A Randomized, Double-Blind Comparison of the Antiemetic Effect of Metoclopramide and Lorazepam With or Without Dexamethasone in Patients Receiving High-Dose Cisplatin

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Thirty-seven patients with advanced incurable malignancies who were receiving their first course of cisplatin (≥ 90 mg/m² bolus), alone or in combination with other antineoplastic agents, were entered in this randomized, double-blind study to determine the antiemetic efficacy of the addition of high-dose dexamethasone to lorazepam plus metoclopramide. All patients received lorazepam (1.5 mg/m²) and metoclopramide (2.0 mg/kg) intravenously (IV) 30 minutes before cisplatin, with the same dose of metoclopramide repeated 1.5, 3.5, 6.5, and 9.5 hours after the 30-minute cisplatin infusion. Patients were randomized to receive dexamethasone (0.5 mg/kg) or placebo by slow bolus injection 30 minutes before cisplatin. All patients were hospitalized for 24 hours and evaluated by observation after cisplatin and a patient questionnaire before discharge. Eighteen patients received metoclopramide and lorazepam without dexamethasone: six (33%) reported no vomiting and four (22%) reported no nausea or vomiting. Nineteen patients also received dexamethasone: 14 (74%) had no vomiting and 13 (68%) reported no nausea or vomiting. These differences were statistically significantly different (P = 0.013 and 0.005, respectively). The side effects attributable to the antiemetic regimen were somnolence (100%), confusion (8%), and diarrhea (46%), and were the same in both arms. Dexamethasone significantly improved the antiemetic efficacy of metoclopramide plus lorazepam without adding toxicity. This three-drug combination gave a high rate of control of acute emesis induced by high-dose cisplatin. *Cancer* 66:443–446, 1990.

CISPLATIN IS AN EFFECTIVE antineoplastic agent for a number of solid tumors.[1] However, a patient's quality of life and acceptance of therapy may be severely hampered by drug-induced nausea and vomiting. Studies have shown that high-dose intravenous (IV) metoclopramide is a more effective antiemetic agent than placebo or conventional-dose prochlorperazine in patients receiving cisplatin.[2] However, only 20% to 40% of patients are rendered symptom-free in the immediate postdrug period by single-agent metoclopramide.[2,3]

Lorazepam and dexamethasone have been shown to have significant antiemetic activity and high patient acceptance as single agents, and the side effects of these two agents are dissimilar enough from those produced by metoclopramide to permit combination drug administration without requiring dose limitation.[4–7] Two-drug combinations of metoclopramide and dexamethasone and metoclopramide and lorazepam have shown improved antiemetic effect compared with single-agent metoclopramide.[3,8] This study was undertaken to determine the antiemetic efficacy of metoclopramide and lorazepam with or without dexamethasone in patients receiving high-dose cisplatin, and to compare the two-drug regimen with the three-drug regimen.

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Patients and Methods

During a 10-month period, 39 consecutive patients who met all eligibility criteria were offered study participation.

TABLE 1. Patient Characteristics

	Male	Female	Median age (yr)	Age range (yr)	Prior chemo.	Cisplatin combination	Primary sites	
MLD	15	4	57	36–67	7 (37%)	12 (63%)	Lung	27 (73%)
ML	11	7	60	43–72	6 (33%)	14 (78%)	Head and neck	6 (16%)
Total	26	11	59	36–72	13 (35%)	26 (70%)	Miscellaneous	4 (11%)

M: metoclopramide; L: lorazepam; D: dexamethasone.

Thirty-seven patients agreed to enter the study. These patients were adults (18 years of age and older) with histologically proven cancer who had been hospitalized to receive their first treatment with cisplatin at doses of 90 mg/m^2 or greater, either as a single agent or in a combination regimen. Only patients who had not previously received the study agents as antiemetics were eligible. Other exclusions included patients with diabetes mellitus, concurrent bowel obstruction, peptic ulcer disease, and central nervous system (CNS) metastases. Patients were screened for eligibility for entry into the study by the clinical research nurse.

