotracheal intubation and received general anesthesia including an induction agent (thiopental, thiamylal, or methohexital), an opioid (fentanyl or alfentanil), and nitrous oxide. In some instances isoflurane or enflurane was administered. Neuromuscular blockade was facilitated with succinylcholine, atracurium, or vecuronium and reversed with an anticholinesterase (neostigmine, pyridostigmine, or edrophonium) with atropine or glycopyrrolate. For the first 2 h after initial response to vocal command in the post anesthesia care unit (PACU), study personnel monitored the patients and recorded the occurrence of emetic episodes, severity of nausea, vital signs, and adverse events. Before the patients were discharged from the PACU, blood samples were taken for laboratory safety studies. The patients were given diary cards on which to record emetic episodes, nausea severity, medications taken, and adverse events for the 22 h after discharge. Patients mailed the completed diary back to the study center and also underwent a

§§ Wetchler B: Control of nausea and vomiting in the postanesthesia care unit. Anesthesiology Review 18(suppl 1):19–22, 1991.

telephone interview to verify data reported during the outpatient period of the study. At the end of the 24-h study blood samples were again taken for laboratory safety studies.

For the purpose of data collection, no distinction was made between vomiting and retching. An emetic episode was defined as a vomiting or retching event or any combination of these events that occurred in rapid sequence (less than 1-min between events). In other words, if a retch or vomit was followed 1 min later by another retch or vomit they would be considered two separate episodes for the purpose of collecting "the number of emetic episodes" experienced by a patient. Nausea was defined on a categorical 11-point linear whole number scale for which 0 represented "no nausea" and 10 represented "nausea as bad as it can possibly be." The study nurse asked the patient to rate their nausea at the following times: prior to study drug infusion, at PACU entry, and then at 30-min intervals for 2 h and again at 24 h after PACU discharge.

Rescue therapy was allowed at any time upon physician determination or patient request, more than three emetic episodes or nausea lasting at least 15 min. The choice of rescue antiemetic was left to the discretion of the investigator and the patient was considered a treatment failure.

All tests were two-sided at a significance level of 0.05. All statistical comparisons in this study were placebo *versus* each ondansetron group. The Mantel-Haenszel test was used to compare each ondansetron group with the placebo group with regard to (1) the proportion of patients with no emetic episodes over the 24-h study, (2) the number of patients with "no nausea" over the entire study period, and (3) the proportion of patients with no emetic episodes or need for alternate antiemetics for the remainder of the study period following discharge and for those patients who had no emetic episodes or need for alternate antiemetics before discharge. For comparing the number of patients reporting "no nausea" during the 24-h study, patients who completed the 24-h study were included in the analyses if nausea scores were available for all times specified by the protocol. Fisher's exact test was used to make pairwise comparisons of the ondansetron groups with the placebo group with regard to adverse events. The individual center data were summarized with respect to the proportion of patients with no emetic episodes over the entire study period and "no nausea" over the entire study period.

Results

Patient Characteristics

A total of 580 patients were enrolled in this study. Table 1 lists those patients in each treatment group who were not included in the analysis of efficacy because of protocol violations that may have altered the interpretation of the results. A total of 36 patients in the study had protocol violations that would have influenced the results. These protocol violations affect either the incidence of postoperative nausea and emesis or the antiemetic effectiveness of ondansetron. Examples of the types of violations that resulted in the exclusion of patients from the efficacy analysis included: receipt of other prophylactic antiemetics in addition to ondansetron, not using an intraoperative opioid or nitrous oxide, intragastric suction postoperatively, and nausea and emesis within 24 h of surgery. Patients ex-

Table 1. Distribution of Patients Experiencing Protocol Violations That Would Have Influenced the Ondansetron Efficacy Results

