Comparison of the Efficacy, Safety, and Pharmacokinetics of Controlled Release and Immediate Release Metoclopramide for the Management of Chronic Nausea in Patients with Advanced Cancer

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Background. **The short elimination half-life of metoclopramide necessitates frequent administration for optimal relief of nausea. This study compares a newly developed controlled release preparation of metoclopramide (CRM) and immediate release metoclopramide (IRM) with respect to efficacy, safety, and pharmacokinetics in patients with chronic nausea associated with advanced cancer.**

Methods. **Thirty-four patients with advanced cancer with nausea lasting more than 1 month and with no evidence of involvement of the gastrointestinal tract, peptic ulcer or gastritis, brain metastases, or metabolic abnormalities were randomized, in a double-blind cross-over study, to receive 40 mg of CRM every 12 hours or 20 mg of IRM every 6 hours for 3 days. Nausea, food intake, and side effects were assessed four times daily. On Day 3, sequential venous samples were taken (12 patients) to determine plasma metoclopramide concentrations.**

Results. **In 29 evaluable patients, the intensity of nausea on Day 3, measured by a 0–100-mm visual analogue scale and 0–3 categoric scale was 15 ± 17 and 0.6 ± 0.6 after IRM, versus 8 ± 9 ($P = 0.033$) and 0.4 ± 0.5 ($P = 0.055$) after CRM, respectively. Visual analogue scale nausea scores recorded by time of day and by day for the 3 treatment days were significantly lower for patients who received CRM compared with those who received IRM ($P = 0.047$ and $P = 0.043$, respectively), but categoric nausea scores were not significantly different between treatments by time of day and by day across the 3 treatment days. No differences were observed in caloric intake or side effects between treatments. In a pharmacokinetic analysis, the CRM/IRM ratio for area under the curve$_{0-12}$ ($\mu g \times$ hours $\times L^{-1}$), C_{max} ($\mu g/L$), and T_{max} (hours) was 100%, 98%, and 2.3 fold, respectively.**

Conclusion. **Controlled release metoclopramide is safe and effective in managing chronic nausea in patients with advanced cancer. Future studies should focus on characterizing this syndrome more clearly and on determining the optimal dose of metoclopramide and the effects of drug combinations that have proven to be useful in managing chemotherapy-induced emesis (i.e., metoclopramide plus corticosteroids). *Cancer* 1994;74:3204–11.**

Key words: Metoclopramide, controlled release, chronic nausea, vomiting, dyspepsia, supportive care, advanced cancer, drug treatment, antiemetic, antinauseant.

Chronic nausea is a frequent symptom in patients with advanced cancer, with a prevalence of 32–68%.[1–4] In a recent survey of 100 consecutive admissions to the Edmonton General Hospital Palliative Care Unit (Edmonton, Alberta, Canada), 98% required antiemetic therapy for chronic nausea before death (Unpublished data, Bruera E, 1994). Although chronic nausea usually is described as a multicausal syndrome, opioid treatment[5,6] and autonomic failure[7,8] have been associated with chronic nausea in advanced cancer. This syndrome has been shown to improve after the administration of metoclopramide in uncontrolled studies.[9–11] Because of the short half-life and duration of action of this drug,[12–16] however, some patients require frequent administration or continuous infusion[9] for optimal results. The need for frequent administration is particularly uncomfortable for patients managed in the community.

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The purpose of this prospective, double-blind crossover study was to compare a newly developed controlled release preparation of metoclopramide with immediate release metoclopramide in patients with chronic nausea associated with advanced cancer.

Methods

A total of 34 patients with chronic nausea caused by advanced cancer were enrolled in the study. All patients were adults with histologically confirmed advanced cancer (defined as locally recurrent or metastatic) with no involvement of the gastrointestinal tract and no clinical evidence of peptic ulcer or gastritis, brain metastasis, or metabolic abnormalities (hypercalcemia or uremia) that could explain their chronic nausea. Seven patients had a history of primary gastrointestinal malignancy and metastatic disease with no evidence of local recurrence. Patients receiving opioid analgesics were eligible for inclusion.

Chronic nausea was defined as nausea lasting more than 1 month, and its intensity was documented on a visual analog scale before entry into the study was allowed. Patients with a documented history of nausea in the period immediately before the study were eligible for randomization to active treatment. The study protocol and informed consent form were approved by an institutional review board, and all patients provided written informed consent before they began participation in the study.

