Metoclopramide Versus *Metoclopramide and Lorazepam*

Superiority of Combined Therapy in the Control of Cisplatin-Induced Emesis

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Sixty-four patients treated with cisplatin-containing regimens were entered into a randomized, double-blinded study examining the antiemetic efficacy of metoclopramide with and without lorazepam for control of cisplatin-induced emesis. Metoclopramide was administered to all patients at 2 mg/kg, intravenously, 30 minutes before chemotherapy and 1.5, 3.5, and 5.5 hours posttreatment. Patients randomized to receive combined antiemetic therapy were administered lorazepam at 2 mg/m^2 (maximum, 4 mg dose) intravenously, 30 minutes before chemotherapy. Those patients not receiving lorazepam were given normal saline placebo. Degree of nausea and number of vomiting episodes were recorded on a data flow sheet with a visual analogue scale. Drug toxicities were evaluated before each administered dose. Patients receiving both metoclopramide and lorazepam experienced significantly less vomiting episodes ($P < 0.05$) and nausea ($P < 0.01$) when compared to patients given metoclopramide alone. Forty-four percent of those receiving the combined therapy reported no nausea or vomiting episodes compared to only 22% receiving metoclopramide alone. Sedation was significantly more common in patients receiving lorazepam (88%) as opposed to patients receiving only metoclopramide (43%), $P < 0.01$. Amnesia was seen in 25% receiving lorazepam. No significant difference in diarrhea, dystonia, or disinhibition was observed between the two arms. The authors conclude that the combination of lorazepam and metoclopramide was superior to metoclopramide alone in the prevention of cisplatin-induced nausea and vomiting, with sedation and amnesia more commonly observed in the combined regimen.

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GREATER THAN 75% of patients receiving cisplatin-containing chemotherapy will experience nausea and vomiting.[1] Inadequate control of these potentially disabling toxicities may interfere with quality of life and decrease patient compliance in chemotherapeutic programs.[2,3] Metoclopramide is an effective agent in decreasing the gastrointestinal toxicities associated with cisplatin.[4–8] To potentiate the antiemetic property of this drug, metoclopramide has been combined with phenothiazines, butyrophenones, corticosteroids, antihistamines, and cannabinoids.[4,9–11]

Benzodiazepines have also been used in combination with metoclopramide in antiemetic regimens. Lorazepam, a benzodiazepine possessing both antiemetic and amnesic effects, has been shown to be an effective antiemetic agent.[12] Although the mechanism of this antiemetic effect is unclear, the amnesic property of lorazepam may contribute to its usefulness in the control of emesis.

Although previous studies have combined metoclopramide and lorazepam in antiemetic regimens, a randomized study comparing metoclopramide alone *versus* metoclopramide and lorazepam has not been previously reported.[13] We report a randomized double-blinded investigation of metoclopramide with and without lorazepam to control nausea and vomiting in patients receiving cisplatin.

Patients and Methods

Adult patients with a histologically confirmed diagnosis of cancer were eligible for this study. All patients must have been offered antineoplastic therapy and scheduled

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to be receiving regimens that included cisplatin. Adequate hepatic (serum bilirubin < 2.0 mg%) and renal function (serum creatinine < 1.5 mg%) must have been present. Each patient had a leukocyte count > 4000/mm^3, a platelet count > 100,000^3, and hemoglobin > 9.0 g%. Informed written consent was obtained from all patients before entry into this study. Nursing mothers and pregnant women were excluded from the study. Patients who had received any antiemetic therapy within 24 hours of the initiation of chemotherapy administration were also excluded. Also, patients with clinically active brain metastases or seizure disorders, patients receiving concurrent psychoactive drugs, monoamine oxidase inhibitors, corticosteroids, or other antiemetic agents were similarly excluded. Only patients receiving cisplatin (singly or in combination) were included in this study.

All patients were hospitalized to receive cisplatin *via* a 30-minute intravenous infusion. Cisplatin treatment followed vigorous intravenous hydration and mannitol diuresis as described by Gralla and associates.[4] Patients were noted to have received cisplatin at a dosage of ≥100 mg/m^2 or <100 mg/m^2.

