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Examination of the correlation of serum metoclopramide levels with antiemetic efficacy in patients receiving cisplatin

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Summary. The existence of a threshold serum metoclopramide level above which total protection from cisplatin-induced vomiting is more likely to occur has been proposed. We monitored serum metoclopramide levels prior to the third metoclopramide dose in the first cisplatin treatment cycle in patients receiving metoclopramide 2 mg/kg ×4 as part of a randomized double-blind crossover study comparing single-agent metoclopramide with combination metoclopramide and dexamethasone. Serum samples from 35 patients (17 receiving single-agent metoclopramide and 18 receiving the combination) were analyzed using reverse-phase high-pressure liquid chromatography (HPLC). A wide variation in metoclopramide levels was observed (range 273–3380 ng/ml). Serum levels obtained from the same patient on multiple treatment cycles were well correlated, and the addition of dexamethasone did not alter serum metoclopramide levels. No threshold level could be identified for the two groups (single-agent or combination antiemetic therapy) considered individually or considered together. However, significantly more vomiting episodes and a lower incidence of total protection were noted in patients with metoclopramide levels above 1469 ng/ml receiving metoclopramide alone. This effect was nullified in the combination antiemetic group. Our data do not support a directly proportional relationship between serum metoclopramide level and antiemetic protection. However, a non-linear relationship with a possible agonist/antagonist effect is suggested.

Introduction

Nausea and vomiting from chemotherapy remain the most feared toxicities of cancer treatment [4]. With the chemotherapeutic agent cisplatin, nausea and vomiting may be the dose-limiting toxicities, leaving patients unable or unwilling to complete a prescribed course of treatment.

The identification of newer agents with significant antiemetic activity has greatly improved the treatment of cisplatin-induced emesis. In addition, prophylactic antiemetic regimens are now commonly used before and after chemotherapy to prevent development of the problem. These approaches have improved the tolerance of cisplatin chemotherapy and may also reduce the incidence of anticipatory nausea and vomiting. Metoclopramide appears to be one of the most effective of the newer agents against cisplatin-induced emesis [7, 12, 14] with a single-agent rate of total antiemetic protection of 36%–55%. However, even this success rate is considered suboptimal, and recent antiemetic studies have attempted to increase complete response rates.

Improved antiemetic efficacy may be achieved either through the combination of agents that are effective when used singly or through optimization of individual agents. Antiemetic regimens containing metoclopramide and dexamethasone, for example, have been shown to be superior to single-agent metoclopramide in several controlled trials [8, 15], and combination regimens are now commonly used to prevent cisplatin-induced emesis. Meyer [13] has investigated dose optimization and has studied the relationship between serum metoclopramide levels and protection against cisplatin-induced emesis. A serum level of 850 ng/ml just before the third 2 mg/kg dose of a four-dose regimen was associated in that study with significantly more effective antiemetic control. Dose escalation in selected patients with a low serum level and poor antiemetic control resulted in improved control when a level of 850 ng/ml was achieved. We recently completed a controlled crossover trial comparing the antiemetic efficacy of single-agent metoclopramide with that of combination metoclopramide and dexamethasone [8]. Serum metoclopramide levels were obtained just before the third 2 mg/kg dose. This report presents the serum level data obtained and the correlation with clinical effects observed in 35 evaluable patients.

Materials and methods

Patient selection. Patients with documented malignant disease scheduled to receive at least two cycles of cisplatin-containing chemotherapy were eligible for entry into the clinical antiemetic protocol. A Karnofsky performance status of 50% or over, an expected survival of longer than 3 months, adequate renal reserve, as indicated by serum creatinine of 1.5 mg% or more, and adequate hepatic reserve, as indicated by serum bilirubin not more than twice the normal value were required. Patients who were receiving concomitant radiation therapy or who had coexisting medical conditions which might cause nausea or vomiting

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were considered ineligible. Patients were permitted to take their routine medications during the study. However, concomitant use of other potential antiemetics or sedatives was not permitted. Patients who had experienced prior adverse reactions to either metoclopramide or dexamethasone were also not entered into the study.