Exclusion criteria included the presence of diabetes, Parkinson's disease, extrapyramidal disorders, pheochromocytoma, concomitant chemotherapy or radiation therapy, pregnancy, or demonstrated hypersensitivity to metoclopramide or other benzamide derivatives.

Eligible patients were assigned randomly to receive controlled release metoclopramide (40 mg every 12 hours) or immediate release metoclopramide (Maxeran, Nordic Merrell Dow, Laval, Quebec) (20 mg every 6 hours). Each treatment was given for a period of 3 days. Patients who were considered unable to tolerate a daily metoclopramide dose of 80 mg could be given 40 mg per day (two patients). At the completion of Phase One, patients proceeded directly to the alternate treatment in Phase Two, without an intervening washout. Breakthrough nausea was treated with rescue dimenhydrinate or prochlorperazine, and its use was recorded at the time of administration. Blindness was maintained by the double-dummy technique, which employs placebos for both controlled release and immediate release metoclopramide.

During the baseline period and during each of the two treatment phases, the following assessments were made:

1. Nausea was assessed in two ways at 800 hours, 1400 hours, and 2000 hours, coinciding with doses of controlled release metoclopramide (800 hours and 2000 hours) and immediate release metoclopramide (800 hours, 1400 hours, and 2000 hours) using: (1) a categoric scale of: 0 denoting an absence of symptoms, 1 denoting mild symptoms (present but not bothersome), 2 denoting moderate symptoms (bothersome, interferes with activity and appetite), and 3 denoting severe symptoms (debilitating, patient was bedridden); (2) a 100-mm visual analog scale anchored with the terms "no nausea" and "extremely severe nausea". An episode of vomiting was defined as one time period, (e.g., 5 minutes) when constriction of abdominal musculature with or without emesis occurred. The number of vomiting or retching episodes per day was scored according to the following scale: 0 indicating no vomiting, 1 indicating 1 to 2 episodes, 2 indicating 3–5 episodes, 3 indicating 6–10 episodes, and 4 indicating 11 or more episodes).
2. Food intake was recorded as the percentage of breakfast, lunch, and supper eaten by the patient. Patients were provided with menus for which caloric content was known, and they were asked to repeat the identical menu for all the meals and snacks during the day on Day 3 of each treatment phase. They also were asked to record as a percentage all the solid and liquid intake received for the 24-hour period. This procedure has been validated previously by our group.[17,18]
3. A checklist was used to record adverse effects at the time of nausea assessment. The checklist consisted of the following items, which were scored on a four-point scale (absent, mild, moderate, severe): drowsiness, dizziness, restlessness, tiredness, headache, diarrhea, and constipation. Spontaneously reported adverse effects also were recorded.
4. Twelve patients underwent sequential venous sampling for plasma metoclopramide concentrations on the final day of each phase. Blood samples were obtained before the morning dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, and 12 hours postdose. Plasma metoclopramide concentrations were determined by a modification of a previously published sensitive and specific high-pressure liquid chromatographic method.[19,20] The lower limit of quantitation was 15 μg/l, the assay was linear up to concentrations of 1000 μg/l, and the coefficient of variation was 2–6%.

On completion of Phase Two, patients were provided the option of receiving ongoing, open-label treatment with controlled release metoclopramide or immediate release metoclopramide for an additional period

Table 1. Characteristics of Evaluable Patients

Characteristic	No.
No.	29
Female/male	13/16
Age (yr)*	65 ± 10
Duration of nausea (mo)*	4 ±4
Patients receiving opioid analgesia	83%
Primary tumor	
Breast	6
Lung	6
Prostate	5
Colon	3
Rectum	2
Ovary	2
Pancreas	2
Scrotum	1
Unknown	2
Total	29

* Mean ± standard deviation.