Thirty-five percent of study patients received a combination of cisplatin and etoposide. Fifty-percent received cisplatin with 5-fluorouracil. Eight percent of study patients received cisplatin with doxorubicin. Seven percent received cisplatin with a variety of antineoplastic agents not considered to be of high emetogenic potential.

Patients were randomized by a pharmacist using a random sequence numbers schema. Pretreatment evaluation included a complete history and physical examination. A prestudy form specifying height, weight, body surface area, age, sex, tumor type and stage, performance status, measurable disease, concurrent medications, and hematologic indices was completed at registration.

All patients in the study received metoclopramide by the intravenous route. Metoclopramide (Reglan, A. H. Robins, Richmond, VA) was diluted in at least 50 ml of 0.9% sodium chloride and infused over a 15-minute period. Treatment "A" consisted of metoclopramide, 2 mg/kg given by intravenous piggyback route, 30 minutes before chemotherapy and 1.5, 3.5, and 5.5 hours after chemotherapy. Lorazepam, 2 mg/m^2 (maximum, 4 mg dose), was given by intravenous piggyback 30 minutes before chemotherapy. Treatment "B" consisted of administering metoclopramide as above, plus normal saline placebo. All patients received four intravenous doses of metoclopramide. Any patient who had intractable nausea and vomiting that exceeded five episodes was considered a nonresponder and was treated with other antiemetics.

No fluids or food were administered orally during the first 12 hours after chemotherapy was infused. No sedative, hypnotic, or antiemetic drugs were administered for 24 hours before and during the study.

TABLE 1. Patient Characteristics

Site of primary	No. of patients	M + L	M
Lung	33	15	18
Head and neck	10	5	5
Unknown primary	3	3	0
Esophageal	3	2	1
Other*	11	7	4
Total	60	32	28
Sex			
Male	43	23	20
Female	17	9	8
Chemotherapy			
No prior chemotherapy	35	20	15
Prior chemotherapy	25	12	13
Cisplatin dose			
≥100 mg/m^2	38	18	20
<100 mg/m^2	22	14	8
Age			
Range 26–74 yr			
Median 57 yr			
Median performance status: 80%			

M: metoclopramide; L: lorazepam;
* Other: ≤ two patients per diagnosis.

To document the efficacy of the treatment plan, the degree of nausea and number of vomiting episodes were recorded on a data flow sheet provided to patients. Subjects were interviewed within 24 hours after treatment by the study investigators. Vomiting episodes were totaled at 2 hours, 4 hours, 8 hours, 16 hours, and at 24 hours after chemotherapy infusion. The degree of nausea, vomiting, and retching was recorded by the patient on a visual analogue scale. Nausea was graded according to the following scale: 0 = no nausea; 1 = mild nausea, defined as no impairment of the patient's physical activity; 2 = moderate nausea, patient's physical activity impaired; and 3 = severe nausea, patient bedridden. Retching episodes were recorded as vomiting.

Only those patients completing the study by receiving all antiemetic agents as indicated in the treatment plan were considered evaluable. A complete response (CR) was defined as no nausea or vomiting. A partial response (PR) was nausea only, one to five vomiting episodes or nausea with one to five vomiting episodes. No response (NR) was nausea with more than five vomiting episodes.

Side effects and symptoms were evaluated before each administered dose of study drug. Sedation was defined as being lethargic, but arousable to verbal stimulation. Diarrhea was defined as more than three loose bowel movements in a 24-hour period. All patients were questioned if they remembered receiving intravenous chemotherapy.

Ridit analysis was utilized for comparison of differences in vomiting episodes between the two treatment groups.[14]

TABLE 2. Antiemetic Response

Response	M + L	M
Complete response (CR)	14 (44%)	6 (22%)
Partial response (PR)	15 (47%)	16 (57%)
No response (NR)	3 (9%)	6 (21%)

M: metoclopramide; L: lorazepam.

Statistical analysis of side effects was performed by the Fisher's zig-zag test.

