High-Dose Versus *Low-Dose Metoclopramide in the Prevention of Cisplatin-Induced Emesis*

A Randomized Crossover Study in Patients With Ovarian Carcinoma

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Forty-six patients with ovarian carcinoma who received single drug cisplatin chemotherapy were evaluated for the antiemetic efficacy of two different doses of metoclopramide. Each patient received during the first two courses a 4-hour continuous infusion of either 8 or 0.8 mg/kg in a random order. Total protection from emesis was achieved in 12 (26%) of the high-dose courses and in three (7%) of the low-dose courses of metoclopramide. Major control (one or two emetic episodes) was achieved in seven (16%) and in four (9%) of the courses, respectively. The higher dose of metoclopramide significantly reduced the degree of nausea as recorded on a visual analogue scale. A significant difference between courses 1 and 2 could only be seen when the high-dose treatment was followed by low-dose metoclopramide. The duration of anorexia after the courses was not influenced by the metoclopramide dosage. Side effects were mild. It is concluded that there is a dose-response relationship for the antiemetic effect of metoclopramide.

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OPTIMUM CONTROL OF NAUSEA and vomiting are important objectives in patients receiving anticancer chemotherapy. A number of trials have been conducted to identify the most active antiemetic agents and schedules. Metoclopramide (MCP) has proven its efficacy against cisplatin-induced emesis.[1] The optimum doses and treatment schedules have not, however, been established. High doses of MCP (up to 10 mg/kg per course) have been advocated as a better means of protection than conventional doses[1–4] although this has not been formally proven by properly designed studies. Some pharmacokinetic studies have shown an association between high plasma levels of MCP (>0.85 ug/ml) and control of emesis,[5,6] whereas others have failed to confirm this finding.[7] The purpose of the study reported in this article was to compare in a randomized and double-blind manner the efficacy of a high dose and a low dose of MCP in patients with ovarian carcinoma receiving single drug cisplatin chemotherapy.

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Patients and Methods

Fifty patients (aged 37 to 75 years) who had a primary operation for epithelial ovarian carcinoma were included in the trial. Cisplatin chemotherapy was started 2 to 4 weeks after surgery. Up to six courses were given with 3 weeks between courses. Doses of 50 mg/m^2 were given to patients with no macroscopic residual tumor (23 patients), whereas patients with residual tumors were given 75 mg/m^2 (27 patients). The criteria for including patients in the antiemesis study were no previous chemotherapy, World Health Organization (WHO) performance status of 0 or 1, and unimpaired gastrointestinal function.

The two first chemotherapy courses were studied. Each course started with 1 hour of prehydration (1000 cc saline intravenously (IV) supplemented with 20 mmol KCl and 20 mmol MgSO4) and furosemid-induced diuresis. A rapid (5 minutes) infusion of cisplatin was then given followed by further hydration (2000 cc of dextrose/electrolyte and 500 cc of mannitol suspensions) for 3 hours.

Metoclopramide, the only antiemetic used, was added to the infusion units in order to give a stable dose rate during the 4 hours of treatment. Two dose levels of MCP were chosen, a low dose, 0.2 mg MCP/kg/hour (that was fairly similar to the regimen used in the past at

our institution) and a high dose, 2 mg MCP/kg/hour (total doses 0.8 and 8 mg/kg per course, respectively). The latter dose corresponded to the antiemetic regimen recently applied in the hospital. Twenty-five patients were randomized to treatment regimen A, which consisted of low-dose MCP during the first course and high-dose MCP during the second course; 25 patients were randomized to treatment regimen B, high-dose MCP during the first course and low-dose MCP during the second course.

The randomization procedure and the coding of preparations were performed at the Department of Pharmacology, and the code remained unbroken until the study was completed. Care was taken not to give other antiemetic or neuroleptic drugs during the infusion period. Such drugs later had to be given to some patients due to an insufficient antiemetic effect or side effects. Four patients participated only in the first course: two patients went off the study because neuroleptic drugs had to be given before the second course due to anxiety; one patient experienced severe nausea and vomiting during the first course and refused to participate further; and one patient had the chemotherapy changed due to rapid tumor progression.

The patients were observed for 18 hours after the cisplatin infusion. The number of emetic episodes and side effects were recorded by the nurse. For practical reasons, the nurse's recordings were done in two observation periods, the first 8 hours and the next 10 hours. Very few patients had vomiting after 8 hours, and the two periods are therefore presented together. Before departing on the next day, the patient recorded the approximate number of emetic episodes experienced during the 18-hour period, and she also indicated the degree of nausea on a 10-cm visual analogue scale. In her home she recorded on a special formulary the number of days before a normal appetite returned.