Event	Placebo [N (%)]	Ondansetron 1 mg [N (%)]	Ondansetron 4 mg [N (%)]	Ondansetron 8 mg [N (%)]
No. of patients	142	139	152	147
No. of patients with efficacy-related deviation*	3 (2)	6 (4)	16 (10)	11 (7)
Receiving excluded antiemetic	2 (2)	3 (2)	7 (5)	8 (5)
No opioid or nitrous oxide during anesthesia	0 (0)	2 (1)	6 (4)	3 (2)
No outpatient data available	0 (0)	1 (1)	2 (1)	1 (0)
Administrative errors	0 (0)	1 (1)	1 (1)	1 (1)
Undergoing gastric suction *via* intragastric tube during or after surgery	1 (1)	1 (1)	0 (0)	0 (0)
Vomiting or retching during 24 h before surgery	0 (0)	0 (0)	1 (1)	0 (0)

* Some patients had deviations in more than one category.

periencing any of the above types of violations were removed from the study population, thereby creating the efficacy subgroup population.

The background characteristics (ethnic origin, weight, age, height, days since last menstrual cycle, and alcohol consumption) of the patients in the efficacy subgroup population were generally similar among the study groups (table 2). The mean duration of anesthesia (approximately 40 min) was also similar among the study groups. The majority of patients in each group had either never before received general anesthesia or had no nausea or vomiting following previous experience with general anesthesia.

All patients received alfentanil or fentanyl during the surgical procedure. Over the 24-h study, the incidence of postoperative opioid analgesic exposure was similar among the study groups (placebo 57%, 1 mg ondansetron 54%, 4 mg ondansetron 61%, and 8 mg ondansetron 55%).

Efficacy

All three doses of ondansetron were more effective than placebo in preventing emesis during the 24 h after surgery (fig. 1A). In patients with a history of vomiting after general anesthesia, 25% of the placebo-treated patients had no emesis (fig. 1B). The 4- and 8-mg doses of ondansetron significantly increased the number of patients without emesis compared to placebo. In placebo-treated patients who had never received general anesthesia or had not vomited following previous general anesthesia, 56% had no emesis (fig. 1C). All doses of ondansetron were significantly more effective than placebo in preventing emesis.

Four patients of the 580 enrolled did not have outpatient data available (*e.g.*, failed to return diary card and did not respond to telephone follow-up; table 1). Analyses of diary card data show that of the patients who had no emesis in the recovery room, approximately 3–10% of ondansetron-treated patients com-

Table 2. Patient Characteristics of the Efficacy Subgroup Population

Event	Placebo	Ondansetron		
		1 mg	4 mg	8 mg
No. of patients	139	133	136	136
Ethnic origin [N (%)]				
White	86 (62)	88 (66)	90 (66)	85 (63)
Black	45 (32)	37 (28)	41 (30)	41 (30)
Asian	2 (1)	0 (0)	0 (0)	0 (0)
Other	6 (4)	8 (6)	5 (4)	10 (7)
Age* (yr)	30.2 ± 0.5	30.2 ± 0.5	31.0 ± 0.5	30.3 ± 0.5
Weight* (kg)	64.2 ± 1.0	64.4 ± 1.1	65.3 ± 1.1	66.0 ± 1.1
Height* (cm)	163 ± 0.6	163 ± 0.6	165 ± 0.6	163 ± 0.5
Last menstrual cycle* (days)	19.0 ± 2.9	18.2 ± 1.8	18.4 ± 2.6	29.1 ± 5.5
Alcohol consumption [N (%)]				
Nonuser	84 (60)	84 (63)	64 (47)	72 (53)
<7 drinks/wk	49 (35)	44 (33)	66 (49)	61 (45)
1–4 drinks/day	6 (4)	5 (4)	5 (4)	1 (<1)
Prior heavy use	0 (0)	0 (0)	1 (<1)	2 (1)
Previous anesthetic experience [(N (%)]				
None	33 (24)	31 (23)	27 (20)	33 (24)
Without nausea/vomiting	62 (45)	60 (45)	65 (48)	57 (42)
With nausea/vomiting	44 (32)	42 (32)	44 (32)	46 (34)
Surgery type [N (%)]				
Laparoscopy for tubal sterilization	81 (58)	73 (55)	83 (61)	74 (54)
Diagnostic laparoscopy	43 (31)	49 (37)	46 (34)	53 (39)
Laser laparoscopy	8 (6)	9 (7)	5 (4)	5 (4)
Laparotomy	3 (2)	0 (0)	2 (1)	2 (1)
Mini laparotomy	3 (2)	2 (2)	0 (0)	2 (1)
Dilation and curettage	1 (1)	0 (0)	0 (0)	0 (0)
Duration of anesthesia* (min)	40.7 ± 2.5	39.1 ± 2.1	39.4 ± 2.5	39.7 ± 2.3
Awakening time* (min)	8.7 ± 0.6	9.0 ± 0.9	9.0 ± 0.7	8.0 ± 0.6

