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Randomized double-blind comparison of three dose levels of intravenous ondansetron in the prevention of cisplatin-induced emesis*

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Abstract. The selective 5-hydroxytryptamine$_3$ ($5HT_3$) antagonist ondansetron has been shown to be an effective antiemetic in patients receiving cisplatin chemotherapy. This double-blind study compared the efficacy and safety of three doses of intravenous ondansetron in the prevention of nausea and vomiting associated with high-dose (≥ 100 mg/m^2) cisplatin chemotherapy. A total of 125 patients were randomized (1:1:1) to receive 0.015, 0.15, or 0.30 mg/kg every 4 h for a total of 3 doses. All patients were monitored for emetic episodes, adverse events, and laboratory safety parameters for 24 h following cisplatin administration. The 0.15-mg/kg dose was superior to the 0.015-mg/kg dose with respect to the median number of emetic episodes ($P = 0.033$) and complete response (no emetic episodes, $P = 0.005$). No statistically significant difference was found between the 0.15 and the 0.30-mg/kg groups. The most common adverse event was headache. Three 0.15-mg/kg doses of intravenous ondansetron are safe, effective, and adequate for the control of cisplatin-induced emesis.

Introduction

Cisplatin, one of the most effective chemotherapeutic agents against a wide variety of cancers, produces emesis in virtually all patients who are not given adequate antiemetic therapy [2, 10]. The magnitude of this problem was illustrated in previous studies using 120 mg/m^2 cisplatin, when patients given placebo or prochlorperazine experienced a median number of 10.5 and 12.0 emetic episodes, respectively, within a 24-h period [2]. The consequences of failing to control emesis include decreasing the patients' quality of life, fluid and electrolyte disturbances, and increasing the possibility that patients may refuse further beneficial (or potentially curative) chemotherapy.

Until recently, high-dose metoclopramide has been the single most effective antiemetic agent available for the control of cisplatin-induced emesis [3]. Metoclopramide was originally thought to act primarily as a dopaminergic receptor antagonist; however, more recent evidence suggests that its action is at least in part due to antagonism of 5-hydroxytryptamine$_3$ ($5HT_3$) receptors [1]. Ondansetron is a selective antagonist of $5HT_3$ receptors and represents the first of a new generation of antiemetic drugs specifically targeted at these receptors. Comparative trials in patients receiving cisplatin have demonstrated the antiemetic superiority of ondansetron over high-dose metoclopramide [5, 9].

Early phase II studies have indicated that a dose of 0.15–0.18 mg/kg ondansetron given every 4 h for a total of three doses is an effective regimen in patients receiving at least 100 mg/m^2 cisplatin [4, 8]. The present study was designed to make a definitive comparison between 0.15 mg/kg, a lower dose (0.015 mg/kg), and a higher dose (0.30 mg/kg) given every 4 h for a total of three doses.

Patients and methods

Study design. This randomized, double-blind, parallel-group, multicenter study was designed to enroll a total of 120 chemotherapy-naive patients who were scheduled to receive a dose of at least 100 mg/m^2 cisplatin.

Patient eligibility. Patients were eligible for the study if they were 18 years of age or older, had not received previous chemotherapy, and had a Karnofsky performance status of at least 60%. All patients were hospital inpatients during treatment. Patients were excluded from the study if they had advanced cardiovascular or cerebrovascular disease, significant psychiatric disease, impaired renal function (a serum creatinine concentration of >2 mg/dl or creatinine clearance of $\leq$50 ml/min), a serum alanine aminotransferase (ALT, SGPT) concentration of more than twice the upper limit of normal, or uncontrolled nausea and vomiting due to other etiologies or if they had vomited within 24 h prior to the study period. Patients could not have received an investigational drug within 30 days before the study period, any antiemetic medication during the 24 h preceding the study period, radiation therapy within 48 h prior to

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the study period, or any of the above during the study period. The antiemetic medications leading to exclusion included phenothiazines, antidepressants, butyrophenones, cannabinoids, antihistamines, metoclopramide, domperidone, trimethobenzamide, anticholinergics, corticosteroids, and benzodiazepines (except triazolam given for sleep prior to the study period). The protocol had to be reviewed and approved by each institution's review board for clinical research. Subsequent to this approval, patients could be entered into the study only after their written informed consent had been obtained.