Informed consent was obtained from all patients. The trial was approved by the National Drug Control and by the Ethical Committee of the hospital. For statistical evaluation of differences the Student's *t* test was used.

Results

Parallel Study

The results of the first chemotherapy course were separately evaluated. Total protection (no emesis) was obtained in five of 25 patients (20%) given the high dose of MCP, whereas six patients (24%) experienced major protection (one or two emetic episodes). In the group receiving the low dose of MCP two of 25 patients (8%) had total protection, and three patients (12%) had major protection. The number of vomiting episodes recorded by the nurse and by the patient was significantly lower in the group receiving high-dose MCP (Table 1). This patient group also experienced less nausea, as indicated by the visual analogue scale. The duration of anorexia after the first chemotherapy course was not significantly different in the two treatment groups.

TABLE 1. Antiemetic Efficacy of Low-Dose *Versus* High-Dose Metoclopramide During the First Course of Cisplatin Chemotherapy (Parallel Study)

Recording	Low-dose MCP (25 patients)	High-dose MCP (25 patients)	Significance
Vomiting episodes, nurse's observation	10.6 (8.7)*	4.7 (5.3)	$P = 0.005$
Vomiting episodes, patient's observation	9.3 (7.3)	5.4 (5.8)	$P = 0.04$
Degree of nausea, recorded on analogue scale (cm)	4.7 (2.6)	3.3 (2.2)	$P = 0.05$
Duration of anorexia (days)	3.3 (3.3)	4.6 (4.7)	$P = 0.25$

MCP: metoclopramide.
* Mean number (standard deviation).

Crossover Study

Among the 46 patients treated by both dosages of MCP, total protection was seen in 12 (26%) of the courses with high-dose MCP as compared to three (7%) of the courses with low-dose MCP. Major protection was achieved in seven courses (16%) and four courses (9%), respectively. When high-dose MCP was given during the first course and low-dose was given during the second (regimen B) a highly significant difference was observed (Table 2), whereas no significant difference was observed when low-dose MCP was followed by high-dose MCP (regimen A). Observations made by the nurse and by the patient were essentially the same. The degree of nausea was also lower in courses with high-dose MCP compared to courses with low-dose MCP, but the difference was significant only for regimen B (Table 3). The period of anorexia after the course was not influenced by the MCP dosage (Table 4). When asked about their preference, 32 patients (70%) preferred the high dose and eight patients (17%) preferred the low dose of MCP; six patients (13%) gave no preference.

Adverse Drug Reactions

Adverse reactions were observed in 50 of the 96 courses (52%), and the frequency was not significantly different for the two dose levels of MCP (Table 5). Muscular restlessness was seen in 16.7% of courses high-dose MCP and in 12.5% of courses with low-dose MCP. Only

TABLE 2. Effect of High-Dose and Low-Dose Metoclopramide on the Number of Emetic Episodes in the Crossover Study

Treatment regimen*	No. of emetic episodes (±SD) Course No. 1 (n = 23)	Course No. 2 (n = 23)	Significance
Nurse's observations			
A	9.6 (8.3)	6.6 (6.3)	$P = 0.11$
B	4.5 (5.5)	11.4 (7.3)	$P = 0.0001$
Patient's observations			
A	8.2 (6.4)	7.5 (6.9)	$P = 0.69$
B	4.8 (5.2)	12.8 (8.0)	$P < 0.0001$

MCP: metoclopramide; SD: standard deviation.
* Regimen A: low-dose MCP followed by high-dose MCP; Regimen B: high-dose MCP followed by low-dose MCP.

one patient, 37 years old, needed medication for this problem. Diarrhea was recorded in 13.5% of the courses and most often when low-dose MCP was given. Diarrhea occurred in three of 44 courses (6.8%) with cisplatin dose of 50 mg/m^2 and in 10 of 52 courses (19.2%) with a cisplatin dose of 75 mg/m^2. Anxiety of such a degree that neuroleptic drugs had to be given was recorded in 8.5% of the courses. A mild sedation was seen in many patients. This reaction was not considered as an unwanted side effect and was therefore not recorded.

Discussion

This study has shown that during cisplatin chemotherapy for ovarian cancer, high-dose MCP (8 mg/kg per course) gives better protection against acute nausea and vomiting than low-dose MCP (0.8 mg/kg per course). Still, only 44% of the patients receiving the highest MCP dose experienced total or major protection. Single drug high-dose MCP as used in this study is therefore insufficient as an antiemetic treatment during cisplatin chemotherapy. The conclusions from the parallel study and those from the crossover study are essentially the same.