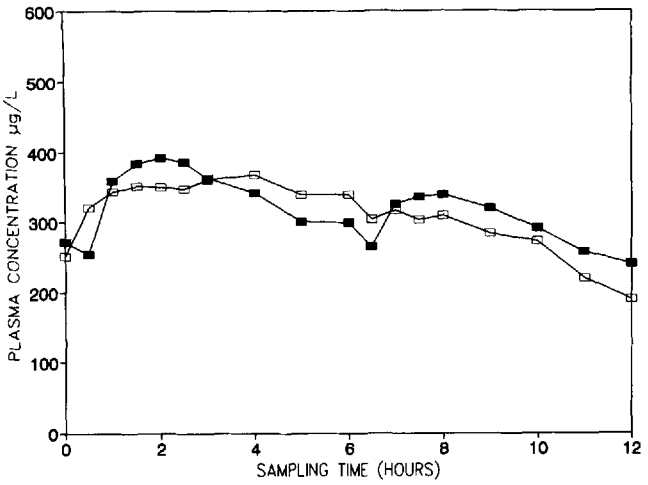

Figure 1. Comparison of the steady-state plasma metoclopramide concentration–time profile after administration of controlled release metoclopramide (40 mg every 12 hours) (open box) and immediate release metoclopramide (20 mg four times a day) (closed box).

of 2 weeks. During this period, the clinical effectiveness and safety of treatment was assessed periodically, and the dosage was adjusted to maintain satisfactory control of nausea.

Pharmacokinetic Analysis

Plasma concentrations of metoclopramide (in µg/l) were dose-adjusted for the amount of drug given per day and for the metoclopramide base content of the two dosage forms. Peak plasma concentration (C_{max}) and time of peak concentration (T_{max}) were determined by visual inspection of the plasma concentration–time profile. The area under the plasma concentration–time curve (AUC) over 12 hours (AUC_{0-12}) was calculated by the trapezoidal method. For statistical analysis, AUC and C_{max} data were log transformed and were compared by treatment using three-way analysis of variance.[21,22] The mean T_{max} values were compared similarly by treatment, without prior log transformation. The relative AUC_{0-12} and C_{max} values were computed with least-square means of log-transformed data. The mean square error term from the analysis of variance was used to compute 90% confidence intervals.

Efficacy Analysis

The primary comparison between treatments was made with the data from the last day of each phase to minimize any carryover effects. Data was averaged across all time points on Day 3 of each phase, and this average was tested for treatment effect using three-way analysis of variance. The nausea scores on Days 1, 2, and 3 also were tested by multivariate analysis of variance for repeated measures to detect differences between times of assessment, day of therapy, and treatments (controlled release versus immediate release metoclopramide). Two analyses were performed: (1) data were averaged across days by each time, patient, and treatment combination, and the factors treatment, time, and time by treatment interaction were tested for significance; and (2) data

Table 2. Summary of Pharmacokinetic Parameters*

Parameter	Immediate-release metoclopramide	Controlled-release metoclopramide	Ratio†	Significance
AUC_{0-12} ($\mu \cdot h \cdot L^{-1}$)	3627 ± 1670	3552 ± 1534	100 (83–119%)	$P = 0.9623$
C_{max} (µg/L)	440 ± 186	423 ± 158	98 (86–112%)	$p = 0.7875$
T_{max} (h)	1.4 ± 0.8	3.2 ± 2.7	2.3	$P = 0.0652$

AUC_{0-12}, area under the steady-state plasma metoclopramide concentration-time curve for 0–12 hours after dose; C_{max}; peak plasma concentration; T_{max}, time to reach C_{max}.

* Data expressed as mean ± standard deviation. Data in parentheses represent 90% confidence interval.

† Ratio of test (controlled-release) to reference (immediate-release) metoclopramide.

