Phase III Double-Blind Comparison of Intravenous Ondansetron and Metoclopramide as Antiemetic Therapy for Patients Receiving Multiple-Day Cisplatin-Based Chemotherapy

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Background. **Ondansetron hydrochloride is a selective serotonin subtype 3 ($5HT_3$) receptor antagonist that has been shown to be an effective antiemetic in patients receiving cisplatin chemotherapy.**

Methods. **This double-blind study compared the safety and efficacy of intravenous ondansetron with metoclopramide in patients receiving a 4- or 5-day regimen of cisplatin (20–40 mg/m²/day) combination chemotherapy. Forty-five patients were enrolled, and efficacy of the drug therapy could be studied for all 45. Patients were randomly assigned (1:1) to receive three daily intravenous doses of either 0.15 mg/kg ondansetron or 1 mg/kg metoclopramide. All patients were monitored daily for the number of emetic episodes (vomiting or retching), severity of nausea, adverse events, and laboratory safety parameters.**

Results. **Seven (30%) patients who received ondansetron had no emetic episodes throughout the entire study period compared with two (9%) who received metoclopramide ($P = 0.077$). The greatest difference in antiemetic efficacy was seen on day 1, when 18 (78%) patients who received ondansetron had no emetic episodes compared with 3 (14%) patients who received metoclopramide ($P < 0.001$). Significantly fewer antiemetic treatment failures (more than five emetic episodes or withdrawal from the study) occurred with patients given ondansetron (9%) than with those given metoclopramide (50%) during the entire study period ($P = 0.002$). The most commonly reported adverse event associated with ondansetron therapy was headache (controlled with acetaminophen), whereas diarrhea and restlessness were the most commonly reported adverse events associated with metoclopramide therapy. Extrapyramidal symptoms were judged to have occurred in 13 patients who received metoclopramide and 1 patient who received ondansetron. However, the patient who received ondansetron subsequently was judged to have had an anxiety attack. In patients with low or normal baseline transaminase values, a greater percentage who received ondansetron had transient increases as great as twice the upper limit of normal in aspartate transaminase (5% versus 0%) and alanine transaminase (17% versus 6%) than those who received metoclopramide.**

Conclusions. **Ondansetron is superior to metoclopramide as antiemetic therapy for multiple-daycisplatin-based chemotherapy. *Cancer* 1992; 70:2524–2528.**

Key words: ondansetron, metoclopramide, cisplatin, emesis, antiemetic therapy.

Emesis is a frequent and potentially hazardous complication of cisplatin-based chemotherapy. Commonly used antiemetic agents often fail to provide sufficient protection against chemotherapy-induced nausea and vomiting, and the agents may be associated with unpleasant side effects. Metoclopramide has been frequently used for the prevention of cisplatin-induced emesis.[1] Although this agent has significant antiemetic efficacy, its use may be complicated by extrapyramidal side effects, which are particularly common in patients younger than 30 years of age.[2,3] Thus, in the relatively youthful population of patients with testicular germ cell tumor (for which cisplatin-based chemotherapy is curative), the usefulness of metoclopramide may be limited.

For a long time, metoclopramide was thought to act primarily as a dopamine receptor antagonist. More recent evidence suggests that metoclopramide may act at least in part as a 5-hydroxytryptamine ($5\text{-}HT_3$) receptor antagonist.[4] Recently, highly selective $5\text{-}HT_3$ receptor

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Support in part by grants 2R35CA39844-05 and the General Clinical Research Center Grant MO-1-RR00-750-15 from the National Institutes of Health. Additional support was provided by a grant from Glaxo Inc., Research Triangle Park, North Carolina.

The authors thank Elaine M. Anderson, Ph.D., for assistance in the preparation of this manuscript.

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Accepted for publication March 13, 1992.

antagonists have been developed for use as antiemetic agents. One such serotonin receptor antagonist, ondansetron, has shown significant activity against cisplatin-induced emesis and has been demonstrated to be superior to metoclopramide for prevention of emesis in patients receiving cisplatin in prospective randomized trials.[5–7] However, most such trials have focused on patients receiving single-day, high-dose cisplatin-based therapy.

