

Improved Control of Cisplatin-Induced Emesis With High-Dose Metoclopramide and With Combinations of Metoclopramide, Dexamethasone, and Diphenhydramine

Results of Consecutive Trials in 255 Patients

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A series of consecutive trials were undertaken to determine whether higher doses of intravenous metoclopramide and combinations of metoclopramide, dexamethasone, and diphenhydramine would improve antiemetic control or decrease treatment-related side effects in patients receiving cisplatin at 120 mg/m². Metoclopramide and dexamethasone were studied because of their proven efficacy as single agents and their differing mechanisms of action and side effects. Diphenhydramine was used because of its possible antiemetic properties and its ability to control acute dystonic reactions. Two hundred fifty-five patients who had never received chemotherapy or antiemetics were observed in the hospital for the 24 hours following cisplatin administration. The addition of dexamethasone or dexamethasone plus diphenhydramine to intravenous metoclopramide 2 mg/kg produced both improved antiemetic control and a decrease in treatment-associated diarrhea ($P = 0.002$). The use of metoclopramide alone at a dose of 3 mg/kg for only two doses appeared as effective as 2 mg/kg for five doses. When dexamethasone and diphenhydramine were given with metoclopramide 3 mg/kg for two intravenous dosages, 81% of patients experienced no emesis and 93% had two or fewer vomiting episodes. The antiemetic results of this 2-hour "short-course" regimen were superior to metoclopramide 2 mg/kg, with ($P = 0.002$) or without ($P = 0.0001$) dexamethasone and diphenhydramine. It was concluded that combinations of metoclopramide plus dexamethasone plus diphenhydramine improve antiemetic control, facilitate the usage of higher doses of metoclopramide, and decrease the incidence of treatment-related side effects.

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VOMITING AND NAUSEA caused by cytotoxic drugs remain crucial issues in the management of patients with cancer. Recent investigations have identified several drugs effective as single agents in the control of acute chemotherapy-induced emesis. Active antiemetics studied in formal trials include metoclopramide,¹⁻⁵ dexamethasone,⁶⁻⁸ haloperidol,⁹ the cannabinoids,¹⁰⁻¹² and

the phenothiazines.¹³ Although control is improved with the use of these available drugs when used individually, it is incomplete in the majority of patients, with many individuals receiving only minor benefit. The approaches to improved antiemetic control investigated in the trials presented in this report are the use of higher doses of an antiemetic drug and the use of active single agents in combination.

The control of emesis involves the blockade of neurotransmitter receptors in the central or peripheral nervous system.¹⁴ The use of higher doses of effective antiemetic drugs or combinations of drugs that act at different receptors and receptor sites could improve the control of vomiting through more complete neuroreceptor blockade. Preclinical data for metoclopramide indicate a dose-antiemetic response relationship.¹⁵ The results of a Phase I study in cancer patients show that metoclopramide can be given safely in even higher doses than those now in use.¹⁶ Combination regimens could attenuate the

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TABLE 1. Treatment Regimens

Trial	Series 1			Series 2			Series 3			"Short course"	
	Metoclopramide (single agent, alteration of dose and schedule)			Dexamethasone (alteration of dose and schedule) plus metoclopramide (constant dose)			Diphenhydramine (alteration of dose and schedule) plus metoclopramide (constant dose) plus dexamethasone (constant dose)			Metoclopramide (3 mg/kg) plus dexamethasone (20 mg) plus diphenhydramine (50 mg)	
	A	B	C	D	E	F	G	H	I	J	
Metoclopramide† (dose and schedule)	2 mg/kg IV Every 2 h 5 doses	2 mg/kg IV Every 2 h 3 doses*	3 mg/kg IV Every 2 h 2 doses	2 mg/kg IV Every 2 h 3 doses							3 mg/kg IV Every 2 h 2 doses
Dexamethasone (dose and schedule)				20 mg IV 30 min before cisplatin	10 mg orally 10 h before cisplatin	10 mg orally 10 h before cisplatin	20 mg IV 30 min before cisplatin				20 mg IV 30 min before cisplatin
Diphenhydramine (dose and schedule)											
							50 mg IV 30 min before cisplatin	25 mg IV 30 min before cisplatin	50 mg IV 30 min before cisplatin		50 mg IV 30 min before cisplatin
								25 mg IV 1.5 h after cisplatin	50 mg IV 1.5 h after cisplatin		

* Final dose given orally.

