Ondansetron for the Prevention of Emesis Induced by High-Dose Cisplatin

A Multi-Center Dose–Response Study

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To determine a dose–response relationship of ondansetron for the prevention of emesis induced by high-dose cisplatin and to study the efficacy of the extended dosing schedule of ondansetron during 20 hours after cisplatin administration, 36 patients with malignant neoplasms who had not previously received chemotherapy but who were currently receiving cisplatin were treated. These patients received a six-dose regimen of 0.01 mg/kg (low dose) or 0.18 mg/kg (high dose) of ondansetron. Seven (41%) patients in the high-dose group had no emesis and four (24%) patients had one or two episodes. One (5%) patient in the low-dose group had no emesis and four (21%) patients had one or two episodes. The difference in the number of emetic episodes was significant ($P < 0.02$). Fifty percent of the high-dose patients reported no nausea or mild nausea, compared with 11% of the low-dose patients. Clinical adverse events included mild, transient headache and dizziness in the high-dose group and headache and diarrhea in the low-dose group, with no significant laboratory abnormalities. There is a parallel relationship between the ondansetron doses and the antiemetic efficacy. The response rate for the six-dose regimen of 0.18 mg/kg was not superior to that for the previously reported 0.18 mg/kg regimen given in a three-dose schedule in a similar clinical setting.
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NAUSEA AND VOMITING are the side effects of greatest concern to patients receiving chemotherapy for malignant neoplasms.[1,2] The consequences of failing to control emesis range from the immediate patient discomfort (prolonged anorexia and fatigue) to medical complications such as esophageal laceration, metabolic derangements, and potential reduction of antineoplastic treatment benefits as a result of delay or refusal of further chemotherapy.[3–6] The single most effective antiemetic currently available is metoclopramide.[7] However, its use is limited by side effects associated with its inherent antidopaminergic characteristics including extrapyramidal reactions, akathisia, and anxiety.[7,8]

Ondansetron (GR 38032F, previously termed GR-C507/75) represents the first of a new generation of antiemetics that antagonize serotonin (5-hydroxytryptamine) neurotransmitters at the 5-HT_3 (selective serotonergic) receptors without a demonstrable interaction with dopaminergic receptors.[9] Preclinical trials have shown that serotonin antagonists reduced the acute emetic response to cisplatin.[10–12] Clinical studies with the intravenous formulation of ondansetron indicate that doses as large as 0.48 mg/kg can be administered safely.[13,14] No reports of significant side effects, including extrapyramidal reaction with ondansetron, have emerged from these trials and other similar studies.[15,16] Recently published comparative trials with this serotonin antagonist demonstrated the antiemetic superiority of ondansetron over placebo[15] or high-

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dose metoclopramide.[16] The acute antiemetic protection of ondansetron at dose levels of 0.1 mg/kg and greater in patients receiving cisplatin-based chemotherapy has been shown previously.[13,14] Currently, however, it has been demonstrated that the reported dose-ranging studies were not carried out in a randomized setting and that cisplatin doses were not identical in all treatment strata. Hesketh *et al.*[17] recently presented the results of a 0.18-mg/kg intravenous dose trial of ondansetron. The ondansetron was administered just before and twice after high-dose ($\geq$100 mg/m^2) cisplatin therapy. This dose level of ondansetron produced an overall antiemetic response to two or fewer episodes over the 24-hour study period in 75% of the patients studied.[17] Interestingly, the antiemetic efficacy of 6-hour *versus* 8-hour dosing schedules of ondansetron in that trial was found to be equivalent. Furthermore, the therapeutic advantage of a regimen using a 2-hour interval, which was tested in another study,[18] is comparable with that of the 4-hour interval program reported by Hesketh *et al.*[17]

In view of those data, the following prospectively randomized multi-institutional trial was initiated to determine a dose–response relationship and to test the impact of an extended dosing schedule during the 24-hour study period on overall antiemetic protection provided by ondansetron.