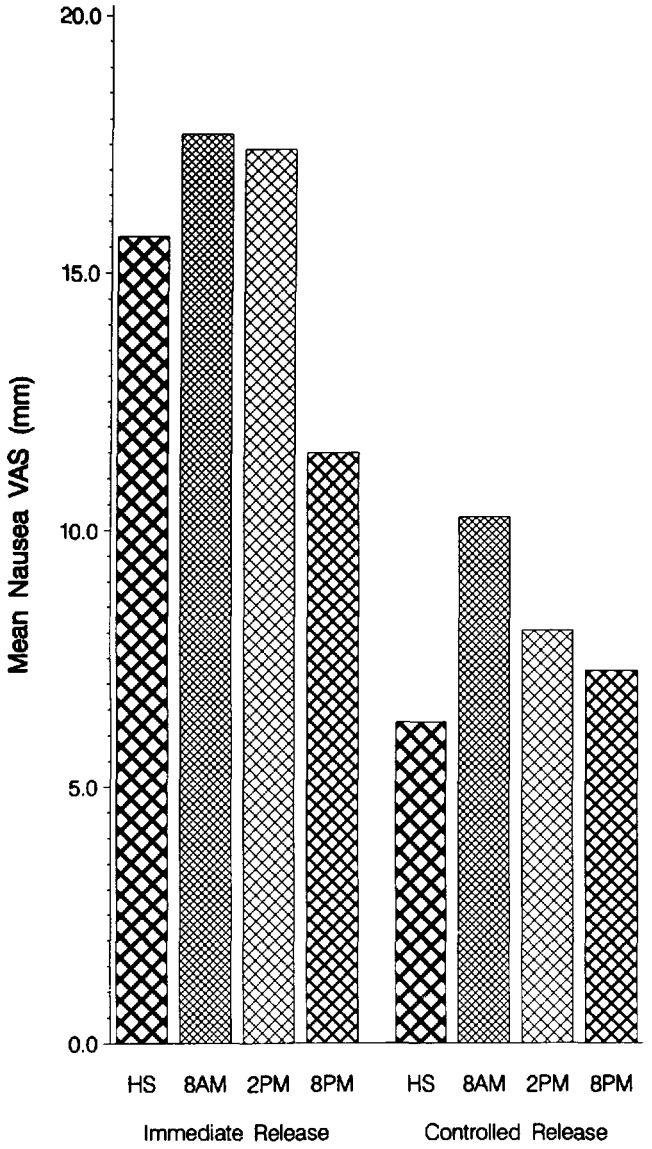

Figure 2. Comparison of the mean Day 3 nausea visual analogue scale scores after the administration of controlled release metoclopramide (right panel) and immediate release metoclopramide (left panel).

were averaged across time by each day, patient, and treatment combination and the factors treatment, day, and day by treatment interaction were tested for significance. Assessment of treatment effect on vomiting and caloric intake was made with a three-way analysis of variance. The average daily rescue antiemetic consumption was compared with a paired Student's *t* test. Patient preference was analyzed by Fisher's exact test.

Results

Approximately 60 patients were screened for participation in the study, and 34 patients enrolled, with 29 completing both phases of the study. Twelve patients participated in the pharmacokinetic component of the study. Reasons for failure to complete the study included intercurrent illness (one patient), inadequate control of nausea (one patient), revocation of consent (one patient), confusion (one patient), and complexity of medication regimen (one patient). Twenty-six patients previously had received at least one course of treatment for chronic nausea with metoclopramide, 14 had received dimenhydrinate, and 2 patients had received prochlorperazine. Characteristics of the 29 evaluable patients are summarized in Table 1.

Figure 1 shows the mean plasma concentration–time profile for controlled release and immediate release metoclopramide, and Table 2 shows the mean AUC_{0-12}, C_{max}, and T_{max} values by treatment for the 12 patients who completed the pharmacokinetic evaluation. No significant differences were observed between the two formulations with respect to AUC or C_{max}. Consistent with its controlled release characteristics, T_{max} for controlled release metoclopramide was 2.3 times longer than that of the immediate release formulation (P = 0.0652).

Figure 2 presents the overall mean nausea visual analogue scale (VAS) scores on Day 3 of each treatment, and as shown in Table 3, the severity of nausea was less on controlled release metoclopramide than on immediate release metoclopramide (P = 0.033). There were no significant differences between treatments for vomiting score, use of rescue antiemetics, or food intake. When analyzed both by time of day and by day across the three treatment days, the intensity of nausea on the visual analog scale was significantly less on controlled release metoclopramide when compared with immediate release metoclopramide (P = 0.047 and 0.043, respectively) (Table 4).

Figure 3 presents the overall mean categoric nausea scores on Day 3 of each treatment, and as shown in Table 3, there was a trend toward statistical significance in favor of controlled release metoclopramide when compared with immediate release metoclopramide (P = 0.055). When analyzed both by time of day and by day across the three treatment days, the intensity of nausea on the categoric scale for controlled release metoclopramide was not significantly different than that for immediate release metoclopramide (P = 0.124 and P = 0.133, respectively) (Table 4).