† First dose given 30 minutes before cisplatin.

IV: intravenously.

untoward effects of single antiemetic drugs or of the cytotoxic chemotherapy. Combinations also have the potential to allow less frequent and simpler antiemetic drug administration.

The single-agent activity and low incidence of side effects make dexamethasone an excellent candidate for combination studies, particularly with metoclopramide. While the mechanism of antiemetic action of dexamethasone is not known, it does not appear to exert its effects by primary blockage of dopamine receptors, the site of the actions of metoclopramide. Moreover, dexamethasone does not accentuate the common adverse effects of metoclopramide: sedation and extrapyramidal reactions.

Although diphenhydramine has not been shown to be an active single agent in formal trials, there are several reasons to consider its use in combination with metoclopramide and dexamethasone. Diphenhydramine is uniformly effective in controlling acute dystonic reactions caused by metoclopramide,¹⁷ it may prevent such reactions in patients at a higher risk,¹⁸ and it may improve antiemetic control through its blockade of histamine re-

ceptors in the brain stem.¹⁴ There are many practical and theoretical reasons to study the efficacy of higher doses of metoclopramide and combinations of metoclopramide, dexamethasone, and diphenhydramine.

This report details the results of consecutive, open-label trials designed to investigate the dose and schedule of the above drugs and to identify effective combinations of these agents for the control of acute cisplatin-induced emesis. Several questions were posed. First, could metoclopramide as a single agent be given less frequently but at a higher dose with improved antiemetic results? Second, what are effective doses and schedules for additional agents used in combination with a constant dose of metoclopramide? Third, is there an advantage in improved antiemetic efficacy or in diminution of adverse effects by combining other agents with metoclopramide? Fourth, could the use of agents in combination with metoclopramide facilitate the use of higher individual doses of the drug?

The regimens investigated in this series of trials are shown in Table 1. Series 1 (Trials A, B, and C) studies metoclopramide as a single agent. Each trial investigates

TABLE 2. Patient Characteristics

Trial	Series 1			Series 2			Series 3			"Short course"
	Metoclopramide (single agent, alteration of dose and schedule)			Dexamethasone (alteration of dose and schedule) plus metoclopramide (constant dose)			Diphenhydramine (alteration of dose and schedule) plus metoclopramide (constant dose) plus dexamethasone (constant dose)			Metoclopramide (3 mg/kg) plus dexamethasone (20 mg) plus diphenhydramine (50 mg)
	A	B	C	D	E	F	G	H	I	J
Patients entered	36	21	24	28	22	29	20	11	22	42
Age (yr)										
Median	58	56	57	53	56	54	58	50	59	55
Range	(40-74)	(35-75)	(38-72)	(29-74)	(31-69)	(35-69)	(40-71)	(39-76)	(29-71)	(36-75)
Sex (no. of patients)										
M:F	26:10	14:7	14:10	15:13	16:6	19:10	15:5	4:7	14:8	31:11
Performance status (no. of patients)										
80 + 90	25	19	17	22	15	21	17	10	13	36
60 + 70	11	2	7	6	7	8	3	1	9	6

varying doses, schedules, and routes of administration of the drug. Series 2 (Trials D, E, and F) tests the alteration of dose, schedule, and route of administration of dexamethasone when used in combination with a constant dose and schedule of metoclopramide. Series 3 (Trials G, H, and I) investigates the alteration of dose and schedule of diphenhydramine when used in combination with a constant dose and schedule of metoclopramide plus dexamethasone. The "short-course" regimen (Trial J) combines the highest individual dose of metoclopramide tested (3 mg/kg) with the best dose of dexamethasone (20 mg) and diphenhydramine (50 mg) determined in the prior trials. In contrast to earlier trials, the entire "short-course" antiemetic regimen is administered in only 2 hours.

Patients and Methods

From April 1980 to June 1983, 255 patients with histologically confirmed cancer were entered into these studies. Only patients who had not previously received chemotherapy and who had a Karnofsky performance status of 60% or greater were eligible for inclusion in the trials. As required for the concurrent chemotherapy protocols, each patient had a leukocyte count above 4000, a platelet count above 120,000, serum creatinine below 1.9 mg/dl and serum bilirubin level below 2.0 mg/l. Written informed consent was obtained from all patients.