Patients and Methods

This was an open-label, randomized, multi-center trial by six independent investigators. The study was approved by each participating Institutional Review Board (IRB) and all patients gave written informed consent. Hospitalized patients who had not received previous chemotherapy, were at least 18 years of age, and were scheduled to receive cisplatin at a dose of 100 mg/m^2 or greater were eligible for enrollment. Patients were excluded if their Karnofsky performance status was less than 60% or if they had been afflicted with a significant cardiovascular, cerebrovascular, renal, hepatic, psychiatric, or hematologic disorder. Additional exclusion criteria included the following: vomiting within 24 hours before the first dose of the study drug, receiving an investigational drug within 30 days of entering the study, and using other antiemetics or steroids during the study. The pretreatment evaluation consisted of a thorough history, including ethanol consumption, physical examination, complete blood count, and serum biochemical profiles of liver and kidney functions and electrolytes.

Patients were randomly (1:1) assigned to receive six doses of either 0.01 mg/kg or 0.18 mg/kg of ondansetron. A random code was provided for each study site. Each dose was administered intravenously in 50 ml of normal saline during 15 minutes. The first dose was given 30 minutes before the start of a 60-minute cisplatin infusion and subsequent doses were given 4, 8, 12, 16, and 20 hours later.

Patients were monitored by the nursing staff for 24 hours after the cisplatin infusion. The primary efficacy variable was the number of emetic occasions that occurred in the 24-hour study period. Each occasion of vomiting was considered an emetic episode, as was up to five retches in 5 minutes. The time of each emetic episode was recorded. The secondary efficacy variables were nausea, as assessed by a visual analog scale, and food intake. A visual analog scale for nausea consisted of a 100-mm line labeled on the left end with "no nausea" and on the right end with "nausea as bad as it could be." Patients indicated the amount of nausea by making a vertical mark on the line. A baseline assessment was made just before the administration of the first dose of ondansetron and a second assessment was made 24 hours after cisplatin. A nausea score was calculated by subtracting the first measurement from the second. Details of food intake and the time of all meals during the 24-hour study period were recorded. The organization of the study procedures is shown in Table 1.

A patient could withdraw from the study at any time due to persistent nausea and/or vomiting and be offered alternative antiemetic therapy. Patients who withdrew prematurely and those who had five or more episodes of vomiting were considered treatment failures. The Wilcoxon rank sum and Van Elteren (stratified by center) tests were used to compare the two treatment groups with respect to the number of emetic episodes. Treatment responses were categorized as complete (zero emetic episodes), major (one to two episodes), minor (three to five episodes), and failure (more than five episodes or requiring rescue therapy). The Mantel–Haensel and Cochran–Mantel–Haensel (stratified by center) tests were used to compare the number of patients with the number of complete response (no emetic episodes). The Wilcoxon rank sum test was used to compare the nausea scores between treatments. The Mantel–Haensel test was used to compare food intake. The safety variables, including frequent vital sign determination, reports of development of adverse clinical events, and precomparison of preondansetron and

TABLE 1. Schedule of Study Procedures

	Time (hr)								
Procedure	−1	−0.5	0	4	8	12	16	20	24
Physical exam	X								
Lab safety studies	X								X
Nausea assessment	X								X
Ondansetron doses		X		X	X	X	X	X	
Cisplatin infusion			X						
Record emetic episodes			X	----------					X

postondansetron hematologic and biochemical profiles, were monitored and recorded.

Results

Thirty-six patients (29 men and 7 nonpregnant women) from six centers were enrolled. Nineteen patients received the low-dose (0.01 mg/kg) regimen and 17 patients received the high-dose (0.18 mg/kg) regimen of ondansetron. The ages of the patients ranged from 27 to 81 years. These patients were receiving chemotherapy for lung cancer (n = 15), head and neck cancer (n = 15), esophageal cancer (n = 3), and other types of cancer (n = 3). The distribution of cancer types differed between the two groups. The low-dose group had a higher percentage of patients with head and neck cancer and a slightly lower percentage of patients with lung cancer than the high-dose group. There was an even distribution of patients who were current or previous heavy ethanol users. All patients received cisplatin at a dose of 100 mg/m^2 or greater, some in combination with one or more other chemotherapy agent(s) of lower emetogenicity. These demographic characteristics of the 36 patients are summarized in Table 2.

Treatment Response

Seven of 17 patients in the high-dose group had no emesis during the 24-hour study period, compared with one of 19 patients in the low-dose group (P = 0.018). Seventeen (89%) of the low-dose patients began to vomit within 6 hours of the cisplatin dose, compared with only one of the high-dose patients. Ten of the low-dose patients and three of the high-dose patients received rescue therapy.