The main purpose of this study was to detect a possible dose-response relationship for the antiemetic effect of MCP. For practical reasons, the two treatment schedules chosen for comparison were those previously and currently used in our institution. To define the optimum dose level of MCP, other dosages and drug combinations should probably have been chosen.

Studies on antiemesis in cancer chemotherapy involve numerous methodological problems,[7] some of which are related to the patient material. In this study the material was well-defined in terms of the type of cancer, performance status, sex, and age. Patients with gastrointestinal problems and patients using emetogenic drugs were excluded. To avoid the influence of anticipatory nausea and vomiting, only previously untreated patients were included. Unintentional bias in the evaluation was prevented by the use of randomization and a double-blind design. Using the crossover design, some problems due to interpatient variability were avoided. A periodic effect may, however, interfere and complicate the interpretation of the results from crossover studies.[8] That point is illustrated in this study where the patients who received low-dose MCP (and had poor antiemetic protection) during the first course also responded poorly to high-dose MCP given during the second course (Tables 2 and 3). From a clinical point of view this observation shows the importance of fully preventing nausea and vomiting from the beginning of the chemotherapy.

The emetic stimulus was standardized to single drug cisplatin. Depending on the tumor burden, two doses of

TABLE 3. Degree of Nausea as Recorded on a 10-cm Visual Analogue Scale Relative to Metoclopramide Dosage in the Crossover Study

Treatment regimen*	Course No. 1 cm (±SD)	Course No. 2 cm (±SD)	Significance
A	4.4 (2.5)	4.0 (2.7)	$P = 0.37$
B	3.1 (2.1)	5.1 (2.6)	$P = 0.0001$

SD: standard deviation.
* Regimen A: low-dose MCP followed by high-dose MCP; Regimen B: high-dose MCP followed by low-dose MCP.

TABLE 4. Days With Anorexia After the Chemotherapy Course Related to the Dosage of Metoclopramide

Treatment regimen*	Course No. 1	Course No. 2	Significance
A	3.5 (3.3)†	3.0 (2.6)	$P = 0.39$
B	4.5 (4.8)	4.2 (4.9)	$P = 0.57$

* Regimen A: low-dose MCP followed by high-dose MCP; Regimen B: high-dose MCP followed by low-dose MCP.
† Numbers in parentheses are ±standard deviation.

TABLE 5. Number of Adverse Drug Reactions Seen During 96 Courses

Type of reaction	Low-dose MCP (48 courses)	High-dose MCP (48 courses)	Total
General weakness	0	1	1
Cold feeling	0	2	2
Headache	1	2	3
Sweating	2	2	4
Palpitations	1	3	4
Anxiety	5	3	8
Diarrhea	9	4	13
Muscular restlessness	6	8	14
Other, urogenital	1	0	1
Total	25	25	50

MCP: metoclopramide.

cisplatin (one low, 50 mg/m^2, and one intermediate, 75 mg/m^2) were used. For both cisplatin doses the high dose of MCP had the best antiemetic effect. We admit that a stratification of the material according to the two cisplatin doses would have strengthened the conclusions.

No significant difference in frequency of side effects between the two treatment schedules was observed. The doses might therefore be increased above 2 mg/kg/hour. Some studies indicate no benefit of increasing the dose above 1 mg/kg.[2,4,7]

The rate of total protection using high-dose MCP was about 25% in our study. This degree of protection is lower than that found in other trials using high-dose MCP.[1-4] Failing to control vomiting by MCP has been ascribed to insufficient plasma concentrations.[5,6] This might have been the case in our study where the dose rate was kept constant throughout the treatment period, and no loading dose was given. Available pharmacokinetic data indicate that an initial loading dose of MCP could have provided higher and more stable plasma MCP levels, possibly improving the antiemetic effect. It might also be that the treatment period in our study (4 hours) was too short. Some nausea and vomiting induced by anxiety could probably have been prevented by proper anxiolytic drugs. For study purposes, however, no additional treatment such as sedatives, steroids, or diphenhydramine were given.

The side effects observed were generally mild, and some of them were probably not related to the antiemetic treatment. Muscular restlessness was the only side effect that appeared more frequently in courses with high-dose MCP than in courses with low-dose MCP (16.7% *versus* 12.5%), but the difference was insignificant. Only one patient, the youngest in the study, needed medication for this problem. It is well known that extrapyramidal reactions and muscular restlessness occur more frequently in younger patients. Diarrhea was seen most often in courses with low-dose MCP. This problem is probably related to the cisplatin dose as the frequency was highest in the courses where the highest cisplatin dose had been given. This study could not help us identify any effect of high-dose MCP on the duration of anorexia after the course. The problem of a delay in the onset of nausea and vomiting was not studied and can therefore not be discussed.

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