We previously have studied ondansetron as antiemetic therapy for multiple-day, cisplatin-based chemotherapy in patients with testicular germ cell cancer in a Phase II trial and found it to be safe and efficacious.[8] The current Phase III trial compared the relative safety and efficacy of ondansetron (0.15 mg/kg, three times a day) with metoclopramide (1 mg/kg, three times a day) in a preponderantly young patient population receiving multiple-day, cisplatin-based chemotherapy. The optimum dose of metoclopramide as antiemetic therapy is not well defined for multiple-day cisplatin chemotherapy. Roila et al.[9] have shown that, although higher doses of metoclopramide may be valuable for patients receiving higher doses of cisplatin, patients receiving lower doses do not receive additional benefit from increasing the metoclopramide dose. Because the patient population in the current study is young and particularly susceptible to extrapyramidal side effects and the dose of cisplatin used was low (20–40 mg/m^2/day), a dose of 1 mg/kg metoclopramide, for a total of three doses each day, was chosen. The use of a three-times-daily regimen also allowed us to easily make the study a double-blind one.

Patients and Methods

Study Design

This prospective, randomized, double-blind, parallel group trial was designed to enroll 42 patients with testicular cancer who had not previously received chemotherapy and who were scheduled to receive a 4- or 5-day regimen of cisplatin at a dose of 20–40 mg/m^2/day.

Patient Eligibility

Male patients who were at least 15 years old were considered eligible for this trial if they were receiving cisplatin 20–40 mg/m^2 for 4–5 days in either an adjuvant or metastatic setting. Patients were required to have a Karnofsky performance status greater than 60; no uncontrolled psychiatric or cardiovascular disease; no uncontrolled nausea and vomiting caused by other organic causes; a serum creatinine of less than 2.0; and an alanine transaminase of less than twice the upper limit of normal, with normal bilirubin. Patients could not have received antiemetics or have vomited during the 24 hours preceding entry into the study. Patients could not have received previous chemotherapy, and no radiation therapy could have been administered within 48 hours before or during the study period. Written informed consent was obtained from all patients, and the protocol was reviewed and accepted by the Institutional Review Board of the Indiana University Hospital.

Antiemetic Therapy

Patients were randomly assigned (1:1) to receive either metoclopramide or ondansetron as single-agent antiemetic therapy according to a computer-generated randomization scheme from the Department of Biostatistics at Glaxo, Inc. Drug was administered in a double-blinded fashion three times daily, the first dose being given 30 minutes before the start of cisplatin therapy. Subsequent antiemetic doses were administered 4 and 8 hours after the initial dose. Ondansetron (Zofran, Glaxo Pharmaceuticals, Research Triangle Park, NC) was administered intravenously at a dose of 0.15 mg/kg, and metoclopramide (Reglan, A.H. Robins Co., Richmond, VA) at a dose of 1 mg/kg. Patients with extrapyramidal reactions were treated with 50 mg of diphenhydramine (Benadryl, Parke-Davis, Morris Plains, NJ) intramuscularly or intravenously every 6 hours as needed to control symptoms. Concomitant use of glucocorticoid hormones was not allowed.

Analysis of Antiemetic Efficacy and Safety

Patients were observed for the number and time of emetic episodes and for occurrence of adverse events. An emetic episode was defined as either one vomiting episode (expulsion of any stomach contents through the mouth) or one to five retches in a 5-minute period. (Retching was defined as an attempt to vomit that was not productive of stomach contents.)

Patients assessed the efficacy of their antiemetic therapy using daily visual analog scales (0–100 mm) for nausea (0, no nausea; 100, nausea as bad as it could be) and satisfaction with control of nausea and vomiting (0, not at all satisfied; 100, totally satisfied). Patients also assessed sedation (0, not at all sleepy; 100, very sleepy) and appetite (using a graded scale: nothing by mouth, liquids only, some solids, as usual, better than usual). All assessments were made at the same time each day immediately before the first dose of study drug. In addition, investigators made a blinded, retrospective analysis to determine the number of extrapyramidal reactions that occurred during the study period. Blood samples were taken within 48 hours before the first dose of study drug, during the study (day 3), and 24 hours after the last dose of cisplatin to monitor complete blood

counts and biochemistry. Abnormal laboratory values considered by the investigator to be possibly, probably, or almost certainly attributable to the study drug were followed up until they returned to normal.

Statistical Methods

The primary response variable was the number of emetic episodes (vomits plus retches) that occurred on each study day. 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 in a 24-hour study day. The therapy also was considered a failure if a patients was withdrawn from the study for any reason. Secondary response variables included severity of nausea, satisfaction with control of nausea and vomiting, and level of appetite.