Antiemetic treatment. Patients were randomly assigned (1:1:1) to receive one of three doses of ondansetron according to a computer-generated randomization scheme from the Department of Biostatistics at Glaxo Inc. The treatment schedule was sealed in an envelope and provided to the pharmacy at each institution. Only the pharmacist had access to the random code; neither the patient, the investigator, nor the study personnel responsible for patient evaluations knew which dose of ondansetron had been given. Ondansetron given as ondansetron hydrochloride dihydrate (Zofran; Glaxo Pharmaceuticals, Research Triangle Park, N.C.) was given intravenously at a dose of 0.015, 0.15, or 0.30 mg/kg every 4 h for a total of three doses, with the first dose being given 30 min prior to the start of cisplatin therapy.

Chemotherapy. Patients received cisplatin at a dose of ≥ 100 mg/m^2, given as a single intravenous infusion over 3 h or less. Other chemotherapy agents were allowed concurrently, except for cyclophosphamide (>1100 mg/m^2), mechlorethamine, or dacarbazine.

Analysis of antiemetic efficacy and safety. Patients were observed for the number and time of emetic episodes and for the occurrence of any known or suspected adverse events during the 24 h following the initiation of cisplatin chemotherapy. Any episode of vomiting (expulsion of stomach contents through the mouth) was recorded as one emetic episode. In addition, one to five retches (an attempt to vomit not productive of stomach contents) within any 5-min period was counted as a single emetic episode.

Using 100-mm visual analog scales, patients assessed the severity of nausea (0 = no nausea, 100 = nausea as bad as it could be) and their global satisfaction with the control of nausea and vomiting (0 = not at all satisfied, 100 = totally satisfied). Additionally, patients assessed their level of appetite over 24 h (appetite better than usual, as usual, not as good as usual – but some solids, liquids only, or nothing by mouth). Nausea assessments were made just prior to the administration of the first dose of study drug and at 24 h after the initiation of cisplatin chemotherapy. Global satisfaction and appetite were assessed 24 h following the initiation of cisplatin treatment. The change in nausea was calculated by subtracting the baseline score from the posttreatment score. Blood samples were taken within 48 h prior to the first dose of study drug and at 24 h after the initiation of cisplatin therapy to monitor complete blood counts and biochemistry. Abnormal laboratory values considered to be possibly, probably, or almost certainly related to ondansetron were followed until they returned to normal or were otherwise explained.

Statistical methods. The sample size was based on the 0.15- and 0.015-mg/kg ondansetron doses. With 40 patients per treatment group, a difference of approximately 30% could be detected between the 0.15- and the 0.015-mg/kg treatment groups, with 80% power, using the 5% level of significance.

The primary efficacy parameter was the number of emetic episodes (vomits plus retches) occurring during the 24-h study period. The number of emetic episodes was used to define the treatment response: complete response = no emesis, major response = 1–2 emetic episodes, minor response = 3–5 emetic episodes, and failure = more than 5 emetic episodes or requirement of rescue antiemetic therapy or withdrawal from the study.

The 0.15-mg/kg treatment group was compared (pairwise) with the 0.015- and 0.30-mg/kg treatment groups for each analysis. Treatment groups were compared with regard to the number of emetic episodes using the Wilcoxon rank-sum test. For testing purposes, patients who reported more than five emetic episodes or who required other antiemetic medication within the 24-h study period (rescue) or were withdrawn for any reason were assigned the same arbitrarily high value (>5) for the number of emetic episodes. Treatments were also compared with respect to the proportion of patients with a complete response using the Mantel-Haenszel test and with respect to time to the first emetic episode (hours from the start of the cisplatin infusion) using the Wilcoxon rank-sum test. Patients with no emetic episode were assigned the same arbitrary time (>24 h). The Wilcoxon rank-sum test was also used to compare treatment groups with respect to severity of nausea and global satisfaction with the control of nausea and vomiting. Appetite assessments were not analyzed statistically because the categories were not mutually exclusive.

