Antiemetic Control and Prevention of Side Effects of Anti-Cancer Therapy With Lorazepam or Diphenhydramine When Used in Combination With Metoclopramide Plus Dexamethasone

A Double-Blind, Randomized Trial

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Combinations of metoclopramide and dexamethasone given intravenously control vomiting caused by high doses of cisplatin. Lorazepam and diphenhydramine are useful adjuncts to antiemetics. In a double-blind trial, 120 patients receiving high-dose cisplatin (120 mg/m^2) for the first time were randomly assigned to receive either lorazepam (1.5 mg/m^2) or diphenhydramine (50 mg) intravenously, 45 minutes prior to cisplatin. In addition, all patients received intravenous dexamethasone (20 mg) 40 minutes prior to chemotherapy along with metoclopramide (3 mg/kg) 30 minutes before and 90 minutes after cisplatin. Patients were directly observed in the hospital after cisplatin administration and completed a subjective assessment questionnaire. Overall, 60% of patients experienced no vomiting, and 83% had two or fewer emetic episodes during the study. There were no significant differences in objective antiemetic control between the two regimens. Only 3% of patients receiving lorazepam experienced treatment-related restlessness as opposed to 19% given diphenhydramine ($P = 0.007$). Less recall of chemotherapy administration ($P < 0.001$), more sedation ($P = 0.003$), and transient enuresis while sedated ($P = 0.0002$) were characteristic of patients receiving lorazepam. Patient-generated ratings revealed less anxiety ($P = 0.0001$) for those individuals given the lorazepam-containing combination. Both regimens were well accepted, with 89% of patients receiving the lorazepam combination and 83% of those given the diphenhydramine regimen wishing to receive the same drugs in the future. Some degree of delayed vomiting occurred in 85% of patients during the 4-day period following this study. During the time that patients are at the greatest risk for emesis, the 24 hours immediately following cisplatin, three drug antiemetic combinations of either lorazepam or diphenhydramine with metoclopramide plus dexamethasone stopped cisplatin-induced emesis for the majority of patients and lessen other treatment-related side effects. Less restlessness and anxiety were observed among individuals receiving the lorazepam-containing combination.

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NAUSEA AND VOMITING after the administration of anti-cancer drugs remain important concerns for patients and medical personnel. Cisplatin, which is part of several potentially curative treatment programs,[1] produces a median of ten emetic episodes during the 24 hours after its administration[2] if appropriate antiemetic medications are not given. Even with the improved control of vomiting in recent years through the use of antiemetic drug programs, the apprehension and anxiety that accompany chemotherapy administration re-

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main difficult obstacles for patients with cancer. New therapies are necessary to further improve the control of emesis and the other side effects of both the chemotherapy and the antiemetic agents.

High doses of intravenous metoclopramide[2-7] and dexamethasone[8-10] have been shown to be safe and effective single agents for the control of vomiting caused by anti-cancer drugs. Improved antiemetic control, less severe side effects, and simpler drug administration have all been achieved when metoclopramide and dexamethasone were used in combination.[11-15] Diphenhydramine, although it has not been shown to be an effective single agent antiemetic in formal trials, has frequently been used as an adjunct to other antiemetic drugs. It is uniformly effective in controlling acute dystonic reactions caused by metoclopramide,[16] it may prevent such reactions in patients at higher risk for them,[17] and, hypothetically, may improve antiemetic control as it blocks histamine receptors in the brainstem emetic center.[18] When diphenhydramine was given with metoclopramide and dexamethasone in two previous consecutive trials in 58 patients, 86% had two or fewer emetic episodes; the majority did not vomit at all during the 24 hours following cisplatin administration.[12,19]

In an effort to further lessen vomiting and decrease patient anxiety, the benzodiazepine, lorazepam, has been given along with antiemetics. Several studies have found lorazepam to be a useful adjunct to other antiemetic drugs.[19-27] Trials using lorazepam as a single agent for the control of chemotherapy-induced emesis have been undertaken.[24,26,28] Although only limited antiemetic activity was observed, there were no major adverse effects, the drug was well accepted by patients, and was found to lessen the anxiety caused by anti-cancer chemotherapy. Two prior trials have shown that lorazepam given intravenously can be given safely with the combination of metoclopramide plus dexamethasone.[19,24] In earlier consecutive, nonrandomized studies,[24] three different dosages of lorazepam were given in addition to metoclopramide plus dexamethasone. Using visual analogue scales, the patients receiving lorazepam at 1.5 mg/m^2 reported more satisfaction, comfort, and sedation with less anxiety, nausea, and emesis than those receiving lower dosages of lorazepam or diphenhydramine instead of lorazepam when each was given in combination with metoclopramide plus dexamethasone.[19] The objective control of emesis was similar for all of these consecutive trials with 56% of patients experiencing neither vomiting nor "dry heaves" during the 24 hours following cisplatin administration.