TABLE 2. Demographic Characteristics

	Ondansetron dose (mg/kg)	
	0.01	0.18
No. of patients	19	17
M	14	15
F	5	2
Median age in yr (range)	62 (27–69)	60 (42–81)
Primary cancer site*		
Head and neck	10 (53%)	5 (29%)
Lung	7 (37%)	8 (47%)
Esophageal	2 (10%)	1 (6%)
Other	0	3 (18%)
Current or previous* heavy alcohol users	5	5
Chemotherapy regimen		
Cisplatin	4	2
Cisplatin/5-FU	7	5
Cisplatin/etoposide	5	4
Cisplatin/5-FU/methotrexate	2	1
Cisplatin/mitomycin	1	2
Other	0	3

* Values indicate number of patients.

TABLE 3. Efficacy Results

	Treatment group (mg/kg)	
	0.01	0.18
Total no. of patients	19	17
No. of emetic episodes*		
0	1 (5%)	7 (41%)†
1–2	4 (21%)	4 (24%)
3–5	3 (16%)	2 (12%)
>5/rescued	11 (58%)	4 (24%)
Time to first episode (hr)*		
0–6	17 (89%)	1 (6%)
>6–12	0	4 (24%)
>12–18	1 (5%)	2 (12%)
>18–24	0	3 (18%)
Nausea score	(n = 13)	(n = 14)
Mean difference from baseline (mm)	57	42
Nausea (posttreatment)*	(n = 18)	(n = 14)
None (score 0–10)	0	4 (29%)
Mild (score 11–40)	2 (11%)	3 (21%)
Moderate (score 41–70)	5 (28%)	2 (14%)
Severe (score 71–100)	11 (61%)	5 (36%)
Food intake*		
Nothing by mouth	4 (21%)	0
Liquids only	8 (42%)	6 (35%)
Light snack	4 (21%)	2 (12%)
Full meal	3 (16%)	9 (53%)†
No assessment	0	0

* Values indicate number of patients.
† Significant difference between treatment groups ($P < 0.02$).

Post-treatment nausea scores were obtained from 13 of 19 low-dose patients and 14 of 17 high-dose patients. Mean post-treatment nausea scores increased significantly from baseline in both groups, but there were no differences between treatment groups in the magnitude of the increase. These results might have been influenced by the number of patients who withdrew early and did not complete the visual analog scales. A qualitative analysis of the data, performed by grouping patients into categories of none, mild, moderate, and severe nausea, suggested that less nausea occurred in the high-dose group. Seven of the high-dose patients had either mild (n = 3) or no nausea (n = 4), compared with only two of the low-dose patients. More than 50% (11 of 19) of the patients on the lower dose reported severe nausea, compared with less than 30% (5 of 17) on the higher dose. More than half (53%) of the patients in the high-dose group ingested a full meal during the 24-hour study period, compared with 16% of those in the low-dose group (P = 0.015).

An assessment of the effect of chronic alcohol consumption on treatment failure showed that none of the heavy alcohol users in the high-dose group failed to respond to ondansetron, whereas three of the five heavy users in the low-dose group failed. The various levels of the efficacy assessment score system and results of antiemetic protection, including nausea response and food intake of both treatment groups, are shown in Table 3.

Safety Profiles

Extrapyramidal reactions or significant sedation were not observed in either study group. Side effects that were considered to be due possibly or probably to ondansetron occurred in two patients of each treatment arm. In the low-dose group, one patient had moderate diarrhea and a mild headache and another patient had a mild headache only. In the high-dose group, one patient complained of mild dizziness and another complained of a mild headache. Serum aspartate aminotransferase (AST) values were elevated after treatment in four patients of the low-dose group and none of the high-dose group. Serum alanine aminotransferase (ALT) values were increased in one patient of each treatment group.