The Mantel–Haensel test was used to compare treatment groups with respect to complete response, and Life Table analysis was used to compare treatment groups with respect to antiemetic treatment failure. The Wilcoxon rank-sum test was used to compare the two treatment groups with respect to nausea and satisfaction with control of nausea and vomiting on a day-by-day basis.

As appropriate, the chi-square test was used to compare the two treatment groups with respect to the proportion of patients having specific adverse events. The Wilcoxon rank-sum test also was used to make day-by-day comparisons of the treatment groups with respect to sedation.

Results

Patient Characteristics

From October 1988 to September 1989, 45 patients between the ages of 16 and 44 years were enrolled in this trial. All patients had testicular cancer, with the exception of one patient who had adenocarcinoma of the lung. Patient characteristics are shown in Table 1. Patient groups were equally balanced with regard to type of chemotherapy, age, and severity of alcohol use.

Table 1. Patient Characteristics

	Ondansetron	Metoclopramide
No. of patients	23	22
Median age (range) (yr)	29 (16–44)	28 (16–37)
Chemotherapy		
Cisplatin+		
Etoposide/bleomycin	16	15
Etoposide	6	7
Etoposide/ifosfamide	1	0
Alcohol consumption		
Nonuser or occasional use (%)	20 (87)	22 (100)
Current or prior heavy use (%)*	3 (13)	0 (0)

* Heavy use is defined as five or more drinks per day.

No statistically significant differences were found between the two treatment groups with respect to these patient characteristics.

Response to Therapy

Response to therapy is shown in Table 2. Eighteen (78%) patients who received ondansetron experienced a complete response (0 emetic episodes) on day 1, compared with 3 (14%) patients who received metoclopramide ($P < 0.001$). Similarly, treatment failure (more than five emetic episodes or withdrawal from the study) occurred in 1 of 23 patients who received ondansetron, compared with 7 of 22 patients who received metoclopramide on day 1 ($P = 0.017$). On subsequent days, the differences between the two antiemetics were not as marked; however, during the 5 days of therapy, cumulative treatment failures were significantly more common in the patients treated with metoclopramide than in the patients treated with ondansetron (11 of 22 versus 2 of 23; $P = 0.002$). Similarly, 7 of 23 (30%) of the patients receiving ondansetron therapy compared with 2 of 22 (9%) of the patients receiving metoclopramide therapy had no emetic episodes during the 5-day period.

Patient estimation of antiemetic efficacy as rated using visual analog scales (Table 2) demonstrated that patients receiving ondansetron were significantly less nauseated on day 1 (median scores: ondansetron, 8; metoclopramide, 58.5; $P < 0.001$). Median nausea scores ranged from 8 to 26.5 (maximum recorded on day 5) for patients receiving ondansetron therapy and from 25.5 to 58.5 (maximum recorded on day 1) for patients receiving metoclopramide. Patients receiving ondansetron were significantly more satisfied than patients receiving metoclopramide on day 1 (median scores: ondansetron 99, metoclopramide 48; $P = 0.003$). Median satisfaction scores were better every day for patients receiving ondansetron (range, 83–99) than for patients receiving metoclopramide (range, 48–74). A greater proportion of patients who received ondansetron reported appetite as usual on each study day.

Safety Assessments

Adverse events reported for each treatment and transaminase elevations are shown in Table 3. Significantly more (41% versus 9%) patients who received metoclopramide experienced diarrhea and extrapyramidal symptoms, such as akathisia and acute dystonic reactions (59% versus 4%). The one extrapyramidal symp-

Table 2. Response to Therapy

	Day 1	Day 2	Day 3	Day 4	Day 5
Emesis					
Complete response					
Ondansetron (%)	18 (78)*	16 (70)	14 (61)	13 (57)	13 (57)
Metoclopramide (%)	3 (14)	10 (45)	8 (36)	10 (45)	11 (50)
Treatment failure					
Ondansetron	1/23	0/22	1/22	0/21	0/21
Metoclopramide	7/22	2/15	1/13	1/12	0/11
P value (cumulative)	0.017	0.004	0.005	0.002	0.002
	Median visual analog scores (0–100 mm)†				
Nausea					
Ondansetron	0	8†	13	25	21.5	26.5
Metoclopramide	0	58.5	25.5	28	34	38

* Statistically significant difference ($P < 0.001$: Mantel–Haensel test).
† Statistically significant difference ($P < 0.001$; Wilcoxon rank-sum test).
+ 0: no nausea; 100: nausea as bad as it could be.