This article details the results of a double-blind, random assignment trial comparing lorazepam given intravenously (1.5 mg/m^2) with diphenhydramine (50 mg) when each is used in combination with intravenous administration of metoclopramide plus dexamethasone given in an identical dosage on the same schedule. The doses of all the studied drugs were the best ones as determined in prior trials.[12,19] Since earlier studies suggested that the main differences between the two regimens would be in improved subjective benefit (such as patient satisfaction and reduced anxiety), visual analogue scales to measure these parameters were used in addition to objective measurements of antiemetic efficacy and side effects. The methods used for both objective and subjective efficacy have been described and tested.[2,7,12,19,29,33,34]

Patients and Methods

This double-blind, randomized trial was intended to assign 60 patients to each of two treatment regimens during an 18-month period. From August 1984 to October 1985, 122 patients with histologically confirmed cancer who consented to the conditions of the study were entered. Written informed consent was obtained from all participants after the nature of the study had been fully explained.

Only patients who had not received chemotherapy and who had a Karnofsky performance status of greater than 50% were eligible. As required for concurrent chemotherapy protocols, each patient had a leukocyte count greater than 4000 μ/l, a platelet count greater than 120,000 μ/l, serum creatinine less than 1.9 mg/dl and serum bilirubin less than 2.0 mg/dl. All patients were inpatients receiving cisplatin at a dose of 120 mg per square meter of body surface area in a 20-minute intravenous infusion. Cisplatin treatment followed vigorous intravenous hydration with mannitol diuresis as described.[2] All patients with non-small cell lung cancer also received vindesine (3 mg/m^2) or vinblastine (4 mg/m^2), agents that generally do not induce emesis.[30,31] Fifty percent of individuals were also given mitomycin, an agent rarely reported to cause severe vomiting.[32] No patient experienced nausea or vomiting of any etiology (including anticipatory vomiting) during the 24 hours preceding the study.

The treatment regimens tested are outlined in Figure 1. Patients were randomly assigned to receive either diphenhydramine or lorazepam 45 minutes prior to their initial dose of cisplatin. The randomization technique (using cards from a computer-generated list in sealed envelopes) and the preparation of the study medications were performed by a person not involved with the care or evaluation of the patient. Identical syringes with equal volumes containing either diphenhydramine or lorazepam were prepared to maintain the double-blind design. Neither the patient, nor the treating oncology research nurse, nor the physician, nor the floor staff

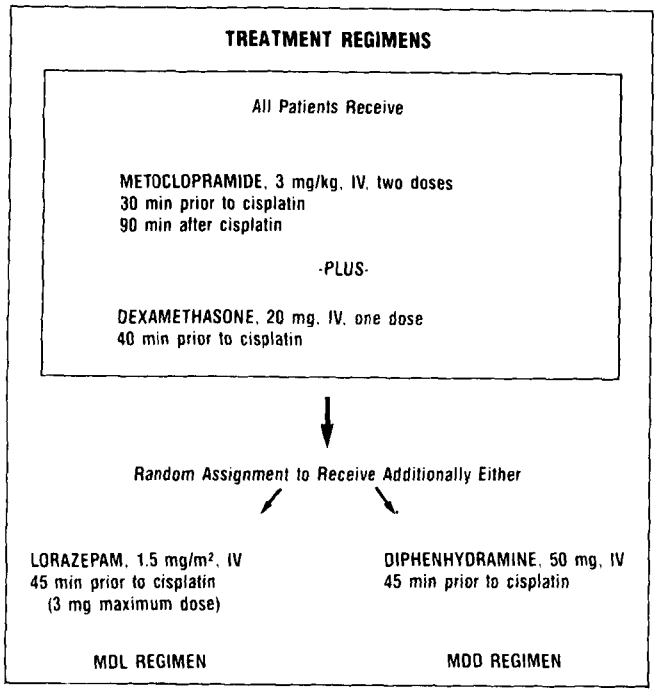

FIG. 1. Treatment regimens.

knew which medication was administered during the 24-hour study period. Diphenhydramine was given in a single 50-mg intravenous dose over 5 minutes, 45 minutes prior to cisplatin. Lorazepam (Ativan, Wyeth Laboratories, Philadelphia, Pa.), at a dose of 1.5 mg/m^2 (maximum dose, 3 mg), was also given by intravenous injection over 5 minutes, 45 minutes prior to cisplatin.