Discussion

The crucial roles of serotonergic neurons and $5HT_3$ receptors of the central and peripheral nervous systems in emetogenic pathways have been demonstrated increasingly.[12] The potential role of serotonin as a chemical mediator of the neural reflex arc of emesis has been further supported by the recent report of Cubeddu *et al.*[15] They detected the significant rise of urinary excretion of a serotonin metabolite (5-hydroxyindoleacetic acid) within 6 hours after the cisplatin administration in parallel with the emesis episodes. Based on these data and the overwhelming antiemetic superiority of the most extensively studied serotonin inhibitor (ondansetron) over placebo,[15] the use of antiserotonergic agents as new antiemetics has been viewed as an attractive proposition and has generated a great deal of enthusiasm in recent years. Among these agents, intravenous and oral ondansetron preparations have emerged as promising formulations in the control of chemotherapy-induced nausea and vomiting. Cunningham *et al.*[19] reported that in a group of 15 patients with nausea and vomiting induced by previous courses of chemotherapy, a regimen consisting of a 4-mg intravenous dose of ondansetron followed by oral therapy prevented emesis in 30 of 31 subsequent courses of chemotherapy. In a dose escalation trial, ondansetron dose levels of 0.15 mg/kg or greater appeared to be effective in the prevention of nausea and vomiting induced by moderately and highly emetogenic chemotherapeutic agents.[13] No therapeutic superiority of one regimen over the other was noticed in a trial comparing regimens of 6-hour *versus* 8-hour administration intervals for ondansetron in 85 patients.[17] A comparison of these results with those of the 2-hour and 4-hour interval dosing schedules of ondansetron used by Kris *et al.*[18] demonstrated only negligible differences.

Results of the current trial indicate that the therapeutic advantage of ondansetron at the 0.18 mg/kg dose level is significantly superior to that at the 0.01 mg/kg dose level for preventing nausea and vomiting induced by high-dose cisplatin and permitting normal food intake. Despite substantial dose differences, the safety profiles of these two treatment arms are similar. Even at the low (0.01 mg/kg) dose level, the antiemetic protective outcomes of ondansetron in our trial appear to be better than the antiemetic results that have been reported with prochlorperazine and placebo.[20]

The overall response rate of 65% (zero to two emetic episodes) with the six-dose regimen of 0.18 mg/kg of ondansetron used in this trial was not superior to that of 75% reported with a three-dose schedule of a 0.18-mg/kg regimen in a patient population receiving comparable cisplatin doses.[17] The inability to suppress emetic episodes occurring more than 19 hours after cisplatin administration in some patients of the current trial who received ondansetron at 16 and 20 hours after cisplatin supports the impression that the serotonin ($5\text{-}HT_3$) receptors are not the only pathway through which cisplatin stimulates emesis.

In view of reported observations[21] of the attenuated emetic reactions to chemotherapy in patients with a history of chronic heavy alcohol intake, we attempted to define the potential impact of this variable on the ultimate antiemetic response rates noticed in both of the strata studied. As the percentage of patients in this trial who fit the criteria for heavy alcohol use was evenly distributed in the low-dose and high-dose groups (26% and 29%, respectively) (Table 2), the chronic ethanol exposure variable did not appear to influence the antiemetic protective outcomes in favor of one dose level of ondansetron or the other.

Based on previous observations[13,17] of subclinical hepatic enzyme profile derangements in patients who were treated with cisplatin and ondansetron, no patients with abnormal baseline hepatic transaminase values were enrolled in this study. It is noteworthy that both regimens of the current trial were tolerated equally well and side effects were minor and transient. As there was no control group in our study (all patients received ondansetron), the cause and effect relationship between any adverse events, including laboratory abnormalities and ondansetron, chemotherapy, or a combination of both, remains speculative. The lack of extrapyramidal or anxiety reactions or excessive sedation in this study and other trials[15-17] presents an attractive alternative to antidopaminergic agents for managing chemotherapy-related emesis. The reported outcomes of a large-scale, prospective, comparative study of ondansetron and the most exhaustively studied and generally accepted antidopaminergic antiemetic agent metoclopramide have definitely demonstrated the therapeutic advantage of ondansetron over metoclopramide in terms of cisplatin-induced emesis control and disturbing dystonic reactions.[16]

The results of this study indicate that further evaluations of ondansetron should be limited to regimens with three or fewer doses. The future direction of the antiemetic studies includes trials of ondansetron in combination with agents that may block other components of emetogenic pathways. Whereas the therapeutic superiority of the 0.18-mg/kg dose level in the prevention of emesis associated with a highly emetogenic agent (*i.e.,* cisplatin) has been clearly demonstrated by this trial, the use of low-dose ondansetron in a setting of chemotherapeutic agents with low to moderate emetogenic potency deserves future consideration.

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