Pretreatment evaluation included the following: complete history and physical examination, a complete blood count, 12-channel biochemical profile, serum electrolytes and creatinine values, 12- or 24-hour urine collection for creatinine, electrocardiogram, and chest

roentgenogram. Follow-up biochemical and hematologic tests were performed twice a week in the first week of treatment and weekly or biweekly thereafter. Physical examination was repeated weekly; the chest roentgenogram and creatinine clearance were obtained monthly.

The characteristics of the 255 patients entered into the trials are shown in Table 2. The median ages for all studies ranged from 50 to 59, with only two individuals under age 30. In all trials, approximately two thirds of the patients were men and 76% had a Karnofsky performance status of 80 percent or greater. Seventy percent of study participants had non-small cell lung cancer, while 18% had epidermoid carcinoma of the esophagus. The remaining 12% of patients had a variety of other solid tumors. Age, sex ratio, Karnofsky performance status, and site of primary cancer did not differ significantly among the ten consecutive trials.

All patients were hospitalized to receive cisplatin at a dose of 120 mg/m² of body surface area in a 20-minute intravenous infusion. Cisplatin treatment followed vigorous intravenous hydration with mannitol diuresis, as previously described.¹ Patients with non-small cell lung cancer also received vindesine (3 mg/m²) or vinblastine (6 mg/m²), agents that generally do not induce emesis.^{19,20} Individuals with esophageal carcinoma routinely received vindesine; several were also given methyl-GAG, an agent reported to cause vomiting in fewer than one third of patients.²¹ Patients with other forms of cancer received no additional chemotherapeutic agents during the 24-hour study period.

Intravenous dosages of metoclopramide (Reglan, A. H. Robins, Richmond, VA) were diluted in at least 50 ml of 0.9% sodium chloride and infused over 15 min-

utes. In Series 1, the three trials designed to investigate varying doses, routes of administration, and schedules of metoclopramide, different administration programs (Trials A, B, and C) were employed and are detailed in Table 1.

In Trial A, metoclopramide was given at a dose of 2 mg/kg, every 2 hours, for five intravenous dosages. The first dose was given 30 minutes before cisplatin, others at 1 1/2, 3 1/2, 5 1/2, and 7 1/2 hours after cisplatin. In Trial B, metoclopramide again was given at a dose of 2 mg/kg, but for a total of three dosages. The first two doses were given intravenously; 30 minutes before cisplatin and 1 1/2 hours afterward. The third dose was given orally 3 1/2 hours following cisplatin. Trial C used metoclopramide at the highest dose of 3 mg/kg for a total of only two doses, given 30 minutes before cisplatin and 1 1/2 hours afterward.

The regimens utilized in the combination trials are also detailed in Table 1. In Series 2 (Trials D, E, and F), the dose, schedule, and route of administration of dexamethasone was altered, whereas the dose and schedule of metoclopramide was kept constant (2 mg/kg intravenously for three doses given 30 minutes before cisplatin, then 1 1/2 and 3 1/2 hours after cisplatin). When given intravenously, dexamethasone was given as an infusion over 5 minutes. In Trial D, dexamethasone was given once in a 20 mg intravenous dose 30 minutes before cisplatin. Dexamethasone was given twice, 10 mg orally 10 hours before cisplatin and 10 mg intravenously 30 minutes before cisplatin in Trial E. In Trial F, dexamethasone was given three times: 10 mg orally 10 hours before cisplatin, 20 mg intravenously 30 minutes before cisplatin, and 20 mg intravenously 1 1/2 hours after cisplatin.

Series 3 (Trials G, H, and I) studied varying doses and schedules of diphenhydramine in combination with constant doses of intravenous metoclopramide (2 mg/kg 30 minutes before and 1 1/2 and 3 1/2 hours after cisplatin; the same doses used in Series 2) and dexamethasone (20 mg intravenously 30 minutes before cisplatin). The dose and schedule of dexamethasone were determined from the Series 2 trials. Diphenhydramine was given in a single 50-mg intravenous dose 30 minutes before cisplatin in Trial G. In Trial H, a 25-mg intravenous dose of diphenhydramine was given twice: 30 minutes before and 1 1/2 hours after cisplatin. Diphenhydramine, 50 mg intravenously, was given twice in Trial I, 30 minutes before and 1 1/2 hours after cisplatin.