* Values are mean ± SE.

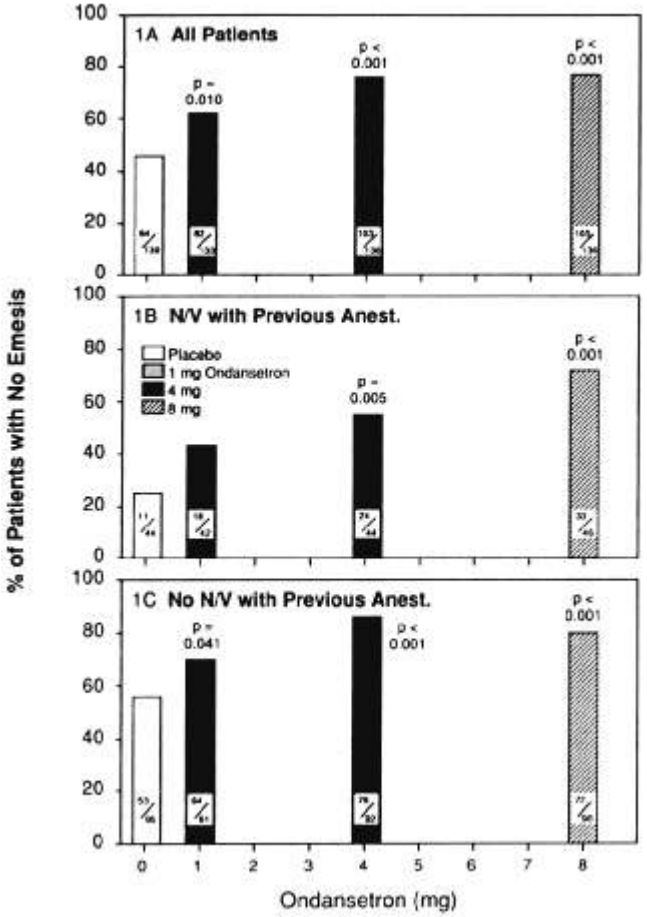

Fig. 1. The percentage of patients in each study group who had no emesis during the 24-h study.

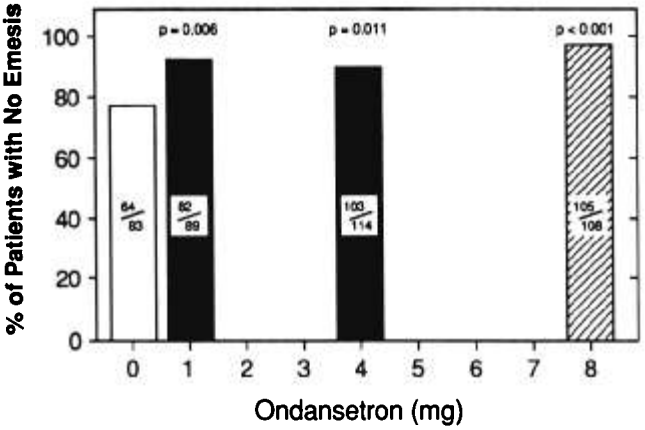

Fig. 2. The percentage of patients in each group who had no emesis or rescue antiemetic before discharge and experienced no emesis over the next 22 h.