Table 1. Patients' characteristics

	Ondansetron dose (mg/kg)		
	0.015	0.15	0.30
Number of patients	39	47	39
Sex:			
M	30 (77%)	29 (62%)	26 (67%)
F	9 (23%)	18 (38%)	13 (33%)
Median age in years (range)	60 (19–79)	56 (33–76)	59 (29–76)
Alcohol use[a]:			
Nonuser or occasional use	18 (46%)	27 (57%)	22 (56%)
Moderate use	3 (8%)	1 (2%)	6 (15%)
Current or prior heavy use	18 (46%)	19 (40%)	11 (28%)
Type of cancer:			
Lung	18 (46%)	21 (45%)	16 (41%)
Head and neck	9 (23%)	17 (36%)	13 (33%)
Gastrointestinal	6 (15%)	4 (9%)	3 (8%)
Genitourinary	1 (3%)	1 (2%)	0 (0%)
Gynecologic	1 (3%)	1 (2%)	4 (10%)
Bone and soft tissue	1 (3%)	0 (0%)	1 (3%)
Other	3 (8%)	3 (6%)	2 (5%)
Chemotherapy:			
Cisplatin alone	7 (18%)	13 (28%)	4 (10%)
Cisplatin plus other agents	32 (82%)	34 (72%)	35 (90%)

[a] Non/occasional use is defined as less than 7 drinks/week, moderate use is defined as 1–4 drinks/day, and heavy use is defined as 5 or more drinks/day

Results

Patient's characteristics

A total of 125 patients between the ages of 19 and 79 years were enrolled into this trial from 11 different centers. The patients' characteristics are shown in Table 1. Patient groups were similar with regard to age and sex distributions. The percentage of patients with prior and current heavy alcohol use was lower in the 0.30-mg/kg group as compared with the other two groups, although the difference was not statistically significant. The study included patients with a large variety of cancer types, the most common being lung or head and neck primaries. In all, 24 patients (19%) received treatment with cisplatin as a single agent and the remainder received cisplatin in combination with other cytotoxic agents. The most common agents used in combination therapy were etoposide

Table 2. Protocol violations resulting in patients' exclusion

	Ondansetron dose (mg/kg)		
	0.015	0.15	0.30
Entry violations:			
Cisplatin dose too low	1	1	0
Received other antiemetic within 24 h prior to the study	0	1	0
Previous chemotherapy	1	1	0
Radiotherapy given within 48 h	1	0	0
During-study violations:			
Received other antiemetic during the 24-h study period	2	2	0
Study drug given incorrectly	0	2	1
Total number of patients excluded	5	7	1

Table 3. Antiemetic efficacy – primary parameters

	Ondansetron dose (mg/kg)		
	0.015	0.15	0.30
Number of patients[a]	33 (100%)	41 (100%)	38 (100%)
Median number of emetic episodes	3.0*	1.0	0.0
Complete response:			
0 EE	5 (15%)**	19 (46%)	22 (58%)
Major response:			
1 EE	6 (18%)	4 (10%)	1 (3%)
2 EE	3 (9%)	3 (7%)	4 (11%)
Minor response:			
3 EE	6 (18%)	4 (10%)	3 (8%)
4 EE	1 (3%)	0 (0%)	2 (5%)
5 EE	1 (3%)	0 (0%)	0 (0%)
Failure:			
>5 EE	8 (24%)	4 (10%)	3 (8%)
rescued <5 EE	3 (9%)	7 (17%)	3 (8%)

[a] Number of patients evaluable for antiemetic efficacy
EE, Emetic episode
* Statistically significant difference between the 0.015- and the 0.15-mg/kg groups ($P = 0.033$, Wilcoxon rank-sum test)
** Statistically significant difference between the 0.015- and the 0.15-mg/kg groups ($P = 0.005$, Mantel-Haenszel test)

(41 patients, 33%) and 5-fluorouracil (39 patients, 31%), both of which have a mild to moderate emetogenic potential. The distribution of chemotherapy regimens was similar in each treatment group.

Antiemetic efficacy

Of the 125 patients randomized, 13 were either ineligible or unevaluable for treatment efficacy due to protocol violations. Table 2 lists the reasons for exclusion of these patients. The antiemetic efficacy data for the remaining 112 evaluable patients are summarized in Tables 3 and 4. The primary efficacy parameters are presented in Table 3 and the secondary efficacy parameters in Table 4. Patients

Table 4. Antiemetic efficacy – secondary parameters

	Ondansetron dose (mg/kg)		
	0.015	0.15	0.30
Median time to onset of emesis (h)	4.75*	21.00	Undefined[a]
Median nausea-score difference[b]	38	20	13.5
Median satisfaction score[c]	68**	87	93