Table 5 summarizes adverse experiences during the clinical trial, which were not significantly different between the two treatment groups. One patient developed a moderate tremor during both treatments. In no case was it necessary to discontinue treatment or reduce the dose because of toxicity, although two patients with a previous history of extrapyramidal side effects with

Table 3. Summary of Clinical Efficacy Scores for Day 3*

Variable	Immediate-release metoclopramide	Controlled-release metoclopramide	*P*
Nausea intensity (0–100 mm VAS)	15 ± 17	8 ± 9	0.033
Nausea intensity (0–3 categoric)	0.6 ± 0.6	0.4 ± 0.5	0.055
Vomiting score (0–4 categoric)	0.2 ± 0.3	0.1 ± 0.3	0.117
Caloric intake (kcal/day)	1024 ± 558	1001 ± 430	0.7188
Frequency of rescue antiemetic (doses/day)	0.69 ± 1.0	0.66 ± 12	0.906

* VAS: visual analog scale.
Data expressed as mean ± standard deviation.

metoclopramide were entered successfully into the trial on the 40-mg-per-day regimen.

On completion of the two phases of the study, 27 patients completed the treatment preference questionnaire. Seven patients blindly expressed preference for the phase in which they received controlled release metoclopramide, 3 patients chose immediate release metoclopramide, and 17 patients expressed no preference ($P = 0.59$, Fisher's exact test). To explore further the nature of patient preference, the relationship between mean VAS nausea score and patient preference was examined. Patients who expressed a treatment preference had scores that were twice as high as those who expressed no preference (16.3 mm vs. 8.1 mm; $P = 0.03$). Patients who preferred controlled release metoclopramide scored 31.3 mm on the VAS for nausea during the immediate release phase, versus 9.9 mm during the controlled release phase ($P = 0.016$). Patients who expressed no treatment preference had nausea VAS scores of 9.2 mm vs. 7.9 mm ($P = 0.75$) on immediate release and controlled release metoclopramide, respectively.

Of the 29 patients who completed the study, 25 participated to some extent in the open-label phase, and 16 patients completed the 2-week open-label evaluation period. Twenty-one patients received controlled release metoclopramide, and four patients received immediate release metoclopramide. Adverse experiences during the open-label phase were similar in nature and severity to those reported in the double-blind phase of the clinical trial. The mean VAS nausea score during open-label treatment with controlled release metoclopramide (10.8 mm) was consistent with that reported during the double-blind evaluation.

Discussion

Chronic nausea is a frequent and distressing symptom of advanced cancer.[1–4] Although chemotherapy-induced emesis has been evaluated extensive,[23] chronic nausea associated with advanced cancer has received very limited attention.

The efficacy of orally administered metoclopramide in treating delayed gastric emptying in patients who do

Table 4. Nausea Scores by Day and Time of Day*

	Controlled-release metoclopramide				Immediate-release metoclopramide			
Scale	***Day 1***	***Day 2***	***Day 3***		***Day 1***	***Day 2***	***Day 3***	
VAS†	8.5 ± 10.3	11.3 ± 11.4	7.8 ± 9.4		12.6 ± 12.1	12.3 ± 13.2	15.2 ± 16.9	
CAT‡	0.4 ± 0.5	0.5 ± 0.5	0.4 ± 0.5		0.5 ± 0.5	0.5 ± 0.6	0.6 ± 0.6	
	Time							
	8:00	***14:00***	***20:00***	***HS***	***8:00***	***14:00***	***20:00***	***HS***
VAS	9.6 ± 10.4	9.6 ± 11.2	9.4 ± 13.6	8.4 ± 7.7	13.4 ± 16.4	15.4 ± 17.4	13.9 ± 13.1	10.0 ± 9.7
CAT‡	0.5 ± 0.5	0.4 ± 0.5	0.5 ± 0.6	0.4 ± 0.4	0.6 ± 0.7	0.7 ± 0.7	0.6 ± 0.6	0.4 ± 0.5

VAS: visual analog scale; CAT: categoric scale; HS: bedtime.
* Data expressed as mean ± standard deviation.
† Significant differences between treatments for VAS nausea scores by day ($P = 0.043$) and time of day ($P = 0.047$).
‡ Nonsignificant differences between treatments for categoric nausea scores by day ($P = 0.133$) and time of day ($P = 0.124$).

not have has been established in a number of controlled clinical trials.[24–28] Metoclopramide also has demonstrated efficacy in reversing tumor-associated gastroparesis [10,29,30] and, in uncontrolled comparisons, anorexia and nausea associated with advanced cancer.[9,11]