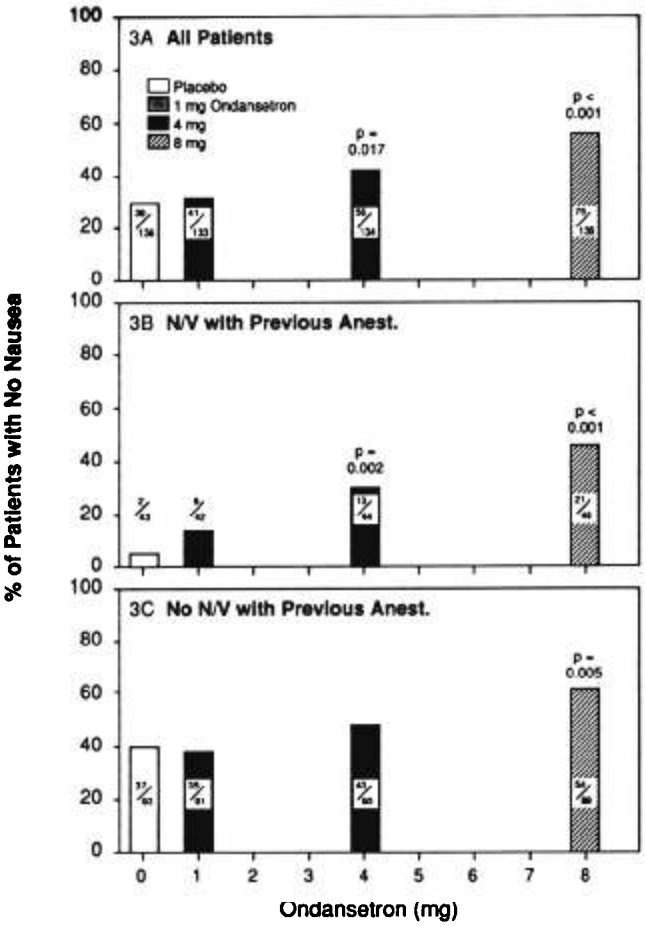

Fig. 3. The percentage of patients in each study group who were nausea-free (score of zero) at every assessment during the 24-h study.

pared with 23% of placebo-treated patients, experienced emesis after discharge (fig. 2). Each dose of ondansetron was more effective at preventing emesis than was placebo.

Ondansetron in 4- and 8-mg doses was more effective than placebo in preventing nausea over the entire 24-h study in all patients and in patients with a previous history of postoperative nausea and vomiting. In patients with no prior history of nausea and vomiting following general anesthesia, only the 8-mg dose was more effective than placebo (fig. 3).

The duration of antiemetic effect of all treatment groups is shown in figure 4. The 4- and 8-mg ondansetron groups had similar percentages of patients developing emesis at each data collection point over the 24-h study.

The study was not sized to detect statistical significance at each individual center, however, the results

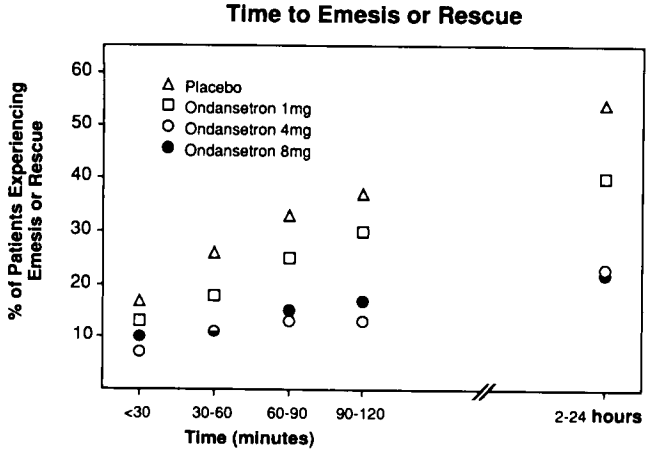

Fig. 4. The percentage of patients experiencing emesis or rescue plotted *versus* time over the entire 24-h study.

by center are similar to the overall results (data not shown).