Results

Sixty-four patients were entered into the protocol. Four patients were excluded from analysis. Reasons for exclusion included concurrent use of sedative agents or corticosteroids, hyperbilirubinemia, and inadequate follow-up. All evaluable patients received full doses of both metoclopramide and lorazepam. Table 1 includes the characteristics of the 60 evaluable patients. Fifty-five percent of evaluable patients were treated for bronchogenic carcinoma and received 120 mg/m^2 of cisplatin. The remaining 45% of patients were treated with a median cisplatin dose of 75 mg/m^2. Seventy-two percent of evaluable patients were men. Fifty-eight percent of patients were previously untreated with chemotherapy.

As indicated in Table 2, 44% of patients receiving both metoclopramide and lorazepam had no vomiting episodes (CR) whereas only 21% of patients administered metoclopramide alone had no vomiting ($P < 0.05$). The metoclopramide and lorazepam arm achieved total response rate (CR + PR) of 91%; whereas, 79% of patients receiving metoclopramide alone achieved a response. Patients receiving metoclopramide alone had significantly more vomiting episodes classified as NR, than did those patients receiving combined antiemetics ($P < 0.05$).

Metoclopramide and lorazepam demonstrated significant activity in controlling cisplatin-induced nausea compared to single-agent metoclopramide (median nausea score 0.75 *versus* 1.43, $P < 0.01$).

TABLE 3. Dose and Antiemetic Response

	CR	PR	NR
<100 mg/m^2			
M + L	8	5	1
M	3	4	1
N = 22	11 (50%)	9 (41%)	2 (9%)
≥100 mg/m^2			
M + L	6	10	2
M	3	12	5
N = 38	9 (24%)	22 (58%)	7 (18%)

CR: complete response; PR: partial response; NR: no response; M: metoclopramide; L: lorazepam.

TABLE 4. Side Effects Profile

	M + L n = 32	M n = 28	
Sedation	28 (88%)	12 (43%)	$P < 0.01$
Diarrhea	2 (6%)	2 (7%)	NS
Dystonia	0	4 (14%)	$P < 0.05$
Amnesia	8 (25%)	0	$P < 0.01$
Disinhibition	3 (9%)	0	NS
None	4 (13%)	11 (39%)	$P < 0.05$

M: metoclopramide; L: lorazepam; NS: not significant.

As seen in Table 3, a 91% total response rate was observed in patients receiving <100 mg/m^2 of cisplatin. A total response rate of 82% was noted in patients receiving ≥100 mg/m^2. Seventy percent of all CR occurred in patients receiving the combined antiemetic therapy whereas 67% of all NR received only single-agent antiemetic therapy.

Table 3 also shows that in those patients receiving <100 mg/m^2 of cisplatin, a total response rate of 93% was achieved for those patients randomized to receive the combination antiemetic regimen. Furthermore, in those patients receiving ≥100 mg/m^2 of cisplatin, a total response of 89% occurred in those receiving the combination regimen. This data suggests that the beneficial effects of combination antiemetic therapy are independent of the administered cisplatin dose.

Table 4 displays the observed side effects in the two treatment arms. Sedation occurred in 88% (28/32) of patients receiving lorazepam as compared to 43% (12/28) of patients receiving metoclopramide alone. Amnesia occurred frequently in patients receiving lorazepam. Twenty-five percent of these patients had no recall of ever receiving chemotherapy. No difference in diarrhea, dystonia, or disinhibition was observed between the two arms. Four patients receiving metoclopramide alone were observed to have dystonic reactions. Dystonia was not reported in any of the patients treated with lorazepam and metoclopramide.

Table 5 compares the observed side effects with the administered cisplatin dose. Sedation was the most commonly observed side effect, occurring in 67% (40/60) of

TABLE 5. Side Effects Related to Cisplatin Dose

	<100 mg/m^2 n = 22	≥100 mg/m^2 n = 38	
Sedation	15 (68%)	25 (66%)	NS
Diarrhea	1 (5%)	3 (8%)	NS
Dystonia	2 (9%)	2 (5%)	NS
Amnesia	2 (9%)	6 (16%)	NS
Disinhibition	1 (5%)	2 (5%)	NS
None	6 (27%)	9 (24%)	NS

NS: not significant.