Our results suggest that controlled release metoclopramide was able to reduce the intensity of nausea significantly more than immediate release metoclopramide. The Day 3 nausea scores on the visual analog scale were significantly lower in the controlled release metoclopramide phase, with a trend toward statistical significance on the categoric scale ($P = 0.055$). When assessed over the 3-day treatment period, VAS but not categoric nausea scores were significantly lower by day and by time of day on controlled release metoclopramide compared with immediate release metoclopramide. Failure to detect significant differences in nausea scores with the categoric scale suggest that the four-point scale used in the present study was not as sensitive as the VAS.

Table 5. Mean Adverse Effect Intensity*†

Adverse effect	Controlled-release metoclopramide	Immediate-release metoclopramide	Significance level
Drowsiness	1.2 ± 0.9	1.3 ± 0.9	NS
Dizziness	0.5 ± 0.7	0.5 ± 0.6	NS
Restlessness	0.6 ± 0.8	0.6 ± 0.7	NS
Tiredness	1.3 ± 0.9	1.3 ± 0.9	NS
Headache	0.1 ± 0.3	0.1 ± 0.5	NS
Diarrhea	0.2 ± 0.6	0.3 ± 0.8	NS
Constipation	0.4 ± 0.8	0.6 ± 0.9	NS

NS: not significant.
* Defined as 0 = none, 1 = mild, 2 = moderate, 3 = severe.
† Data expressed as mean ± standard deviation.

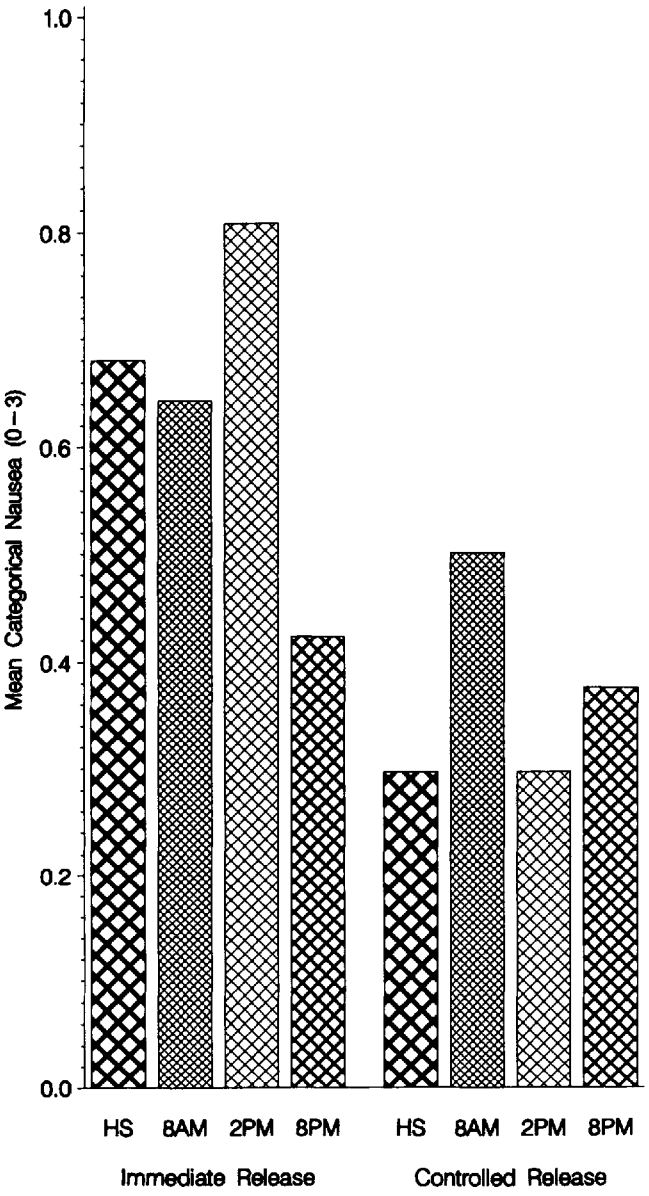

Figure 3. Comparison of the mean Day 3 categoric nausea scores after administration of controlled release metoclopramide (right panel) and immediate release metoclopramide (left panel).