Safety

All 580 patients enrolled in the study were included in the safety evaluation of ondansetron. Adverse events reported at least 5% of the time in any treatment group are listed in table 3. Adverse events occurred in significantly more patients in the placebo group than in any of the ondansetron groups (table 3). The most frequently occurring events were dizziness and headache, for which the incidences in the placebo group were either more than (dizziness) or similar to (headache) the incidences in any of the ondansetron groups.

Drowsiness occurred in 3–9% of the patients in each treatment group and in most cases was considered to be mild or moderate in severity and unrelated to study drug administration. Another important indicator of sedation is the time from anesthesia reversal to response to vocal command. The mean awakening times were similar for the ondansetron groups (8–9 min) and placebo group (8.7 min, table 2). All doses of ondansetron were similar to placebo with regard to sedation.

Following study drug infusion up to 120 min after PACU entry, mean vital signs were similar among the study groups and were within clinically acceptable ranges.

Changes in clinical laboratory test results were generally similar among the placebo and ondansetron groups at 2 and 24 h after surgery. Significant changes occurred in all study groups in leukocyte counts including differentials; however, these changes were consistent with those expected in this surgical population.

Five patients who received ondansetron (1 mg, 2 patients; 4 mg, 1 patient; 8 mg, 2 patients) had a notable increase in hepatic transaminase levels. One of these patients had an increase in serum AST from 39 U/l 7 days before enrollment to 80 U/l at 24 h posttreatment, and the other had an increase in serum AST from 72 U/l 2 days before enrollment to 163 U/l at 2 h posttreatment. The only patient in the 4-mg ondansetron group who had notable elevations in serum transaminases had an increase in AST from 14 U/l at baseline to 112 U/l 5 days posttreatment, and in ALT from 9 U/l at baseline to 124 U/l at 5 days posttreatment. Of the

Table 3. Incidence of Adverse Events*

Event	Placebo [N (%)]	Ondansetron 1 mg [N (%)]	Ondansetron 4 mg [N (%)]	Ondansetron 8 mg [N (%)]
No. of patients with any adverse events	97 (68)	75 (54)†	85 (56)†	80 (54)†
No. of patients with any:				
Dizziness	26 (18)	20 (14)	21 (14)	14 (10)†
Headache	18 (13)	21 (15)	21 (14)	17 (12)
Shivering	15 (11)	12 (9)	11 (7)	11 (7)
Drowsiness/sedation	9 (6)	13 (9)	11 (7)	5 (3)
Injection site reaction	9 (6)	8 (6)	7 (5)	6 (4)
Malaise/fatigue	8 (6)	3 (2)	7 (5)	5 (3)
Postoperative CO_2-related pain‡	6 (4)	3 (2)	7 (5)	6 (4)
Anxiety/agitation	8 (6)	1 (<1)†	2 (1)	3 (2)

* Adverse events reported at least 5% of any individual treatment category.

† Statistically significant ($P < .05$) differences in comparison with placebo group.

‡ Postoperative CO_2-related pain refers to postoperative pain in the neck and upper torso secondary to abdominal CO_2 insufflation during the laparoscopic procedure.

two patients in the 8-mg ondansetron group who had notable increases in serum transaminases, one had a serum AST of 23 U/l at baseline that increased to 134 U/l at 24 h posttreatment and had evidence of previous infection with hepatitis A. The other had an increase in serum ALT from 33 U/l 7 days before enrollment to 112 U/l at 24 h posttreatment. In all but two instances in which no laboratory values subsequent to the elevated values were available, all notably high increases in transaminases had decreased to preoperative values at subsequent assessments.

Discussion

Of the ondansetron doses tested in this trial, a single 4-mg intravenous dose appeared to be the lowest acceptable dose to prevent postoperative nausea and vomiting. It did not alter vital signs and did not prolong sedation. In addition, ondansetron is effective in preventing postdischarge emesis in those patients who do not vomit in the recovery room. Furthermore, based on the amount of emesis reported following PACU discharge and information on the time to development of emesis or receipt of rescue therapy, it appears that ondansetron continues to be an effective antiemetic over the entire 24-h study. This important finding reduces the fear that the ambulatory patient will develop postoperative vomiting necessitating readmission after discharge. The explanation for the duration of antiemetic effect of ondansetron is unknown considering that the plasma elimination half-life of intravenous ondansetron is approximately 3–4 h in normal volunteers.[10]

A history of nausea and vomiting after previous exposure to general anesthesia is a positive predictor of similar complications after subsequent exposure to general anesthesia.[9] This study was stratified according to each patient's previous experience with general anesthesia. For patients with a history of nausea and vomiting after general anesthesia, ondansetron continued to be an effective prophylactic antiemetic.