[a] Undefined since <50% of patients had an emetic episode
[b] Difference = posttreatment – pretreatment nausea score
[c] Measured on a 100-mm scale; 0 = not at all satisfied, 100 = totally satisfied
* Statistically significant difference between the 0.015- and the 0.15-mg/kg groups ($P < 0.001$, Wilcoxon rank-sum test)
** Statistically significant difference between the 0.015- and the 0.15-mg/kg groups ($P = 0.048$, Wilcoxon rank-sum test)

receiving 0.15 mg/kg ondansetron experienced fewer emetic episodes than did those receiving 0.015 mg/kg (median, 1 vs 3; $P = 0.033$), with no significant difference being observed between the 0.15- and the 0.30-mg/kg groups (median, 1 vs 0; $P = 0.317$). In all, 46% of the patients receiving 0.15 mg/kg ondansetron had a complete response to therapy (no emetic episode), which was significantly better than the 15% of the patients with a complete response in the group receiving 0.015 mg/kg ($P = 0.005$). Of the patients receiving 0.30 mg/kg, 58% had a complete response, which was numerically but not statistically superior to the response of the group receiving 0.15 mg/kg ($P = 0.308$). Failure rates were higher both in patients receiving 0.015 mg/kg ondansetron as compared with those receiving 0.15 mg/kg (33% vs 27%) and in those receiving 0.15 mg/kg as compared with those receiving 0.30 mg/kg (27% vs 16%). However, neither difference reached statistical significance ($P = 0.546$ and $P = 0.236$, respectively).

The time to the onset of emesis was significantly shorter in the 0.015-mg/kg group (median, 4.75 h) than in the 0.15-mg/kg group (median, 21 h; $P < 0.001$), with no significant difference being observed between the 0.15- and the 0.30-mg/kg groups. Patient assessment of nausea did not statistically differ between either the 0.15- and the 0.015-mg/kg groups ($P = 0.086$) or the 0.15- and the 0.30-mg/kg groups ($P = 0.598$) with respect to the change from baseline scores, although these scores decreased numerically with increasing ondansetron dose. Global satisfaction with the control of nausea and vomiting was significantly higher in the 0.15-mg/kg group (median, 87) than in the 0.015-mg/kg group (median, 68; $P = 0.048$) but did not statistically differ from that of the 0.30-mg/kg group (median, 93; $P = 0.820$). In all, 50% of the 0.15-mg/kg dose patients rated their appetite "as usual" as compared with 30% of the 0.015-mg/kg patients. The 0.15- and 0.30-mg/kg groups were similar with respect to appetite assessment.

Safety assessments

All 125 patients who received study medication were included in the evaluation of safety (Table 5). The most

Table 5. Safety results

	Ondansetron dose (mg/kg)		
	0.015	0.15	0.30
Number of patients	39 (100%)	47 (100%)	39 (100%)
Most common events:			
Headache	6 (15%)	13 (28%)	13 (33%)
Drowsiness	1 (3%)	7 (15%)	5 (13%)
Diarrhea	6 (15%)	1 (2%)	3 (8%)
Dry mouth	1 (3%)	4 (9%)	3 (8%)
Dizziness	1 (3%)	2 (4%)	2 (5%)
Transaminase elevations[a]:			
AST (SGOT)	3/32 (9%)	3/40 (8%)	2/28 (7%)
ALT (SGPT)	2/36 (6%)	4/42 (10%)	0/27 (0%)

[a] Transient increases to at least twice the upper limit of normal in patients who had normal or below-normal baseline values

common adverse events reported were headache, drowsiness, diarrhea, dry mouth, and dizziness. A greater proportion of patients receiving 0.15 or 0.30 mg/kg ondansetron experienced headaches as compared with those receiving 0.015 mg/kg. These headaches were mild or moderate in nature and treatable with acetaminophen. On the other hand, diarrhea was more common in patients in the 0.015-mg/kg group than in those in the 0.15- or 0.30-mg/kg group. Neither of these trends achieved statistical significance. Of the 13 patients listed with drowsiness as an adverse event, 11 came from one center, and 12 of the patients were also receiving analgesics or sedatives. There was no other notable difference in adverse events between the three groups.

The 0.15-mg/kg dose group did not significantly differ from the higher- or lower-dose groups with respect to any laboratory indices of safety, including transaminase elevations. Indeed, of the patients who experienced transient increases in either or both of the hepatic transaminases, neither the proportion of patients involved in each dose group nor the degree of increase was dose-related.

