A Prospective, Randomized Double-Blind Trial Comparing Metoclopramide Alone With Metoclopramide Plus Dexamethasone in Preventing Emesis Induced by High-Dose Cisplatin

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We observed 50 patients receiving high-dose cisplatin-based chemotherapy in a prospective, randomized double-blind trial. One group received metoclopramide (MCP) alone (total dose, 6 mg/kg), whereas the other group was given dexamethasone (DMS) (total dose, 60 mg) in addition to MCP. The patient characteristics of the two groups were comparable, confirming satisfactory randomization. Multivariate regression analysis failed to show any statistical significance in the antiemetic response between the two treatment groups. However, female patients receiving Adriamycin (Adria Laboratories, Columbus, OH) concurrently and obese persons exhibited more vomiting. The overall antiemetic response rate was 66%. Because the side effects were minimal, a higher dose of MCP is expected to improve emetic control without increasing toxicity. The use of a 36-hour assessment period in our study gave more meaningful data. An exponential increase in the dose of MCP is probably required, with respect to weight, to obtain the same antiemetic efficacy.

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HIGH DOSES of metoclopramide (MCP) (up to 10 mg/kg) have been recommended as the most effective antiemetic agent in patients receiving high-dose cisplatin chemotherapy.[1] Such a protocol has distinct disadvantages (*i.e.*, it has to be given over 10 to 12 hours precluding its application for outpatients, it is expensive, it has significant toxicity, and it does not give complete protection from nausea and vomiting in approximately 40% of the cases).[2–4] Besides, the antiemetic efficacy of MCP may not be as closely related to its serum levels as believed previously.[5] Hence, such high doses of MCP may not be necessary. Studies have shown that dexamethasone (DMS) has antiemetic potential alone or in combination with MCP.[2,3,6] Therefore, we designed a prospective, randomized study comparing two short course antiemetic regimens capable of being administered on an outpatient basis to patients receiving high-dose cisplatin chemotherapy at Tata Memorial Hospital.

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Patients and Methods

From May 1987 to October 1987, all consecutive patients scheduled for chemotherapy consisting of 100 mg/m^2 of cisplatin were offered entry into this study. Once their informed consent was obtained, patients were randomly assigned to receive either treatment I or II. Treatment I consisted of 2 mg/kg of MCP in 100 ml of normal saline administered as a 30-minute infusion three times, 30 minutes before and at 180 and 360 minutes, respectively, after cisplatin (total dose, 6 mg/kg). In treatment II, the dosage and administration of MCP remained the same. In addition, 20 mg of DMS was added in each infusion (total dose, 60 mg). Cisplatin was administered as an intravenous infusion over 3 hours with hydration, diuresis, and magnesium supplementation.[7] There was no restriction on food intake for the patient. No other antiemetics were given during the 36-hour observation period.

All patients exhibiting nausea, vomiting, diarrhea, and restlessness before chemotherapy, and those who had radiotherapy, cerebral metastasis, and peptic ulcer disease, were excluded from the study. The evaluation during the

TABLE 1. Patient Characteristics

	MCP + DMS	MCP
No. of patients	22	28
Age (yr)		
Median	41	43
Range	19–80	18–61
Sex		
M	12	14
F	10	14
Performance status		
1	18	25
2	4	3
Type of cancer		
Oesophagus	3	9
Ovary	9	7
Head and neck	7	5
Other	3	7
Prior chemotherapy		
Yes	13	17
No	9	11
Concurrent Adriamycin		
Yes	7	6
No	15	22

MCP: metoclopramide; DMS: dexamethasone.

36-hour period included information on the number of vomits, extrapyramidal reactions, diaphoresis, restlessness, convulsions, diarrhea, and tremors. The antiemetic response was graded as follows: complete (no vomits), partial (one to three vomits), or nil (four or more vomits).

Univariate analysis was performed using the Mann–Whitney U test. Because the sample size in each group was large, this U statistic was transferred to the normal variate (Z). Multivariate regression analysis was performed using age, sex, performance status, prior chemotherapy, simultaneous use of Adriamycin (Adria Laboratories, Columbus, OH) in the treatment protocol, and antiemetic response as variables. This was first done with the treatment protocol and then with the antiemetic response as the dependent variable.

The aim of doing multivariate regression analysis was to ensure that the two treatment groups were strictly comparable and to clarify whether any individual variable had statistical significance independent of the others.

Results

Fifty patients were entered into this study. Patient characteristics are mentioned in Table 1. This table documents satisfactory randomization between the two treatment groups with respect to all of the variables except the type of cancer.

Overall complete protection from emesis was seen in 40% of the cases (Table 2). Antiemetic efficacy (complete response and partial response) was seen in 66% of the cases. There was no statistical significance between the two treatment groups when comparing the antiemetic response among those who had received prior chemotherapy and those who were administered Adriamycin concurrently.

Univariate analysis, counting the exact number of vomits in the two treatment groups, showed no statistical significance (Z value, 1.095×10^5).

Multivariate regression analysis, using the antiemetic treatment protocol as the dependent variable, failed to show any overall or independent significance (Table 3). It was then repeated using the antiemetic response as the dependent variable and the rest as independent variables. This showed statistical significance between the various groups for sex ($P < 0.001$), simultaneous use of Adriamycin (P value range, <0.01 to <0.001), and weight (P value range, <0.01 to <0.001). Prior use of chemotherapy on the patients showed a difference ($P < 0.01$) between only complete and partial responders.