The characteristics of the patients entered into this study are shown in Table 1. The patients were stratified on the basis of prior *versus* no prior chemotherapy and single-agent cisplatin *versus* a combination regimen including cisplatin. Neither the patients nor the administering nurse knew to which arm the patient was randomized. All patients had a Karnofsky performance status of 80% or greater. Cisplatin was administered IV during 30 minutes.[9] Antiemetic drugs were administered IV on the schedule illustrated in Table 2. After receiving the initial dose of metoclopramide and lorazepam with or without dexamethasone and for the next 18 to 24 hours, the patients were assessed at frequent intervals for nausea, vomiting, extrapyramidal reactions, somnolence, and other toxicities that might be attributable to the study drugs. These observations were made and documented by the clinical research nurse coordinating the study and by the staff nurses of the oncology unit. On the day after treatment with cisplatin and the study drugs, each patient was asked to complete a short, self-administered questionnaire similar to that used by Ungerleider.[10] Both documented objective observations and the patients' self-assessment questionnaires were evaluated for determination of response and toxicity. An episode of emesis was defined as any vomiting productive of liquid or one or more retches within a 5-minute period.[3]

A complete response (CR) was defined as no nausea or vomiting. A partial response (PR) was mild to moderate nausea and/or one to four episodes of vomiting, or severe nausea with no vomiting. Nonresponders were those who had more than five episodes of vomiting or severe nausea with one to four vomiting episodes. All nausea, vomiting, and toxicities were graded on a scale of 0 to 3+. Only the first course of therapy was used for evaluation of response and toxicity. Nonresponders were removed from the study after one course, whereas responders (CR or PR) were observed for at least two courses when possible. The statistical evaluation of this study was performed by the Biostatistical Unit of the Comprehensive Cancer Center using chi-squared analyses. This study was reviewed and approved by the Institutional Review Board of the University of Alabama at Birmingham in compliance with an assurance filed with the Department of Health and Human Services.

Results

Antiemetic Effect

Of 37 patients who were entered into the study, 18 were randomized to the two-drug arm and 19 to the three-drug arm. Patient characteristics were similar in both arms of the study, particularly with respect to the important prognostic factors of age, sex, and performance status.[11] The results of this study are shown in Table 3. The group who received metoclopramide and lorazepam alone had a CR rate of 22% and a PR rate of 67%. Two of the 18 patients were nonresponders, having experienced five or more episodes of vomiting. The 19 patients who received metoclopramide and lorazepam plus dexamethasone had a significantly higher CR rate of 68% ($P = 0.005$), whereas 21% (four of 19 patients) had a PR. Of 46 reported episodes of emesis, 47% occurred within the first 4 hours and an additional 21% from 4 to 6 hours after cisplatin administration.

The number of vomiting episodes also were compared because the presence of any degree of nausea, even without vomiting, was considered a PR. Fourteen of the 19 patients receiving dexamethasone (74%) experienced no episodes

TABLE 2. Treatment Regimen

−30 minutes	D	0.5 mg/kg or placebo
	M	2 mg/kg
	L	1.5 mg/m^2
+1½ hours	M	2 mg/kg
+3½ hours	M	2 mg/kg
+6½ hours	M	2 mg/kg
+9½ hours	M	2 mg/kg

M: metoclopramide; L: lorazepam; D: dexamethasone.

TABLE 3. Response to Metoclopramide With or Without Dexamethasone

	No. of patients	CR	PR	NR	No. of emesis 0	1	2	3	4	≥5
MLD	19	13 (68%)*	4 (21%)	2 (11%)	14†	2	1	—	—	2
ML	18	4 (22%)	12 (67%)	2 (11%)	6	3	3	3	1	2

M: metoclopramide; L: lorazepam; D: dexamethasone; CR: complete response; PR: partial response; NR: no response.
* MLD *versus* ML, $P = 0.005$.
† MLD *versus* ML. $P = 0.013$.

of vomiting, whereas six of 18 patients (33%) not receiving dexamethasone had no vomiting ($P = 0.013$). When comparing the assessment tool used by the clinical research nurse or oncology staff nurses with the patients' self-assessment questionnaire, we found that of 76 evaluable courses of the study regimens there were 27 discrepancies or an incidence rate of 35%. These discrepancies invariably had the patient reporting some degree of nausea that the nurses did not note. When these reporting discrepancies occurred, we used the patient's evaluation to assess response. Discrepancies in reporting episodes of emesis also were noted (15 of 76 or 28%).

Only the first course of treatment was used to compare antiemetic response. However, patients who received two or more courses had response and toxicity relative to the first course assessed. In the two-drug arm, 11 patients received a second course of therapy. Seven patients had an improved response or the same response (64%). Eleven patients receiving dexamethasone also were treated. Five had an improved or stable response (45%). Overall, 12 of 22 (55%) study patients had an improved or continued response with two or more courses of treatment.