The results of the three series of trials were utilized to design the short-course regimen (Trial J). Metoclopramide was given at a dose of 3 mg/kg for two intravenous doses, 30 minutes before cisplatin and 1 1/2 hours afterward. Single doses of dexamethasone (20 mg) and di-

phenhydramine (50 mg) were given intravenously to all patients 30 minutes before cisplatin administration.

Food or fluids by mouth were not allowed during the initial 12 hours of all trials; no sedative or other antiemetic drugs were given 10 hours before the study or during the study. Patients who had antiemetic benefit from metoclopramide alone or in combination were offered the same regimen during subsequent chemotherapy.

The number of episodes of emesis was recorded for each patient. Any vomiting productive of liquid was recorded as an emetic episode. In addition, one to five retches (vomiting not productive of liquid) within any 5-minute period were also counted as a single emetic episode. All patients were directly observed in the hospital for the 24 hours after cisplatin administration. Side effects of treatment were also directly observed and recorded: sedation, number of bowel movements, and acute dystonic reactions. Sedation was graded as follows: none; mild (patient lethargic but aroused by verbal stimuli and completely oriented to time, place, and person when awakened); moderate (patient aroused only by physical stimuli and completely oriented when awakened); and marked (patient aroused only by physical stimuli and disoriented when awakened). Patients were awakened if necessary and side effects assessed before each dose of study medication, at the conclusion of the 24-hour observation period, and at least every 3 hours during the trial.

Statistical Analysis

The results of the ten trials were analyzed in four stages. The three dose-setting metoclopramide trials (Series 1) were compared first. The results of the regimens with altering dosages of dexamethasone (Series 2) were evaluated next, followed by an analysis of the three studies with varying dosages of diphenhydramine (Series 3). Lastly, the results from the first three series were compared, together with the final short-course trial.

Pearson's chi-square test was used to compare the frequencies of the observations collected. For Series 1, 2 and 3, for each response, the results of the individual trials were compared. Since this resulted in three pairwise comparisons for each response, a *P* value of 0.016 or less was required for statistical significance in order to control for the problem of multiple comparison. For the final stage of the analysis, the results of Trial A were compared to those of Series 2, Series 3, and the short-course regimen (Trial J). The results of Trial J were also compared to those of Series 2 and 3. Since for each response five comparisons were made, a *P* value of 0.01 or less was required for statistical significance at the 0.05 level overall. In addition, the results of Trial J were com-

TABLE 3. Antiemetic Results and Observed Side Effects of Consecutive Trials

Trial	Series 1			Series 2			Series 3			"Short course"
	Metoclopramide (single-agent, alteration of dose and schedule)			Dexamethasone (alteration of dose and schedule) plus metoclopramide (constant dose)			Diphenhydramine (alteration of dose and schedule) plus metoclopramide (constant dose) plus dexamethasone (constant dose)			Metoclopramide (3 mg/kg) plus dexamethasone (20 mg) plus di- phenhydramine (50 mg)
	A	B	C	D	E	F	G	H	I	J
Percent of patients with										
0 Emetic episodes	39	19	25	54	50	55	60	55	55	81
0, 1, or 2 Emetic episodes	64	33	67	79	82	83	85	73	77	93
Sedation										
None	19	38	46	68	23	41	40	27	23	21
Mild	81	62	54	32	77	59	60	73	77	79
Diarrhea*	42	29	29	11	14	7	10	18	14	5
Acute dystonic reactions	3	0	8	0	0	0	0	0	0	0

* Greater than three bowel movements.

pared to those of Series 2 and Series 3 combined. These results are consistent with those of Series 2 and Series 3 compared separately with Trial J.

Results

Table 3 shows the antiemetic and toxicity observations from the ten trials. Series 1 (Trials A, B, and C) studied the alteration of dose, schedule, and route of administration of metoclopramide used as a single agent. There is no significant difference ($P = 0.09$) in the percentage of patients experiencing zero, one, or two emetic episodes when Regimen B (metoclopramide 2 mg/kg for two intravenous dosages and one oral dosage) is compared to the other two regimens (A and C) using only intravenous metoclopramide. The complete antiemetic response rate ranged from 19% to 39% among the three trials, and the major antiemetic response rate (zero, one, or two episodes) ranged from 33% to 67%. The number of patients experiencing no emesis, mild sedation, greater than three loose bowel movements, or acute dystonic reactions did not differ significantly among the three regimens. An 8% incidence of acute dystonic reactions was seen when metoclopramide alone was given at the highest dose, 3 mg/kg (Trial C).

