The Addition of Ondansetron to the Combination of Metoclopramide, Dexamethasone, and Lorazepam Did Not Improve Vomiting Prevention in Patients Receiving High-Dose Cisplatin

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Background. **Serotonin has been shown to be an important mediator of chemotherapy-induced vomiting. Ondansetron is a potent and highly specific antagonist of the 5-HT_3 serotonin receptor. The objective of the current trial was to determine if the addition of ondansetron to the combination of metoclopramide, dexamethasone, and lorazepam (MDL) could improve the control of vomiting in patients receiving high-dose cisplatin. The three-drug MDL antiemetic regimen has been shown to prevent vomiting in 67% of patients receiving high-dose cisplatin.**

Methods. **Thirty-two patients receiving initial cisplatin (greater than or equal to 100 mg/m^2) were given intravenous lorazepam, 1.5 mg/m^2 (maximum dose, 3 mg), one dose 45 minutes before cisplatin; metoclopramide, 3 mg/kg 40 minutes before and 90 minutes after cisplatin; ondansetron, 0.3 mg/kg 25 minutes before and 3.5 hours after cisplatin; and dexamethasone, 20 mg, one dose 10 minutes before cisplatin. Patients were followed for 24 hours after cisplatin administration.**

Results. **Vomiting was prevented in 67% of patients (95% confidence interval, 47–83%). Adverse effects were mild and transient and included sedation, headache, serum aspartate transaminase, and alanine transaminase elevations, akathisia, and hiccups.**

Conclusions. **Vomiting was prevented in two thirds of patients treated with MDL plus ondansetron, a result similar to that observed in earlier trials of MDL alone. The lack of improvement in emetic control by the addition of ondansetron suggests that vomiting mediated through 5-HT_3 receptors is already effectively blocked. Emesis that occurs despite pretreatment with MDL is likely mediated by other mechanisms.** ***Cancer*** **1994; 73:720–3.**

Key words: antiemetic, cisplatin, ondansetron, metoclopramide, dexamethasone, lorazepam, emesis, nausea, supportive care.

Several safe and effective antiemetic agents have been identified that work by blocking different neurotransmitter receptors. Combinations of these antiemetic drugs may enhance the control of vomiting by blocking different types of receptors simultaneously. These multidrug antiemetic regimens have improved the control of chemotherapy-induced vomiting, lessened side effects, and reduced the length of treatment.[1–3]

Although metoclopramide blocks both serotonin (5-HT_3) and dopamine receptors (D2), the extent, location, and duration of its receptor blockade is unknown. Incomplete blockade at any receptor site may explain why some patients vomit despite prophylaxis. Ondansetron is a potent and specific 5-HT_3 receptor blocking agent that has the potential to induce more profound 5-HT_3 blockade than metoclopramide. In addition, because it has few side effects and a convenient dosing schedule, ondansetron is an excellent choice for combination antiemetic programs. Combining ondansetron and dexamethasone has already been shown to improve antiemetic efficacy with minimal side effects compared with ondansetron alone.[4,5] The current study was undertaken to see if the addition of ondansetron to

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the established antiemetic regimen of metoclopramide, dexamethasone, and lorazepam (MDL) could further control vomiting in patients given high-dose cisplatin. Because the three-drug MDL regimen had been extensively studied in similar patients, we planned to evaluate the effect of adding ondansetron by comparing the results obtained with MDL plus ondansetron to the previous results reported of the MDL combination without ondansetron.

Patients and Methods

From July 1991 to November 1992, 32 patients receiving cisplatin were entered. Eligibility criteria included a Karnofsky performance status of greater than or equal to 60%, age 18 years or older, leukocyte count greater than or equal to 3000/μl, platelet count greater than or equal to 75,000/μl, serum bilirubin level less than or equal to 1.5 mg/dl, serum creatinine level less than or equal to 2.0 mg/dl, a stable heart rhythm, no active angina, and no clinical evidence of congestive heart failure. The use of any antiemetic, benzodiazepine, antihistamine, or sedative (with the exception of triazolam or temazepam for sleep) in the previous 24 hours excluded patient entry. Patients with any nausea or vomiting within 24 hours before the study were not enrolled. Written informed consent was obtained from all participants, and the protocol and consent were approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center, New York, New York.

Pretreatment evaluation included a complete medical history and physical examination, complete blood cell count, serum 12-channel biochemistry profile, serum creatinine level, and electrocardiogram. Follow-up laboratory examination the day after treatment included a complete blood cell count, 12-channel biochemistry profile, and serum creatinine analysis. Laboratory abnormalities were graded using the National Cancer Institute Common Toxicity Criteria.