The toxicities of the two antiemetic regimens are similar and are summarized in Table 4. Somnolence was the side effect most frequently noted in patients on both arms of the study. Twenty-seven of the 37 patients evaluated were noticed to be sleepy but easily aroused (Grade 1). Another nine patients were assessed as being difficult to arouse (Grade 2). Only one patient who had marked somnolence was noticed to be unarousable for 8 hours after antiemetic drug administration. All patients were fully alert and functional by the next morning. Thirty patients reported amnesia for at least a portion of the preceding 24 hours.

Diarrhea was the second most commonly reported toxicity, ranging from mild to moderate in those patients who experienced it. Diarrhea occurred in both arms of the trial, but was seen less frequently in patients receiving dexamethasone (six of 19) than in patients receiving the placebo (11 of 18). The diarrhea rapidly resolved after diphenoxylate and atropine (Lomotil, G.D. Searle & Co., Chicago, IL) administration. Patients in whom diarrhea developed during the first cycle of therapy were premedicated with Lomotil during any subsequent courses, and the diarrhea did not recur.

Three patients, all 70 years of age or older, experienced confusion after administration of the antiemetics. In two instances, this was described as mild disorientation. One patient was markedly confused. Extrapyramidal reactions were not observed in this patient population.

Discussion

This study was undertaken to determine the effectiveness of adding dexamethasone to metoclopramide and lorazepam in preventing acute cisplatin-induced nausea and vomiting. Both the two-drug and three-drug regimens demonstrated significant antiemetic effect, with an overall response rate (CR and PR) of 89% for each. The dexamethasone-containing regimen, however, was clearly more effective both in terms of the CR obtained and the reduction in the number of episodes of emesis. Overall, 74% of patients receiving at least a 90 mg/m^2 bolus of cisplatin had no episodes of emesis.

Prior studies have shown improved antiemetic activity with the addition of either dexamethasone or lorazepam to metoclopramide.[3,8] The addition of lorazepam to the combination of metoclopramide and dexamethasone also produced increased patient satisfaction.[12] However, not

TABLE 4. Toxicity of Metoclopramide With or Without Dexamethasone

	No. of patients								
	Somnolence				Diarrhea			Confusion	
Grade	0	1	2	3	0	1	2	+	−
MLD	0	14	5	0	13	5	1	1	18
ML	0	13	4	1	7	8	3	2	16

M: metoclopramide; L: lorazepam; D: dexamethasone.

all single-agent dexamethasone trials have demonstrated a major antiemetic effect in patients receiving cisplatin,[13,14] and an objective improvement in antiemetic effect with the addition of dexamethasone has not been a universal finding.[15,16] In addition, high-dose dexamethasone aggravates diabetes mellitus and may have other adverse effects, including cataract formation, immunosuppression, or, theoretically, stimulation of tumor growth or metastases.[16,17] Therefore, any benefit resulting from the use of dexamethasone in a three-drug regimen should be validated in a randomized trial. This study further establishes the superiority of the three-drug combination and documents the role of dexamethasone. The positive findings reported here could be related to the high dose of dexamethasone administered.

In those patients who did report at least one episode of emesis, the majority occurred within 6 hours of receiving cisplatin. This suggests that prolonging the duration of antiemetic drug administration will have little benefit or improvement in antiemetic efficacy and will require the use of additional agents, higher doses of these agents, or improved administration schedules.[18]

The toxicities observed were comparable for both groups and were those expected. There were no side effects specifically attributed to dexamethasone. The majority of patients reported amnesia and somnolence. These side effects were generally considered by these patients to be beneficial, thus supporting the use of lorazepam in either the two-drug or three-drug combination. However, the observation of three episodes of confusion in patients older than 70 years of age suggests that lower doses should be used in these older patients. An additional benefit of the lorazepam may be suppression of the extrapyramidal side effects of metoclopramide. There were no episodes of extrapyramidal reactions in our patients despite the exclusion of diphenhydramine from the regimen.

In summary, the three-drug combination of metoclopramide, lorazepam, and dexamethasone demonstrated a greater efficacy in reducing the incidence of nausea and vomiting compared with the two-drug combination of metoclopramide and lorazepam, without additional side effects or toxicity. Dexamethasone clearly adds to the efficacy of the regimen. Eighty-four percent of patients had zero or one episode of emesis, thus demonstrating that this is a highly effective combination for the prevention of acute, high-dose cisplatin gastrointestinal toxicity in hospitalized patients.

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