In Series 2 (Trials D, E, and F), the dose and schedule of dexamethasone was altered, while the dose of metoclopramide was kept constant. Complete emetic control ranged from 50% to 55% of treated patients and the major response rate ranged from 79% to 83%, as seen in Table 3. There are no significant differences in antiemetic response or side effects other than sedation among the three regimens. Since antiemetic effects were similar

and observed side effects were not bothersome, the simplest schedule (20 mg intravenously 30 minutes before cisplatin) was chosen for use in further combination studies.

In Series 3, diphenhydramine (given in three regimens varying dosage and/or schedule) was then added to a constant dose of metoclopramide (2 mg/kg for three intravenous doses) plus dexamethasone (20 mg/kg intravenously). As shown in Table 3, complete control of vomiting was seen in 55% to 60% of patients treated in this series of trials, and major responses ranged from 73% to 85%. Antiemetic efficacy and adverse effects did not differ significantly among the three regimens containing varying doses of diphenhydramine. Again, the most convenient schedule of diphenhydramine administration (50 mg intravenously 30 minutes before cisplatin) was chosen for use in further trials.

The results of Trial J, which utilized the short-course regimen of metoclopramide 3 mg/kg for two intravenous doses, combined with the previously determined doses of dexamethasone plus diphenhydramine, are shown in Table 3. Eighty-one percent of the 42 patients receiving this regimen experienced no emesis, and 93% experienced two or fewer vomiting episodes during the 24 hours after cisplatin administration. In contrast to earlier studies using metoclopramide alone at 3 mg/kg, no acute dystonic reactions were seen in this combination trial. Although not formally measured, as the number of metoclopramide doses was decreased, it appeared that the incidence of delayed emesis (vomiting beginning more than 24 hours after chemotherapy) may have increased. Formal studies are now underway to evaluate this observation.

TABLE 4. Antiemetic and Side Effects of Consecutive Series of Trials With Regimens Using Metoclopramide Alone and in Combination

Regimens	No. of patients	Efficacy (percent of patients)		Side effects (percent of patients)			Acute dystonic reactions
		No emesis	0, 1, or 2 Emetic episodes	Sedation		Diarrhea	
				None	Mild		
Single agent: Trial A Metoclopramide (2 mg/kg × 5)	36	39	64	19	81	42	3
Series 2: Trials D, E, F Metoclopramide (2 mg/kg × 3) plus Dexamethasone (20-50 mg)	79	53 <i>*P = 0.155</i>	81 <i>*P = 0.047</i>	44	56 <i>*P = 0.108</i>	10 <i>*P = 0.0001</i>	0
Series 3: Trials G, H, I Metoclopramide (2 mg/kg × 3) plus Dexamethasone (20 mg) plus Diphenhydramine (50-100 mg)	53	57 <i>*P = 0.101</i>	77 <i>*P = 0.251</i>	30	70 <i>*P = 0.256</i>	13 <i>*P = 0.002</i>	0
Short course: Trial J Metoclopramide (3 mg/kg × 2) plus Dexamethasone (20 mg) plus Diphenhydramine (50 mg)	42	81 <i>*P = 0.0001</i>	93 <i>*P = 0.002</i>	21	79 <i>*P = 0.829</i>	5 <i>*P = 0.00008</i>	0
		<i>†P = 0.002</i>	<i>†P = 0.047</i>		<i>†P = 0.169</i>	<i>†P = 0.209</i>	

* Regimen compared with single-agent metoclopramide 2 mg/kg × 5 (Trial A).

† Metoclopramide 3 mg/kg combination (Short course) compared with combinations using metoclopramide 2 mg/kg (Series 2 plus Series 3).