All patients received the following intravenously: lorazepam, 1.5 mg/m^2 (maximum dose, 3 mg) 45 minutes before and 90 minutes after cisplatin (two doses); ondansetron, 0.3 mg/kg, 25 minutes before and 3.5 hours after cisplatin (two doses); and dexamethasone, 20 mg, 10 minutes before cisplatin (one dose). Cisplatin (ordered as 3 mg/kg or greater than or equal to 100 mg/m^2) was given as a 30-minute infusion.

All patients were observed in the hospital by a research nurse during the 24-hour period after cisplatin administration. The number of emetic episodes was recorded. Any vomiting productive of liquid was recorded as an emetic episode. In addition, one to five dry heaves within any 5-minute period were counted as a single emetic episode.

Side effects were documented. These included sedation, number of bowel movements, headache, insomnia, hiccups, epigastric burning, akathisia, and dystonic reactions. Diarrhea was defined as three or more loose bowel movements during the 24-hour observation period. Sedation was graded as follows: 0, none; 1+, mild (patient lethargic but arousable by verbal stimuli and completely oriented to time, place, and person when awake); 2+, moderate (patient aroused only by physical stimuli but oriented when awakened); and 3+, severe (patient aroused only by physical stimuli and disoriented when awakened).[1] Sedation was evaluated by the nurse-observer before each antiemetic dose infusion, immediately before chemotherapy administration, and at hourly intervals for 4–6 hours after chemotherapy. Heart and respiratory rate and supine and erect blood pressures were obtained at the initiation and completion of the 24-hour study period. Supine and standing pulse rates and blood pressures were obtained frequently during the 24-hour observation period. Food or fluids by mouth were not allowed during the study.

Patients were asked to complete 100-mm visual analogue scales measuring nausea, vomiting, sedation, anxiety, and comfort immediately before study entry and again 24 hours after chemotherapy. Patients were also asked to record their satisfaction with emetic control at the end of the study on a visual analogue scale. Past trials have shown these instruments to be valid, reliable, and feasible.[3,6,7]

Table 1. Patient Characteristics

Characteristics	MDL plus ondansetron
No. of patients	30
Median age (yr) (range)	54 (38–73)
Men:women (%)	47:53
Karnofsky performance status	
60–70%	27%
80–90%	73%
Primary cancer site	
Lung	93%
Other	7%
Prior cisplatin therapy	0%

MDL: metoclopramide, dexamethasone, and lorazepam.

Results

Thirty-two patients were entered; all but two were adequate for both toxicity and antiemetic response assessment. The two patients erroneously received additional antiemetic medication before the end of the study period even though they had not experienced emesis. Patient characteristics are presented in Table 1.

Overall, 67% of patients had no emesis and 83% experienced two or fewer emetic episodes (Table 2). The median values of the patient-generated visual analogue

Table 2. Antiemetic Results for MDL Plus Ondansetron and the Prior Experience with MDL Alone

	MDL plus ondansetron (current study)	MDL alone[3,6,18,19]	Observed difference (95% CI)
No. of patients	30	191	—
No emesis	67%	67%	0% (−18 to 18%)
0, 1, 2, emetic episodes	83%	86%	3% (−17 to 12%)

CI: confidence interval; MDL: metoclopramide, dexamethasone, and lorazepam.

scales (0 mm, the least; 100 mm, the most) for the patients receiving MDL plus ondansetron were as follows (before treatment, n = 29; 24 hours after treatment, n = 28): nausea 0,3; vomiting 0,2; sedation 9,70; anxiety 44,37; comfort 79,72; and posttreatment satisfaction 91. The median visual analogue scale values obtained 24 hours after treatment are depicted in Table 3.

Side effects of MDL plus ondansetron were for the most part mild, and all were transient. Sedation lasting 2–6 hours was observed in all patients receiving MDL plus ondansetron. Sedation was mild (1+) in 20%, moderate (2+) in 70%, and severe (3+) in 10% of the patients. Vital signs were not affected during the period of sedation. Mild headache was seen in 27% of patients and rarely required treatment. When therapy was requested, the headache was controlled with acetaminophen (650 mg given orally). Transient 1+ elevations of serum aspartate transaminase and/or alanine transaminase (38–93 U/l) occurred in 17% of patients. Two patients experienced transient 2+ elevations in serum aspartate transaminase and alanine transaminase levels (94–185 U/l). Three patients (10%) receiving MDL plus ondansetron experienced akathisia, and three had passing hiccups. One patient reported transient amnesia. Mild hypotension was observed once and was resolved with intravenous fluids. No patient experienced more than three loose stools or acute dystonic reactions. Orthostatic hypotension or changes in heart rate were not observed. No changes were seen on posttreatment serum creatinine or hematologic studies.