Study design. A randomized, double-blind crossover design was used. Randomization was performed by the minimization method [18] with Karnofsky performance status and prior chemotherapy as stratification factors. Metoclopramide 2 mg/kg per infusion was administered i.v. over 30 min with the infusions beginning 30 min before and 1.5, 3.5, and 5.5 h after cisplatin. Dexamethasone 20 mg (5 ml) or normal saline 5 ml was administered i.v. over 2 min immediately before the first dose of metoclopramide. Cisplatin was administered over 1 h. Other chemotherapy was administered after the cisplatin infusion was completed.

Patients were hospitalized overnight to receive cisplatin chemotherapy. The occurrence of nausea, vomiting and/or adverse effects was documented by the oncology ward nurse. Patient interviews were conducted by the oncology research nurse on the morning following chemotherapy to confirm the recorded observations ant to assess other subjective findings. The study was performed after approval by the Human Research Committee of the Los Angeles County-University of Southern California Medical Center. Informed consent was obtained from all patients.

Serum metoclopramide analysis. A 10-ml blood sample was obtained prior to the third 2 mg/kg metoclopramide infusion (3.5 h after the start of cisplatin administration). Serum was harvested and frozen for subsequent metoclopramide analysis.

Metoclopramide was assayed using reverse-phase high-pressure liquid chromathography (HPLC) according to the method of Cohen [5]. None of the other chemotherapeutic agents used, dexamethasone, or known metoclopramide metabolites interfere with this HPLC procedure. The mean coefficients of variation between runs were 7.1% within the concentration range of 20–2000 ng/ml. Using a 2-ml serum sample, the practical limit of sensitivity for the assay was 2.5 ng/ml.

Data analysis. Serum level data were analyzed to determine the relationship of metoclopramide levels to patient characteristics and the relationship of serum levels to antiemetic response. The presence or absence of antiemetic protection between treatment arms for the entire patient sample was assessed using the Chi-square test with Yates correction factor [11]. Antiemetic response for patients achieving a given threshold serum level was compared with that of patients not achieving that serum level using a Chi-square test with Yates correction factor [11]. For patients completing crossover, serum metoclopramide levels on each arm were compared using a paired *t*-test and the Pearson product moment coefficient [11].

Patients were divided into tertiles according to serum metoclopramide level to determine whether there was a trend across serum levels in the proportion of patients who did not vomit for each treatment group. The Mantel-Haenzsel test for trend was used to evaluate the significance of the linear trend [3]. Differences in the average number of vomiting episodes by treatment group and by category of serum metoclopramide level were evaluated using a two-factor analysis of variance [11]. All *P*-values reported are two-sided.

Results

Patient characteristics

Of the patients enrolled in the clinical antiemetic protocol, 35 had serum metoclopramide levels drawn during the first chemotherapy/antiemetic cycle and 23 had levels drawn during both cycles. To avoid the possibility of sequence effect on antiemetic efficay, adverse effects, or metoclopramide metabolism, results from only the first chemotherapy/antiemetic cycle were used for comparison and overall analysis, with crossover results used only for intrapatient correlations. Characteristics were similar in patients who received single-agent metoclopramide or combination therapy, with no imbalance noted among patients when classified according to age, Karnofsky performance status, disease, previous chemotherapy, or cisplatin dose (Table 1). Female patients constituted a greater percentage of the combination group (9/18, 50%) than of the single-agent group (2/17, 12%).

Efficacy

The number of emetic episodes was determined for each cycle of chemotherapy, with total protection defined as no emesis, and major protection defined as one or two emeses. Antiemetic responses were determined for all treatment cycles during which serum metoclopramide levels were drawn.

Table 1. Patient characteristics

	Metoclopramide	Metoclopramide + dexamethasone	All patients
Evaluable	17	18	35
Prior chemotherapy			
Yes	2	4	6
No	15	14	29
Karnofsky performance status			
High (80%–100%)	15	13	28
Low (50%–70%)	2	5	7
Sex			
Male	15	9	24
Female	2	9	11
Age (years)			
Mean	49.6	49.9	49.8
Median	53	53.5	53
Range	19–74	23–66	19–74
Diagnosis			
Lung cancer	7	6	13
Head and neck cancer	5	4	9
Other	5	8	13
Cisplatin dose (mg/m^2)			
Mean	85.2	83.1	84.1
Median	95	97.5	95
Range	50–100	40–100	40–100