All patients received metoclopramide and dexamethasone intravenously. 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 minutes. Metoclopramide was given at a dose of 3 mg/kg for two doses, 30 minutes prior to and 90 minutes after cisplatin. Dexamethasone was given as an infusion over 5 minutes in a single, 20-mg intravenous dose 40 minutes prior to cisplatin.

Food or fluids by mouth were not allowed during the initial 12 hours of all trials; no other sedative or antiemetic drug was given 10 hours before the study or during the study. Patients who had antiemetic benefit were offered the same regimen during subsequent chemotherapy. In general, both antiemetic control and patient satisfaction were preserved during subsequent chemotherapy courses.

The number of episodes of emesis was recorded for each patient. Any vomiting that produced liquid was recorded as an emetic episode. In addition, one to five "dry heaves" (vomiting that did not produce liquid) within any 5-minute period were also counted as a single emetic episode. All patients were directly observed in the hospital after cisplatin administration. Side effects of the treatment were also directly observed and recorded. This included assessments of sedation, number of bowel movements, the occurrence of akathisia (restlessness), acute dystonic reactions, and disturbances of micturition. 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). Diarrhea was defined as greater than three loose bowel movements during the 24-hour observation period. Patients were awakened if necessary, and side effects were 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. Patients were asked whether or not they remembered receiving both their chemotherapy and an object shown to them at the time of cisplatin administration.

At the completion of the 24-hour study period, all patients gave their assessment of antiemetic control and side effects. By means of 100-mm visual analogue scales, patients indicated the degree of emesis, nausea, comfort, satisfaction, sleepiness, and anxiety they experienced. This instrument was shown to be feasible, reliable, and associated with acceptable convergent validity in prior trials among similar patients.[19,29,33] All patients were asked to recall the number of emetic episodes experienced and whetherthey wished to receive the same antiemetic therapy again if they received cisplatin-containing chemotherapy in the future.

Pearson's chi-square test or, where appropriate, Fisher's exact test, were used to compare the frequencies of the observations collected. To compare the results of the subjective assessments (visual analogue scale scores), a two-sample *t*-test was employed after the data were transformed by taking the arc sine of the square root of the score divided by 100. Hotelling's T2 test was used to screen for overall differences in the subjective assessments. To summarize the results, the medians of the visual analogue scale scores are provided in Table 1.[35] Associations between the subjective scores were summarized using Pearson's correlation coefficient, also using the transformed scores. *P*-values for the correlations were computed using the corresponding parametric test.

Sixty patients per regimen allowed us to estimate the difference in the proportions of the complete responses to the two antiemetic regimens such that if the two regimens were equivalent, then with probability 0.71 (0.86), the upper 90% confidence limit of the difference would not exceed 0.20 (0.25), and the lower 90% confidence limit would not exceed −0.20 (−0.25).[36] Sixty patients per arm yields a power of 0.90 for comparing the two

TABLE 1. Patient Subjective Evaluations of Antiemetic and Side Effects

	Metoclopramide + dexamethasone + diphenhydramine (n = 57)	Metoclopramide + dexamethasone + lorazepam (n = 63)
Median measurement of visual analogue scale scores (mm): 0 = the least; 100 = the most)		
Emesis	3	2
Nausea	5	4
Comfort	69	76
Satisfaction	93	93
Sleepiness	70	82*
Anxiety During Therapy	66	22*
Percent of patients who:		
Remember Chemotherapy Administration	98	51*
Remember an object shown at the time of chemotherapy	98	87*
Want the same antiemetic treatment with future chemotherapy	83	89

* $P < 0.05$.

regimens using a two-sided 0.05-level *t*-test for the transformed visual analogue scale scores, when the true mean difference between the arms exceeded 0.6 standard deviations. With the randomization results of 57 and 63 patients assigned to the two arms, the actual sensitivity was essentially the same as the planned one. Randomization was based on a permuted block design, the block size varying randomly from 2 to 4 to 6.