In Table 4, the antiemetic results and side effects of the consecutive combination trials and metoclopramide alone given at 2 mg/kg for five intravenous dosages are compared. Since there are no substantive differences among the three varying-dose dexamethasone (Series 2) or diphenhydramine (Series 3) regimens, the results of each series were combined for purposes of comparison. Metoclopramide 2 mg/kg for five intravenous dosages is used for comparison as this is the current recommended dose and schedule for the drug and other regimens using metoclopramide alone do not provide better efficacy or fewer side effects. There is a significant difference in the number of patients experiencing no emesis when the regimen combining the highest individual dose of metoclopramide (3 mg/kg) plus dexamethasone plus diphenhydramine (Trial J) is compared with metoclopramide alone (81% versus 39%, $P = 0.001$). When Trial J is compared with combinations using metoclopramide at lower doses (2 mg/kg; Series 2 and 3), the difference is also significant (81% versus 55%, $P = 0.002$). When the number of patients experiencing a major antiemetic response (zero, one, or two episodes of emesis) is studied, again a significant difference is seen when the regimen combining metoclopramide (3 mg/kg) plus dexamethasone and diphenhydramine (Trial J) is compared to metoclopramide alone (93% versus 64%). When the number of patients experiencing no emesis ($P = 0.096$) or two or fewer episodes of emesis ($P = 0.051$) in Series 2 and 3 are combined and compared to metoclopramide

as a single agent (Trial A), an advantage is seen for the combination trials, but this difference is not significant. The percent of patients experiencing no emesis in Trial J is significantly greater than that seen in series 2 or Series 3 (combination trials using metoclopramide at the lower dose of 2 mg/kg).

Metoclopramide alone and combinations containing metoclopramide, dexamethasone, and diphenhydramine were well-tolerated. Few serious side effects were seen regardless of the dose, schedule, or route of drug administration employed (Tables 3 and 4). Mild sedation was the most frequent side effect observed, ranging from 32% to 81% of all patients treated. There was no difference in the degree of sedation when each of the combination regimens was compared to metoclopramide alone or when combinations using metoclopramide at 2 mg/kg were compared to the combination using metoclopramide 3 mg/kg. Metoclopramide plus dexamethasone regimens (Series 2) were associated with the least sedation (56%).

Diarrhea has been noted in earlier clinical studies¹ with high intravenous doses of metoclopramide given to control emesis following administration of high doses of cisplatin with mannitol-induced diuresis. A similar incidence of diarrhea has been seen in both the metoclopramide-treated and placebo arms in the previous randomized studies.¹ In all regimens adding dexamethasone to metoclopramide, the percentage of patients experiencing diarrhea (range, 5%–18%) was significantly de-

creased when compared to those receiving metoclopramide as a single agent (42%). There was no difference in the incidence of diarrhea among the three combination regimens (Series 2, Series 3, and Trial J).

Three patients (two men and one woman, aged 38, 61, and 62, respectively) treated with metoclopramide alone had acute dystonic reactions (1.2% overall incidence). All three experienced trismus, and two had a sensation of a thickened tongue. All reactions cleared completely within 5 minutes of an intravenous injection of 50 mg of diphenhydramine and did not recur with subsequent administration of metoclopramide with and without concomitant diphenhydramine. No acute dystonic reactions were seen in patients who received metoclopramide with dexamethasone, or with dexamethasone and diphenhydramine regardless of the dose of metoclopramide employed. Occasional episodes of restlessness, headache, chills, and diaphoresis were noted but did not require treatment. No ataxia, dizziness, hypotension, dysphoria, hyperglycemia, fluid retention, or hallucinations were observed.

Antitumor activity was similar in all of the consecutive trials and did not differ from that observed in prior studies using the same chemotherapeutic agents in patients with esophageal and non-small cell lung cancer. Sites of tumor recurrence and metastasis also did not differ among the trials or when compared to earlier trials using similar antineoplastic agents. The degrees of nephrotoxicity from cisplatin; neurotoxicity from cisplatin, vindesine, or vinblastine; and myelosuppression from all agents were not altered by metoclopramide alone or in combination with dexamethasone and diphenhydramine.

Discussion

The results of these consecutive trials again demonstrate that high doses of intravenous metoclopramide are well-tolerated and effective in controlling emesis after the administration of cisplatin. Combinations of metoclopramide plus dexamethasone plus diphenhydramine are more efficacious and have fewer side effects than metoclopramide given alone in the doses and schedules tested.