Table 2. Correlation of serum metoclopramide (MCP) level and emesis

	Metoclopramide		Metoclopramide + dexamethasone		Total	
	No emesis	Emesis	No emesis	Emesis	No emesis	Emesis
All patients (%)	7/17 (41)	10/17 (59)	11/18 (61)	7/18 (39)	18/35 (51)	17/35 (49)
Mean MCP level	954	1296	1256	1388	1138	1334
High-dose CDDP	6/13 (46)	7/13 (54)	8/12 (67)	4/12 (33)	14/25 (56)	11/25 (44)
Mean MCP level	933	1333	1235	1024	1105	1220
Low-dose CDDP	1/4 (25)	3/4 (75)	3/6 (50)	3/6 (50)	4/10 (40)	6/10 (60)
Mean MCP level	1079	1211	1311	1659	1235	1543
Age < 44 years	2/6 (33)	4/6 (67)	1/5 (20)	4/5 (80)	3/11 (27)	8/11 (73)
Mean MCP level	781	1265	1854	1149	1139	1207
Age ≥ 44 years	5/11 (45)	6/11 (55)	10/13 (77)	3/13 (23)	15/24 (62)	9/24 (38)
Mean MCP level	1023	1317	1196	1707	1138	1447
High KPS	6/15 (40)	9/15 (60)	7/13 (54)	6/13 (46)	13/28 (46)	15/28 (54)
Mean MCP level	979	1312	1302	1056	1153	1210
Low KPS	1/2 (50)	1/2 (50)	4/5 (80)	1/5 (20)	5/7 (71)	2/7 (29)
Mean MCP level	803	1154	1175	3380	1101	2267
No prior chemotherapy	6/15 (40)	9/15 (60)	8/14 (57)	6/14 (43)	14/29 (48)	15/29 (52)
Mean MCP level	950	1277	1296	1494	1148	1364
Prior chemotherapy	1/2 (50)	1/2 (50)	3/4 (75)	1/4 (25)	4/6 (67)	2/6 (33)
Mean MCP level	974	1469	1147	755	1104	1112

Antiemetic responses of the patients in the present study were representative of those in the full clinical study [8]. A higher rate of total antiemetic protection with combination metoclopramide and dexamethasone than with metoclopramide alone was demonstrated (61% vs 41%). Younger patients (under 44 years of age) had a significantly lower rate of total protection than older patients with combination metoclopramide and dexamethasone treatment (20% vs 77%; $P < 0.05$). No age-related difference in total protection rate was observed in patients receiving metoclopramide alone (33% vs 45%, $P > 0.60$; Table 2).

Serum levels

A wide variation in serum metoclopramide levels was observed with more than a 12-fold difference between the lowest and highest values (range 273–3380 ng/ml, mean 1233 ng/ml). Examination of serum level data adjusted for age, Karnofsky performance status, disease, and history of previous chemotherapy did not explain this variation. For crossover patients, serum levels with metoclopramide alone were highly correlated with those on combination therapy ($r = 0.65$, $P < 0.001$). There was no evidence that the addition of dexamethasone altered serum metoclopramide level (paired t-test; $P = 0.52$).

Serum levels versus clinical response

Attainment of a serum metoclopramide level of 850 ng/ml was not associated with a decreased number of emetic episodes or an increased probability of achieving total antiemetic protection ($P = 0.63$). Since a threshold serum metoclopramide level for total antiemetic protection other than 850 ng/ml might exist, analysis of response data was performed using all levels from 650 ng/ml to 1850 ng/ml at intervals of 100 ng/ml as potential threshold values. No serum metoclopramide level was identified that could serve as a threshold value for significant improvement in total antiemetic protection.

Since dexamethasone itself increases antiemetic protection, the threshold serum metoclopramide level for combination antiemetic therapy might be lower than the threshold serum metoclopramide level for single-agent antiemetic therapy. Assignment of metoclopramide-equivalent levels to dexamethasone to be added to the measured metoclopramide levels of the combination regimen was performed. Even with a range of various assigned metoclopramide-equivalents for dexamethasone, no threshold value for total antiemetic protection could be identified for the two groups individually or combined.