Results

One hundred and twenty-two individuals entered this trial; 120 patients completed the 24-hour study, yielding a 98% adequacy rate. One individual did not receive the prescribed study medications at the discretion of the treating physicians, and another refused to complete the visual analogue scales. The former inevaluable patient had six emetic episodes, and the latter had two. The characteristics of the 120 evaluable patients on the two study arms in this trial are displayed in Table 2. There were no significant differences in the patient characteristics of the two regimens. The majority of patients had non-small cell lung cancer and a good performance staus. Data on whether or not a patient had a history of a chronic high alcohol intake was available on only 39 individuals. Three of 16 patients receiving diphenhydramine and 13 of 23 given lorazepam had such a history.

Observed therapeutic results are shown in Table 3. Sixty-three percent of patients receiving lorazepam and 56% receiving diphenhydramine, each in combination

TABLE 2. Patient Characteristics

	Metoclopramide + dexamethasone + diphenhydramine (n = 57)	Metoclopramide + dexamethasone + lorazepam (n = 63)
Age: median (range)	54 (35–73)	56 (31–69)
	Percent of patients	
Sex: Male to female	67:33	65:35
Karnofsky performance status:		
80 + 90%	70	67
60 + 70%	30	33
Primary Site of Cancer		
Non-small cell lung	93	95
Other	7	5
Chemotherapy regimen		
Cisplatin* + vindesine or vinblastine	52	49
Cisplatin* + vindesine or vinblastine + mitomycin	48	51

* Cisplatin given at a dose of 120 mg/m^2 over 20 minutes in all cases.

with metoclopramide plus dexamethasone, experienced no vomiting or dry heaves during the 24-hour period following cisplatin administration ($P = 0.41$). Eighty-six percent of individuals given the lorazepam combination and 81% of those receiving the diphenhydramine-containing regimen experienced two or fewer emetic episodes ($P = 0.46$).

Observed side effects of therapy are presented in Table 3. The lorazepam-containing combination pro-

TABLE 3. Observed Antiemetic and Side Effects

	Metoclopramide + dexamethasone + diphenhydramine (n = 57)	Metoclopramide + dexamethasone + lorazepam (n = 63)
	Percent of patients	
0 emetic episodes (complete control)	56	63
0, 1 or 2 emetic episodes (major control)	81	86
Sedation		
None	23	0*
Mild	70	43*
Moderate	7	49*
Marked	0	8*
Diarrhea	9	13
Acute dystonic reactions	2	0
Akathisia (restlessness)	19	3*
Transient enuresis during forced hydration	0	14*
Delayed vomiting†	86	84
Cost to pharmacy for drugs for a 70-KG person	$53.64	$55.25

* $P < 0.05$.
† Data available on 88 patients.

duced more sedation ($P < 0.003$), which lasted from 2 to 6 hours. Only 8% of individuals, however, experienced marked sedation (disoriented when awakened). Three percent of patients receiving lorazepam with metoclopramide and dexamethasone experienced akathisia (restlessness) during the 24-hour study period in contrast to the 19% receiving diphenhydramine ($P = 0.007$). Nine patients (14%) who received lorazepam experienced transient enuresis while sedated and receiving intravenous hydration and mannitol-induced diuresis ($P = 0.003$). Seven of these nine individuals experienced moderate or marked sedation. There were no significant differences in the incidences of diarrhea (9% *versus* 13%, $P = 0.57$) or acute dystonic reactions (2% *versus* 0%, $P = 1.00$) as a result of the diphenhydramine- and lorazepam-containing regimens, respectively. The one acute dystonic reaction that did occur was noted in a patient who received the diphenhydramine combination. No orthostatic hypotension was observed.

The cost to the hospital pharmacy of the drugs needed to treat a 70-kg person was $53.64 for the diphenhydramine-containing regimen and $55.25 for the lorazepam-containing regimen.

Subjective evaluations of efficacy and adverse effects for the two regimens were obtained at the end of the 24-hour study period and are also presented in Table 1. Median visual analogue scale scores from individuals who received lorazepam in combination with metoclopramide and dexamethasone revealed less anxiety during therapy (22 *versus* 66; 100 = the most; $P = 0.0001$) and more sleepiness (82 *versus* 70; $P = 0.003$) than those who received diphenhydramine. There were no significant differences in median visual analogue scale scores between the lorazepam- and diphenhydramine-containing regimens for comfort (76 *versus* 69, $P = 0.26$), satisfaction (93 *versus* 93, $P = 0.90$), emesis (2 *versus* 3, $P = 0.51$), or nausea (4 *versus* 5, $P = 0.72$).