These trials employed methodology similar to that used in the previous randomized studies at our institution.¹ All patients received the same dosage of cisplatin, were observed in the hospital, and had no previous exposure to either the antiemetic agents or cytotoxic chemotherapy. Cisplatin was chosen as the emesis-producing agent for study because of its widespread use, efficacy in combination in the treatment of several cancers,²²⁻²⁴ and the severity and predictability of the nausea and vomiting it produces (median, 10.5 vomiting episodes in 24 hours).^{1,23,25}

The trials designed to study varying doses and schedules of metoclopramide demonstrate that similar antiemetic efficacy can be achieved with a lower total dose of the drug and fewer administrations when the drug is given at a higher dosage (3 mg/kg). Although higher doses of metoclopramide as a single agent are generally well-tolerated, acute dystonic reactions appear to be somewhat more common.

The addition of dexamethasone at any of the tested doses and schedules improved both the complete and major antiemetic control rate despite a lowering of the total dose and number of metoclopramide doses. Moreover, the incidence of treatment-associated diarrhea was significantly decreased. No corticosteroid-related toxicity was seen. Since there was no clinically significant difference among the three regimens in either antiemetic efficacy or side effects, the simplest schedule of dexamethasone administration was chosen for subsequent combination trials: 20 mg intravenously 30 minutes before chemotherapy administration.

Trials have not shown diphenhydramine to be an active antiemetic when used alone. Although our studies adding diphenhydramine did not indicate greater antiemetic activity, there appeared to be a trend toward a decreased incidence of acute dystonic reactions. No acute dystonic reactions were seen in any of the combination trials; however, their incidence is low in the population studied. Even though no increased antiemetic activity was seen when diphenhydramine was added, the absence of increased side effects and the potential for decreasing extrapyramidal symptoms made this a suitable drug for inclusion in future combination trials using the most convenient dose and schedule: 50 mg intravenously 30 minutes before cisplatin.

Preclinical studies of metoclopramide have shown improved antiemetic efficacy against cisplatin at doses of 3 mg/kg when compared with 1 mg/kg.¹⁵ Trial C, using metoclopramide at 3 mg/kg for only two doses, gave comparable results to metoclopramide 2 mg/kg for five doses (Trial A). Based on this experience, a combination regimen using a higher dose and shorter administration schedule was studied. The results support the hypothesis that higher doses of metoclopramide in combination with other agents could further improve the control of vomiting. Others have correlated the degree of antiemetic control with the plasma level of metoclopramide and found improved effects in those patients with higher plasma levels of the drug.²⁶ In Trial J, the short-course regimen, antiemetic efficacy was improved when the regimen using metoclopramide at a dose of 3 mg/kg for two doses was compared with metoclopramide at 2 mg/kg, with or without the addition of dexamethasone and diphenhydramine. No increase in toxicity was noted, and no acute dystonic reactions were seen using the com-

ination. Moreover, this regimen can be administered in just over 2 hours, making it suitable for use in an outpatient setting. With a lower total dose of metoclopramide and a decreased number of drug infusions, the cost of administration will be decreased. The short-course regimen using metoclopramide at 3 mg/kg with dexamethasone and diphenhydramine has shown the highest antiemetic efficacy and fewest side effects of the combinations examined.

The results of these trials confirm the previously reported single-agent activity of metoclopramide and of dexamethasone and demonstrate the dose-antiemetic response relationship for metoclopramide when used in combination. These studies also support the hypothesis that the use of combinations of antiemetics with differing toxicities and mechanisms of action can improve the control of nausea and vomiting compared with a single agent. Combinations containing metoclopramide and dexamethasone have increased the number of patients experiencing no emesis or two or fewer episodes during the 24 hours after the administration of cisplatin. These combinations have also lowered the incidence of side effects caused by chemotherapy administration (diarrhea) and possibly by agents that are part of the antiemetic regimen (acute dystonic reactions caused by metoclopramide). The use of the best antiemetic combination has also permitted a shorter and less cumbersome schedule of administration that potentially allows better control of nausea and vomiting at a lower cost.

The conclusions of this report are the product of the comparison of the results of consecutive trials, each designed to use active antiemetic agents and combinations and define toxicities. These data are encouraging and support the initiation of randomized trials comparing these regimens against active single agents or against other active combinations of agents.

We conclude that the combination of high doses of intravenous metoclopramide, dexamethasone, and diphenhydramine is a safe and effective antiemetic regimen for patients receiving cisplatin chemotherapy. Using a simpler and shorter schedule of administration, the three drugs used together produce improved control of vomiting than that observed in earlier studies using only the single agents.

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