Eight patients received repeated courses of MDL plus ondansetron with subsequent cycles of chemotherapy. Six patients received one additional course and two patients received two. Complete control (no emesis) occurred in 9 of 10 repeated courses (90%), and two or fewer emetic episodes were observed in 100% of the patients. No cumulative toxicity was seen.

Discussion

Several safe and effective single-agent antiemetics, such as metoclopramide,[8–10] dexamethasone,[11,12] haloperidol,[13] and ondansetron,[14,15] are available. The use of antiemetic combinations has further improved emetic control.[3,4,16,17] The combination of intravenous MDL improved the control of emesis caused by cisplatin (greater than or equal to 100 mg/m^2) in four trials. Among the 191 patients entered, 67% had no emesis and 86% experienced two or fewer emetic episodes (Table 2).[3,6,18,19] Despite the advancement of combination antiemetic therapy, some patients still vomit after chemotherapy.

Although metoclopramide blocks both serotonin (5-HT$_3$) and dopamine receptors (D2), the extent, location, and duration of receptor blockade is unknown. Incomplete receptor site blockade while the emetic stimulus is present may explain why some patients still vomit. Ondansetron potently and specifically blocks the 5-HT$_3$ receptor. Two doses of ondansetron (0.15 mg/kg) have been found to be equivalent to three in an antecedent trial combining it with dexamethasone.[20] Individual doses of 0.3 mg/kg of ondansetron provided better complete control of vomiting than doses of 0.15 mg/kg.[21] Based on these studies, we added ondansetron, 0.3 mg/kg (two doses), to the antiemetic regimen of MDL.

Although the addition of ondansetron to the MDL regimen ($17.49) would increase pharmacy acquisition cost by $180.47 (based on a 70-kg patient), the current trial was designed to improve emetic control and in that way justify the increased cost. The acquisition cost of the combination of a standard daily dose of intravenous ondansetron (0.45 mg/kg in a 70-kg patient) and dexamethasone (20 mg) is $135.68.

A comparison of the antiemetic results from the current trial with our prior experience with MDL alone is shown in Table 2. Sixty-seven percent of patients receiving MDL plus ondansetron had complete control of emesis, which duplicated the 67% control rate observed in patients receiving MDL alone in four previous trials.[3,6,18,19] The 95% confidence interval of the observed difference (0%) in antiemetic efficacy between MDL plus ondansetron and MDL alone is −18% to +18%. Comparison of the median patient-generated visual analogue scores of patients treated with MDL plus

Table 3. Median Visual Analogue Scale Scores (mm) 24 Hours After Cisplatin

Visual analogue scale	MDL plus ondansetron (n = 30)	MDL alone (n = 63)*
Nausea	3	4
Vomiting	2	2
Sedation	70	82
Anxiety	37	22
Comfort	72	76
Satisfaction	91	93

* Kris et al., 1987.[3]
MDL: metoclopramide, dexamethasone, and lorazepam.

ondansetron and MDL alone is shown in Table 3. The addition of ondansetron did not increase or diminish the degree of nausea or other subjective effects experienced by the patients. The incidence of sedation in the MDL-plus-ondansetron group (100%) paralleled what was previously seen when the MDL combination was administered to 100 patients with cancer given identical chemotherapy.[3,6,19] The incidence of headache and 1+ elevations in serum aspartate transaminase/serum alanine transaminase levels were significantly higher ($P < 0.001$ and $P = 0.009$, respectively) in patients receiving MDL plus ondansetron versus MDL alone (N = 191).[3,6,18,19] Headache and serum aspartate transaminase/alanine transaminase elevations are common side effects reported with ondansetron.[4,15,18,21]

The addition of ondansetron (a potent and specific 5-HT_3 antagonist) to the combination of high-dose metoclopramide, dexamethasone, and lorazepam (MDL) resulted in emetic control analogous to that seen with MDL alone. This suggests that 5-HT_3 receptors stimulated in cisplatin-induced vomiting and affected by 5-HT_3 antagonists antiemetics are adequately blocked by the MDL regimen. Vomiting despite prophylaxis with MDL may be mediated by other mechanisms not involving 5-HT_3 receptors. To improve the control of acute chemotherapy-induced emesis further, research should target other receptor sites.

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