Fifty-one percent of individuals who received lorazepam remembered the actual administration of their chemotherapy as compared with 98% of patients who received diphenhydramine ($P < 0.001$). All but one patient who received diphenhydramine correctly recalled an object (a picture of a dog or a dollar bill) shown at the time of chemotherapy administration, while 87% of individuals given lorazepam were able to do so ($P = 0.03$). Eighty-nine percent of patients given lorazepam plus metoclopramide plus dexamethasone and 83% receiving the diphenhydramine combination wanted to receive the same antiemetic regimen the next time they received cisplatin ($P = 0.43$).

Ninety-eight percent of patients receiving lorazepam and 98% given diphenhydramine were able to recall whether or not they vomited at all ($P = 1.00$). Of those patients who did vomit, 74% of those receiving lorazepam and 72% receiving diphenhydramine were able to exactly recall the number of emetic episodes they experienced ($P = 1.00$). The percentage of patients having no emesis (60% *versus* 59%, $P = 0.93$) or two or fewer emetic episodes (84% *versus* 82%, $P = 0.71$) were similar whether patients did or did not remember receiving chemotherapy. Visual analogue scores for comfort and satisfaction were also similar for patients who did and did not remember receiving chemotherapy ($P = 0.09$ and 0.50, respectively).

The degree of sleepiness reported did not correlate with the patient-generated assessments of nausea ($r = 0.05$, $P = 0.31$), vomiting ($r = 0.10$, $P = 0.24$), or satisfaction ($r = 0.15$, $P = 0.17$). For all patients in the study, satisfaction was strongly associated with the subjective assessments of nausea ($r = -0.48$, $P = 0.001$) and vomiting ($r = -0.48$, $P = 0.001$). As an additional test of the validity of the patient-generated visual analogue scales, we looked for an acceptable correlation between the vomiting scores and observed number of emetic episodes (Spearman rank correlation = 0.82, $P < 0.001$), and between the sleepiness scores and the ratings made on the sedation scale by observers (Spearman rank correlation coefficient = 0.28, $P = 0.002$).

Although not a specific aim of this study, after the 24-hour observation period was completed, we looked for any vomiting during the 4 days following the study to determine whether or not delayed emesis occurred. Observations were based on methods previously described.[29,34] Such information was available from 88 patients. The majority of patients experienced some vomiting during the 4 days following the 24-hour, in-hospital observation period. The percentage of patients experiencing delayed emesis was greatest from 48 to 72 hours following cisplatin administration. Overall, the incidence of delayed vomiting did not differ significantly in the lorazepam- and diphenhydramine-containing combinations (84% *versus* 86%, $P = 0.76$). Delayed nausea and vomiting did not effect the patient's desire to receive the same, three-drug antiemetic regimen for the control of acute emesis with subsequent cisplatin courses.

Discussion

The results of this trial confirm that antiemetic combinations containing high doses of intravenous metoclopramide and dexamethasone are well tolerated and effective in controlling vomiting during the 24 hours following cisplatin. The majority of patients given these drugs on an appropriate dose and schedule on the day of cisplatin treatment experience no vomiting. Additional antiemetic therapy, however, is necessary to control delayed vomiting, which occurs 24 or more hours after cisplatin is administered in most patients not specifically

treated for this condition. The use of antiemetic combinations has also allowed easier administration, produced less sedation, and has been associated with fewer cases of diarrhea.[12] Furthermore, this study also confirms the high patient acceptance and the safety of both lorazepam and diphenhydramine when each is used in combination with other antiemetics.