tom reported by the investigator for a patient receiving ondansetron was a patient who, in retrospect, was found to have had an anxiety attack. A greater percentage of patients receiving metoclopramide experienced restlessness (32% versus 9%). The incidence of headaches experienced by patients was greater for those who received ondansetron (39%) than for those who received metoclopramide (18%). The headaches were mild and treatable with acetaminophen. Sedation was similar for both groups. Mild and routinely transient elevations of hepatic transaminases were seen more commonly in patients receiving ondansetron than in patients receiving metoclopramide, but none were associated with clinical signs or symptoms. The differences between the two treatment groups in alanine transaminase or aspartate transaminase levels did not reach statistical significance.

Discussion

There is growing evidence that a significant portion of chemotherapy-induced emesis is mediated via 5-hydroxytryptamine$_3$ (serotonin) receptors located peripherally on vagal afferent nerve terminals or centrally in the area subpostrema and associated structures.[10,11] Blockade of these receptors, either with nonselective agents, such as metoclopramide, or with highly selective $5HT_3$ antagonists, such as ondansetron, can sub-

Table 3. Safety Results

	Ondansetron (%)	Metoclopramide (%)	*P* value (chi-square)
No. of patients	23	22	
Patient-reported events			
Headache	9 (39)	4 (18)	NS
Diarrhea	2 (9)	9 (41)	0.012
Restlessness	2 (9)	7 (32)	0.053
Injection site reactions (pain, swelling, erythema)	3 (13)	2 (9)	NS
Anxiety	4 (17)	3 (14)	NS
Dyspnea	4 (17)	1 (5)	NS
Flushing	4 (17)	4 (18)	NS
Insomnia	3 (13)	2 (9)	NS
Diaphoresis	0 (0)	4 (18)	0.032
Investigator-assessed events			
Extrapyramidal symptoms	1 (4)	13 (59)	< 0.001
Transaminase elevations*			
AST	1 (6)	0 (0)	NS
ALT	3 (18)	1 (6)	NS

NS: not statistically significant; AST: aspartate transaminase; ALT: alanine transaminase.
* Transient increases to at least twice the upper limit of normal in patients who had low or normal baseline values.

stantially reduce emesis induced by cisplatin and other chemotherapy agents.[10–12]

The current study has demonstrated the superiority of ondansetron over metoclopramide in the prevention of emesis in primarily young patients receiving multiple-day, cisplatin-based chemotherapy for testicular cancer. This superiority was shown in terms of complete control of emesis, treatment success, control of nausea, patient satisfaction, and overall safety. The greatest difference between the two treatment groups was in the number of patients who had no emetic episodes was seen on the first day, when 78% of patients who received ondansetron had no emetic episodes, compared with 14% of patients who received metoclopramide. On subsequent days, although the differences between the two antiemetics were not as marked, more patients who received ondansetron had no emetic episodes. These results confirm and extend our previous results from an open study of patients receiving ondansetron for multiple-day, cisplatin-based chemotherapy.[8] In addition, other studies have demonstrated the superiority of ondansetron over metoclopramide in patients receiving single-day, high-dose, cisplatin-based chemotherapy.[5–7]

This study also emphasizes the high frequency of extrapyramidal side effects induced by metoclopramide in a young patient population. Other than extrapyramidal symptoms, the most commonly occurring side effect of metoclopramide was diarrhea. For ondansetron, the most common side effect was headache. A greater proportion of patients who received ondansetron experienced headaches than those who received metoclopramide; however, the headaches were mild and treatable with acetaminophen. Mild, reversible, and asymptomatic elevations in aspartate transaminase and alanine transaminase occurred in both treatment groups, and the incidence of elevation increased during the study period in both groups, indicating a possible association with cumulative cisplatin dose, which has been suggested by Hesketh et al.[13]

Although ondansetron has demonstrated clear superiority over metoclopramide as a single agent and general excellence as an antiemetic, 70% of patients treated with ondansetron in this study experienced at least one emetic episode during the 5-day treatment period. In addition, the superiority of ondansetron was most pronounced during the first day of treatment, despite the antiemetic challenge being present on each day. Clearly, much remains to be accomplished in the management of nausea and vomiting in such patients.

Additional trials will study the use of ondansetron in combination with other antiemetic agents. Recent studies have suggested that the combination of ondansetron with dexamethasone may improve the antiemetic efficacy of ondansetron.[14,15]

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