There was no difference in patients' blinded preference for treatment with immediate or controlled release metoclopramide (17 patients indicated no preference). This may reflect a good level of nausea control achieved with both treatments. It is noteworthy, however, that 7 patients who expressed a preference for controlled release metoclopramide had a significantly higher level of nausea while receiving immediate release metoclopramide than while receiving controlled release metoclopramide. In addition, the nausea score of this subgroup while receiving immediate release metoclopramide (31 mm) was higher than that of the total group of patients during the same phase (15 mm). This suggests that differences in nausea scores of this magnitude are perceived by patients as clinically meaningful. Because the choice was blinded by use of matching placebos, the potential advantage of a 12-hourly dosing frequency for controlled release metoclopramide could not be evaluated fully in the present study. As patients with advanced cancer frequently are elderly and usually are receiving multiple medications, less frequent administration probably would reduce the possibility of medication errors and make home management easier.

A significant number of patients with cancer receive opioid analgesics, whose contributory role in cancer-associated dyspepsia cannot be discounted easily. Three possible mechanisms for opioid associated nausea have been postulated—vestibular stimulation,[31–36] delayed gastric emptying,[5,37] and direct stimulation of the chemoreceptor trigger zone located in the area postrema.[38–40] The area postrema appears to have one of the highest densities of opioid receptors.[41–44] The presence

of opioid receptors in the area postrema is consistent with the observation of morphine- and enkephalin-induced emesis in the dog after local or systemic administration, the later responses being abolished by ablation of the area postrema.[45,46] Morphine and related μ-agonists also have appreciable affinity for lambda and kappa receptors.[47,48] Opioid agonist stimulation of lambda receptors (which is not antagonized by naloxone) can cause the release of dopamine, suggesting that at least some of the emetic effects of opioids are mediated by dopaminergic neurons.[49]

Metoclopramide is a benzamide derivative that demonstrates marked D_2-receptor antagonism[48] and weak antagonism at the 5-HT_3 receptor.[50,51] In addition to its local effects in the gastrointestinal tract, metoclopramide demonstrates potent antiemetic properties through antagonism of D_2 receptors in the chemoreceptor trigger zone located in the area postrema.[15,50] At high doses, metoclopramide produces 5-HT_3 receptor blockade, which may contribute to its antiemetic activity.[15,51–53] Metoclopramide also has been found to be highly effective in treating meperidine- and morphine-associated postoperative nausea and vomiting.[12,15] These pharmacologic effects of metoclopramide provide a rational basis for its use in chronic nausea associated with advanced cancer.

Unfortunately, the short elimination half-life of metoclopramide necessitates frequent administration to provide optimal relief of nausea. Consequently, in evaluations of metoclopramide for postoperative nausea and vomiting, the timing of dose has been demonstrated to be perhaps the single most important factor in determining outcome. The short duration of action of metoclopramide in clinical trials[12–14] supports the view that sustained plasma metoclopramide concentrations are required to suppress nausea, vomiting, and possibly other gastrointestinal symptoms associated with advanced cancer. Preliminary data suggest that continuous subcutaneous infusion of metoclopramide is superior to intermittent administration for the management of chronic nausea in advanced cancer.[9] Our pharmacokinetic results demonstrate that controlled release metoclopramide provides sustained blood levels when administered every 12 hours, thereby reducing the need for more frequent dosing by the oral route or administration by continuous subcutaneous infusion.

Although metoclopramide is generally well tolerated, serious extrapyramidal reactions have been reported, particularly in younger patients.[48] In the present study, no serious adverse drug reactions were observed, and there were no significant differences in adverse effects between the controlled and immediate release metoclopramide formulations. The experience of patients during the open-label phase provides further support for the safety and effectiveness of controlled release metoclopramide in treating chronic nausea associated with advanced cancer. Patients who are unable to swallow intact tablets are not candidates for controlled release medications, because crushing of tablets may result in a bolus drug effect.

We conclude that the controlled release dosing of metoclopramide is safe and effective in the management of chronic nausea of cancer. Future studies should focus on a better characterization of this syndrome, evaluation of the efficacy of other antiemetics, determination of the optimal dose of metoclopramide, and assessment of the efficacy of drug combinations that have proven to be successful in the management of chemotherapy-induced emesis (i.e., metoclopramide plus corticosteroids).

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