This trial employed previously established methods for both the subjective and the objective assessment of antiemetic efficacy and side effects.[2,7,12,19,29] All patients received the same dosage of cisplatin, were directly observed in the hospital, and had no previous exposure to either 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,[1] and the severity and predictability of its associated nausea and vomiting (median, 10.5 vomiting episodes in 24 hours).[2]

The major advantage demonstrated in this study was the improvement in subjective parameters observed with the metoclopramide plus dexamethasone plus lorazepam combination. A significant reduction in restlessness (akathisia), an adverse and bothersome effect of the metoclopramide plus dexamethasone combination, was experienced by patients who received lorazepam. Additionally, less anxiety during therapy was reported by patients who received the lorazepam-containing regimen. The proportion of individuals experiencing no emetic episodes, or two or fewer episodes was similar. This was an expected finding since both lorazepam and diphenhydramine have demonstrated only limited single-agent antiemetic activity;[24,28] prior trials of either drug used with metoclopramide and dexamethasone have shown objective antiemetic effectiveness similar to the two-drug combination of metoclopramide plus dexamethasone.[12,19] The observed percentages of patients having no emesis or two or fewer emetic episodes were similar to those obtained in previous, nonrandomized trials of both regimens at our institution.

Overall, both regimens were well tolerated and no serious side effects were observed. Although sedation was greater and more common in patients who received the lorazepam-containing combination, it did not interfere with medical care or patient comfort. No clinically apparent respiratory depression was observed in this group of patients with lung cancer and chronic obstructive pulmonary disease. The transient enuresis during forced diuresis observed only in lorazepam-treated patients appears to be related to the degree of sedation experienced. This problem resolved completely as sedation lessened, did not affect patient satisfaction with the regimen, and probably can be further reduced by asking the patient more frequently to urinate. As expected, fewer patients who received lorazepam (an agent with dose-related amnestic effects) recalled the actual administration of chemotherapy. Overall, both regimens were well accepted by the individuals treated, as evidenced by the fact that 86% of patients wanted to receive the same antiemetic treatment with future chemotherapy.

In an attempt to define the specific effects of the antiemetic regimens that affect patient comfort and satisfaction, these parameters were correlated with sleepiness, nausea, and emesis. Both patient comfort and satisfaction were significantly affected by the amount of nausea and emesis (both subjectively and objectively measured) experienced, but were not affected by the degree of sedation observed. There was no correlation between the sleepiness and nausea or vomiting scores. Importantly, these data suggest that overall patient comfort depends on the actual degree of objective antiemetic control achieved and not on the degree of sedation.

What is the contribution of memory loss to the overall effectiveness of these antiemetic regimens? The objective control of emesis as directly observed in this trial was unaffected by whether or not a patient could remember the administration of chemotherapy or an object shown at the time of chemotherapy. Of 120 patients, 118 (98%) correctly knew whether or not they vomited at all when questioned at the end of the study period. Among the patients who vomited, 73% knew the exact number of emetic episodes. The ability to recall the occurrence and number of emetic episodes was similar among patients receiving either diphenhydramine or lorazepam. The subjective measures of patient comfort and satisfaction were not correlated with the degree of memory impairment. Although amnesia is a prominent effect of lorazepam at the doses administered in this trial, it did not affect emetic control, the patient's ability to recall the occurrence of vomiting, or subjective assessments of comfort and satisfaction.

As mentioned, estimates of the frequency of delayed vomiting were obtained. As in our prior experience with metoclopramide plus dexamethasone plus either lorazepam or diphenhydramine,[19,29] the majority of patients experienced some vomiting from 24 to 120 hours after cisplatin administration. Those patients with complete emetic control on the day of cisplatin experienced significantly less delayed emesis as well. The severity of delayed vomiting (median, up to two emetic episodes during a 24-hour period)[29] is much less than that experienced during the initial 24 hours following cisplatin administration if no antiemetics are given (median, 10.5).[2] Nevertheless, the occurrence of any emesis lessens patient comfort. Several preliminary reports suggest that delayed emesis can be decreased through the use of available antiemetic drugs.[34,37,38] In a recent, random, placebo-controlled trial, use of the combination of oral metoclopramide and dexamethasone resulted in

less delayed vomiting compared with dexamethasone alone or placebo.[39]

The three drug combinations of lorazepam plus metoclopramide plus dexamethasone, and of diphenhydramine plus metoclopramide plus dexamethasone, control cisplatin-induced emesis, have manageable side effects, and are highly acceptable to patients. Patients who received the lorazepam-containing regimen demonstrated less anxiety during therapy and less restlessness (akathisia) than those who were given diphenhydramine. With the demonstration of significantly improved subjective efficacy, the three-drug combination of lorazepam plus metoclopramide and dexamethasone, using the doses and schedule described, is the preferred regimen for patients receiving high-dose cisplatin.

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