Statistically significant observations did appear when the concept of a directly proportional relationship between

Table 3. Incidence of total antiemetic protection by serum level and treatment group (patients without emesis/all patients)

		Metoclopramide	Metoclopramide + dexamethasone	Total
Serum metoclopramide level (ng/ml)	≤852	4/6	3/6	7/12
	853–1469	3/7	3/4	6/11
	>1469	0/4	5/8	5/12
	Total	7/17	11/18	

Table 4. Average number of vomiting episodes (± SEM) by serum level and treatment group

		Metoclopramide	Metoclopramide + dexamethasone	Total
Serum metoclopramide level (ng/ml)	<852	0.50 ± 0.34	0.67 ± 0.33	0.58 ± 0.23
	853–1469	2.57 ± 1.23	1.25 ± 1.25	2.09 ± 0.89
	>1469	5.25 ± 1.38	1.38 ± 0.80	2.67 ± 0.86
	Total	2.47 ± 0.73	1.11 ± 0.44	

serum metoclopramide level and antiemetic protection through the full range of serum metoclopramide levels was abandoned. A trend toward a lower incidence of total protection in patients with the higher serum metoclopramide levels was detected in the group receiving metoclopramide alone ($P = 0.09$) (Table 3). Examination of the average number of vomiting episodes demonstrated an advantage for combination antiemetic treatment over metoclopramide alone when adjusted for serum metoclopramide levels ($P = 0.04$) and also demonstrated a disadvantage for patients with the highest serum metoclopramide levels when adjusted for treatment group ($P = 0.03$) (Table 4). Patients receiving metoclopramide alone who fell into the tertile with the highest serum metoclopramide levels had a greater number of vomiting episodes than all other groups.

Adverse effects

Adverse effects of antiemetic treatment included mild drowsiness, akathisia, and two cases of severe dystonia. These responded promptly to treatment with i.v. diphenhydramine or diazepam. There was no relationship between serum metoclopramide levels and the occurrence of adverse effects.

Discussion

Our results do not support the contention [13] that serum metoclopramide levels drawn at a specific point during bolus metoclopramide therapy can be related to antiemetic efficacy in a directly proportional manner. A wide variation in serum levels was noted within the patient sample, and mean levels in patients who achieved total antiemetic protection were not significantly greater than mean levels in those who did not. A multiple bolus regimen using an agent with a serum half-life of several hours, such as metoclopramide, could produce wide swings in peak and trough levels [16]. However, a specified trough level might still have some predictive value. Our results are thus in contrast to those of Meyer [13] and Kerr [10], which suggest the existence of a threshold serum metoclopramide level for complete antiemetic protection. Yet our results are consistent with a more complex non-linear relationship between serum metoclopramide level and emetic/antiemetic effect. The size of our sample tertiles prevented the detection of a difference in efficacy between low and moderate serum metoclopramide levels. However a definite disadvantage in antiemetic protection for patients with the highest serum metoclopramide levels receiving metoclopramide alone was identified. Our observations might therefore be consistent with effective agonist/antagonist activity of metoclopramide at dopaminergic or related receptors [6, 9] leading to increased antiemetic protection at moderate serum levels but reversal of protection at high levels.

Dexamethasone exerts an excellent antiemetic effect both as a single agent [1] and in combination regimens [8, 15]. Our data demonstrate that the efficacy of dexamethasone combination regimens cannot be attributed to alteration of the metoclopramide level itself. The contribution of dexamethasone to antiemetic protection is particularly notable in the group of patients with high metoclopramide levels, where metoclopramide alone may be less effective or possibly counterproductive. The ability of dexamethasone to "rescue" this particular group of patients may be a major factor in the overall improvement in antiemetic control seen with combination regimens.

Recent trials [2, 17] which have investigated the antiemetic effects of high-dose oral metoclopramide have included serum level data to validate the absorption of this drug by the oral route. Although such data may be valuable for understanding the pharmacokinetics of metoclopramide, use of serum metoclopramide levels to adjust doses for optimal antiemetic control, particularly in combination antiemetic regimens, will depend on a better understanding of the various antiemetic agents and of the interactions between metoclopramide and its receptors.

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