TABLE 6. Side Effects Related to Antiemetic Response

	CR (n = 20)	PR (n = 31)	NR (n = 9)
Sedation	12 (60%)	23 (74%)	5 (56%)
Diarrhea	1 (5%)	3 (10%)	0
Dystonia	1 (5%)	1 (3%)	2 (22%)
Amnesia	2 (10%)	5 (16%)	1 (11%)
Disinhibition	1 (5%)	1 (3%)	1 (11%)
None	8 (40%)	6 (19%)	1 (11%)

CR: complete response; PR: partial response; NR: no response.

all patients. There was no significant difference in observed side effects when patients were stratified by cisplatin dose.

Table 6 compares the antiemetic response in study patients to the observed side effects. Patients who did not respond to either the single or combination antiemetic regimens were seen to have less sedation and more dystonia, however, these values were not significant.

Discussion

The administration of antineoplastic agents has frequently been associated with nausea and vomiting.[15-17] Cisplatin, a potent emetogenic antineoplastic drug, frequently produces refractory nausea and vomiting.[4] The severity of this toxicity interferes with quality of life, and may also prevent the administration of potentially curative treatment.

Metoclopramide, a substituted benzamide, has been extensively studied in the control of emesis induced by antineoplastic agents.[6-8,11,18,19] This drug, a dopamine antagonist, acts centrally by inhibiting output from the chemoreceptor trigger zone to the vomiting center. Peripheral actions of metoclopramide include an increase in lower esophageal sphincter tone, promotion of gastric emptying and decrease in small bowel transit time. Higher doses of the drug with maintenance of therapeutic blood levels may optimize the antiemetic effect.[20]

Lorazepam, an anxiolytic agent of the benzodiazepine class, has been investigated as an antiemetic agent.[21] This drug acts primarily on the limbic system *via* enhancement of gamma-amino butyric acid (GABA) activity. Other sites of action include the cerebral cortex and reticular system.[22] Lorazepam frequently produces amnesia for 3 to 12 hours postadministration.[23]

Metoclopramide has been demonstrated to be a superior single-agent antiemetic drug when compared to prochlorperazine, haloperidol, dexamethasaone, and cannabinoids.[4,24-27] Metoclopramide has been studied in combination antiemetic trials. The addition of dexamethasone or diphenhydramine to metoclopramide has demonstrated an improved antiemetic response.[10] A combination of metoclopramide and lorazepam was studied to evaluate the effect of an anxiolytic agent when added to metoclopramide.

Our findings demonstrate patients receiving a combination of metoclopramide and lorazepam had significantly fewer vomiting episodes than individuals receiving metoclopramide alone. In examining patients who had complete responses (no nausea or vomiting episodes), the combination antiemetic regimen demonstrated superiority. Combination antiemetic therapy also proved to be more effective than metoclopromide alone in controlling nausea.

Side effects were easily managed in each treatment group. As expected, sedation was more commonly observed in the combination treatment arm containing lorazepam. Although marked somnolence, lethargy, confusion, and hypotension have been reported to occur in patients receiving lorazepam, we had no incidence of these significant adverse effects in our study population. Drowsiness was not only acceptable but desirable for most patients. Sedation may be useful in controlling emesis.[21]

Extrapyramidal symptoms of dystonia occurred in 14% of patients receiving metoclopramide alone. These symptoms were not observed in any patient receiving lorazepam. This suggests that lorazepam may aid in controlling extrapyramidal side effects of metoclopramide. By facilitating transmission of GABA, lorazepam will prevent the pharmacologic effect of dopamine antagonism of metoclopramide.[22] The absence of extrapyramidal side effects with a combination regimen that included metoclopramide and lorazepam has been previously reported.[28]

In our study, 25% of patients experienced amnesia resulting from lorazepam. Patients deemed this effect as beneficial. Since anticipatory nausea and vomiting may occur in 20% of patients receiving chemotherapy, attempts to diminish recall of previous chemotherapy may improve tolerance to further drug infusions.[10,22,29-32]

Patients receiving combined antiemetics had significantly less vomiting episodes and nausea. Although sedation and amnesia were more common with the use of lorazepam, these effects were easily tolerated by study patients. Extrapyramidal effects of metoclopramide were not observed with the concomitant use of lorazepam. Because of the enhanced antiemetic efficacy, and the tolerable toxicity profile of metoclopramide with lorazepam, this combination is preferred to single-agent metoclopramide in the control of cisplatin-induced nausea and vomiting.

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