A recent dose-ranging study by Kenny *et al.* evaluated the effectiveness of oral ondansetron as a prophylactic postoperative antiemetic.[11] Oral ondansetron in doses of 1, 8, or 16 mg or placebo given three times daily was administered to females undergoing major gynecologic surgery. The present study was designed to compare 1, 4, or 8 mg intravenous ondansetron to placebo for preventing postoperative nausea and vomiting in female outpatients undergoing gynecologic laparoscopies. Differences in the two studies included route of administration of ondansetron, doses and dosing regimens and patient populations (inpatient *vs.* outpatient surgery). Even with these differences ondansetron was an effective prophylactic antiemetic in both studies. In the Kenny *et al.* study, 8 and 16 mg oral ondansetron were similar with both doses significantly more effective than 1 mg ondansetron and placebo. In this study, 4 and 8 mg intravenous ondansetron were statistically better than placebo, whereas the 1-mg ondansetron dose was not significantly different from placebo in some efficacy variables.

Commonly used antiemetics are generally effective in the management of postoperative nausea and vomiting. Drowsiness is of particular concern in ambulatory surgical patients because of extended recovery room stay at times necessitating overnight hospital admission, thus increasing patient and hospital costs. Unfortunately all newly developed medications are likely to be more expensive than established medications in current use.

Because of differences in study design, results from this trial cannot be directly compared with those from trials of other commonly used antiemetics. However, in one study in which similar data were collected for a 24-h postoperative period, intravenous droperidol (5 mg) was 24% more effective than placebo in preventing vomiting.[12] In this study the 4-mg ondansetron dose was 30% more effective than placebo in preventing emesis. Because of a marginal improvement in the efficacy of ondansetron compared with droperidol, a trial that directly compares these two compounds is needed.

Ondansetron also effectively reduced postoperative nausea. Regardless of anesthesia history, the number of nausea-free patients during the 24-h study was higher with increasing doses of ondansetron.

Ondansetron appears to be a safe antiemetic. Headache, dizziness, and drowsiness were observed in patients who had received ondansetron, but at occurrence rates not significantly different from those seen in patients who had received placebo.

The use of ondansetron in patients receiving chemotherapy may cause transient increases in hepatic transaminase levels. Although five of 405 patients (1.2%) who received ondansetron had notable increases in hepatic transaminase levels to approximately 2–3 times the upper limit of the normal range, the elevations were transient in nature and returned to baseline levels within 7–18 days, according to information available.

In chemotherapy-induced emesis clinical trials, patients receiving ondansetron concurrently with high-dose ($\geq$100 mg/m^2) cisplatin experienced elevations in transaminase levels approximately 25% of the time.‖ ‖ The authors felt that increasing doses of cisplatin contributed to the increased frequency of transaminase elevations following ondansetron treatment. In the study in patients receiving chemotherapy as well as in the present study, there was no apparent relationship between ondansetron dose and transaminase elevation.

In summary, ondansetron given intravenously to prevent postoperative nausea and emesis was highly effective in both 4- and 8-mg doses in women having ambulatory surgery. No significant changes in signs or symptoms occurred involving cardiac, respiratory, or central nervous systems. Hematology and blood chemistry results in patients receiving 1, 4, or 8 mg intravenous ondansetron were not significantly different from those in patients receiving placebo.

‖ ‖ Hesketh PJ, Twaddell T, Finn A. A possible role for cisplatin (DDP) in the transient hepatic enzyme elevations noted after ondansetron administration (abstract). Proceedings of the American Society of Clinical Oncology 6:323, 1990.

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