Discussion

In early phase I and II trials, the antiemetic efficacy of ondansetron was examined over a wide range of doses. In one study [4], patients receiving between 60 and 120 mg/m^2 cisplatin were given doses of ondansetron ranging from 0.01 to 0.48 mg/kg every 4 h for a total of three doses. Ondansetron demonstrated excellent antiemetic efficacy over this dose range except for 0.01 mg/kg, with 44% of patients experiencing no vomiting and 81% of patients experiencing two or fewer emetic episodes overall. Although the number of patients at each dose level was limited, the best results appeared to be seen at approximately 0.30 mg/kg. The results of a second study [7], in which cisplatin was given only with higher doses of ondansetron, indicated that a dose of at least 0.15 mg/kg given every 2 h for a total of three doses was efficacious in patients receiving cisplatin at a dose of 120 mg/m^2. In this instance, 39% of patients experienced no vomiting and 58% experienced two or fewer emetic episodes overall. Another phase II study [6] compared doses of 0.01 and 0.18 mg/kg given every 4 h for a total of six doses in patients receiving at least 100 mg/m^2 cisplatin. This study demonstrated the superior efficacy of the 0.18-mg/kg dose over the 0.01-mg/kg dose, with 41% and 5% of patients experiencing no vomiting, respectively (P <0.02). It is noteworthy, however, that the efficacy of six 0.18-mg/kg doses of ondansetron in the latter study did not appear to be any greater than that obtained with three 0.18-mg/kg doses in previous studies [4, 7, 8].

The data available from these early studies therefore suggested that three doses of 0.15–0.18 mg/kg ondansetron given at 4-h intervals would be an efficacious regimen in patients receiving high-dose cisplatin. However, all of these previous studies were small and were either open-label or single-blind in design. The current study employed a randomized double-blind design and was large enough to enable a definitive comparison of a three-dose regimen of 0.15 mg/kg ondansetron with a lower (0.015 mg/kg) and a higher (0.30 mg/kg) dose in patients receiving at least 100 mg/m^2 cisplatin. The results obtained were consistent with those found in earlier studies in that three 0.15-mg/kg doses of ondansetron were markedly superior to three 0.015-mg/kg doses in the prevention of emesis in this patient population. Additionally, three 0.30-mg/kg doses of ondansetron were numerically superior to three 0.15-mg/kg doses in the prevention of emesis. However, this difference did not reach statistical significance and was not of a magnitude to justify doubling the ondansetron dose. The complete response rates were also similar to those previously reported, with 46% of patients receiving 0.15 mg/kg ondansetron experiencing no vomiting. Although the response of patients receiving 0.015 mg/kg ondansetron was much lower, with only 15% of patients experiencing no vomiting, ondansetron was nonetheless efficacious at this dose as evidenced by a response rate higher than that reported for placebo or prochlorperazine [2]. Similarly, an earlier study [6] demonstrated that 0.01 mg/kg ondansetron produced a greater effect than the response rates reported for placebo [2].

The adverse events associated with ondansetron were generally quite modest and similar to those reported in previous studies. The most common event reported was headache (controlled with acetaminophen), and this was more common in patients receiving higher doses of ondansetron. In contrast, diarrhea was more commonly experienced by patients receiving the lowest dose of ondansetron, suggesting a possible dose-dependent constipative effect of ondansetron. Drowsiness was more common in patients receiving higher doses of ondansetron in this study. However, since most of these patients were receiving concurrent analgesics or sedatives, it is difficult to assess the role that ondansetron played. In addition, previous dose-ranging studies have not demonstrated this trend [4, 7]. Finally, no dose relationship was found for hepatic transaminase elevations in terms of either the proportion of patients with elevations or the degree of increase, an observation that is consistent with the findings of previous dose-ranging studies [4, 7].

In conclusion, a dosage regimen of 0.15 mg/kg ondansetron given every 4 h for a total of three doses is effective, safe, and adequate to prevent emesis induced by high-dose cisplatin chemotherapy. In this study, a lower dose of ondansetron was inadequate for the prevention of cisplatin-induced emesis, whereas a higher dose resulted in only a minor therapeutic gain. The appropriate dose of ondansetron for less emetogenic chemotherapy and the possibility of a simplified schedule of administration should be further explored.

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