The side effects of the antiemetic protocols are documented in Table 4. Their pattern was similar between the two groups. No further MCP was administered to the two patients with extrapyramidal reactions. The other seven patients had only minor side effects (restlessness [n = 4], drowsiness [n = 2], and diaphoresis [n = 1]), which did not require any alteration in the treatment schedule. Convulsions, diarrhea, or tremors did not develop in any of the patients.

Discussion

Cisplatin-based chemotherapy has a high emetic potential. Several drug combinations have been used to

TABLE 2. Patient Distribution and Antiemetic Response

Antiemetic response	Total		Prior chemotherapy given		Concurrent Adriamycin administered	
	MCP + DMS	MCP	MCP + DMS	MCP	MCP + DMS	MCP
Complete	11	9	5	6	1	2
Partial	5	8	3	4	2	1
None	6	11	5	6	4	3

MCP: metoclopramide; DMS: dexamethasone.

TABLE 3. Statistical Significance of Various Variables for Antiemetic Protocol and Response Using Multivariate Regression Analysis

	P value of independent variables						
Dependent variables	Age	Sex	Prior chemotherapy given	Concurrent Adriamycin	Weight	Antiemetic therapy	Antiemetic response
Antiemetic protocol	NS	NS	NS	NS	NS	—	NS
Overall antiemetic response	NS	<0.001	NS	<0.001	<0.001	NS	—
Complete antiemetic response *versus* no response	NS	<0.001	NS	<0.05	<0.01	NS	—
Complete antiemetic response *versus* partial response	NS	<0.001	<0.01	<0.001	<0.05	NS	—
Partial antiemetic response *versus* no response	NS	<0.001	NS	<0.01	<0.05	NS	—

NS: not significant.

counter the resulting nausea and vomiting.[1-3,8,9] High-dose MCP alone is successful in 30% to 70% of the cases.[1] Basically, chemotherapy-induced vomiting involves the chemoreceptor trigger zone. However, peripheral impulses and higher cortical centers also influence this vomiting.[1] The success of high-dose MCP lies in its dual action.[1] At both low and high doses, it increases normal gastrointestinal motility resulting in reduced pheripheral input to the chemoreceptor trigger zone. In addition, at high doses, it also penetrates the central nervous system to interfere with dopaminergic conduction within the chemoreceptor trigger zone. Several trials have reported the addition of DMS to MCP in the antiemetic protocols.[2,3,6,10-12] However, an analysis of some of these studies has failed to demonstrate the beneficial effect of the addition of DMS.[2,11,12] These trials also had several limitations (*i.e.*, small number of patients, observation period of only 24 hours, less than optimal dosage and method of administration of MCP and variable dose of cisplatin). Our study was designed to overcome some of these problems by performing a prospective, randomized trial, with an observation period of 36 hours, on 50 patients treated with the same dose of cisplatin at a single center. It must be stressed that maximum nausea and vomiting was reported between 12 and 36 hours after chemotherapy administration.[8] Hence, our observation period of 36 hours was expected to yield more meaningful data. We decided to give other chemotherapeutic agents concurrently. This is more convenient for the outpatient and is likely to be the situation most often encountered in clinical practice. For the same reason, we did not exclude patients who had received prior chemotherapy. During analysis, we did not consider the degree of nausea because it could not be assessed accurately.[1]

Both univariate and multivariate regression analysis failed to show better antiemetic efficacy by the addition of DMS. In addition, multivariate regression analysis showed no difference between the two treatment groups (Table 3). Hence, the randomization of patients between the two groups was satisfactory.

When the antiemetic response was used as the dependent variable, multivariate regression analysis showed interesting results. Female patients who weighed more than 50 kg and had received Adriamycin concurrently had an increased incidence of vomiting.[5,8,10,13] Age was of no statistical significance, unlike in previous reports.[13] Women consistently exhibited an increased incidence of vomiting. The addition of Adriamycin to the chemotherapy made the most significant impact between complete and partial responders. The significance of weight was evident throughout the antiemetic response range, although not as much as the significance of sex and Adriamycin. Does this mean that as weight increases there is an exponential rise in the requirement of MCP for equivalent antiemetic response? If proven correct, this would explain why some studies have found no corelation between antiemetic response and serum levels of MCP.[5] Therefore, we recommend higher doses of MCP for female patients receiving Adriamycin concurrently and for obese persons.[13] The antiemetic efficacy also is likely to be increased by restricting oral intake.[2,13,14]

The toxicity of MCP with or without DMS was low. Hence, there is room to escalate the dose of MCP. The dose used in this study was safe, effective, and easily ad-

TABLE 4. Side Effects of the Antiemetic Protocols

Side effect	MCP + DMS	MCP
Extra pyramidal reaction	1	1
Restlessness	1	3
Drowsiness	1	1
Diaphoresis	—	1

MCP: metoclopramide; DMS: dexamethasone.

ministered to outpatients receiving high-dose cisplatin. The addition of DMS failed to have any effect on the overall antiemetic response of 66% of the cases. However, other trials have shown the efficacy of DMS as a potent antiemetic agent.[3,6,10] Further studies are warranted to clarify this issue. Currently, we have initiated a pilot study using a higher dose of MCP in female patients receiving Adriamycin concurrently, and we welcome suggestions on the use of a semi log graph to adjust the dose of MCP in overweight persons.

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