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Improved Control of Cisplatin-Induced Emesis with a Combination of High Doses of Methylprednisolone and Metoclopramide: a Single-Blind Randomized Trial

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Abstract—*Forty-seven patients undergoing their first course of chemotherapy containing cisplatin in combination with other drugs were randomized to compare the antiemetic efficacy of high dose metoclopramide vs. high dose methylprednisolone added to metoclopramide. The number of patients who experienced no emetic episodes was significantly higher with the combination regimen* ($P < 0.01$). *In addition, both the mean number of emetic episodes* ($P = 0.01$) *and the duration of nauseas* ($P = 0.025$) *were decreased with the combination regimen. Both antiemetic regimens were well tolerated. Sex affected the response, with women having more nausea and vomiting than did men* ($P < 0.05$).

INTRODUCTION

NAUSEA and vomiting represent the preeminent side-effect reported by cancer patients treated with chemotherapy. Even curable patients may delay or suspend their therapy because of marked nausea and vomiting [1]. Cisplatinum (CDDP) is universally emetogenic [2] when the dose delivered reaches or exceeds 75 mg/m^2. Among the antiemetic medications which have been evaluated so far in CDDP-induced emesis, high dose metoclopramide (MCP) appeared to be one of the most active drugs [3, 4]. A dose of 3 mg/kg may give comparable results to those obtained with higher doses up to 10 mg/kg [3, 5]. Corticosteroids have proved to be active [6–8] but their efficacy against severe nausea and vomiting induced by CDDP remains controversial [9–12]. Some reports have been made of improved digestive tolerance when they were associated with metoclopramide [13–15]. This led us to conduct a single blind randomized trial to assess the interest of combining high dose methylprednisolone (MPN) with high dose MCP in preventing nausea and vomiting induced by CDDP in chemotherapy.

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PATIENTS AND METHODS

From March to November 1985, 47 patients, with a median age of 53 years (range 21–75 years), who were to receive their first course of chemotherapy, were included in this study. All patients had a performance status < 2 according to the ECOG scale. None presented with contra-indications for corticosteroid or metoclopramide treatment. A pretreatment work-up was performed: eligible patients were required to have normal hematological renal and hepatic functions. Table 1 shows the different tumor locations presented.

The chemotherapy regimens delivered were dependent on the types of cancers treated, but, in every case, cisplatin was included at a minimal dose of 75 mg/m^2 (75 mg/m^2 to 100 mg/m^2). Cisplatin was administered as a 4 hr infusion, diluted in 1000 ml of 0.9% sodium chloride solution and following hyperhydratation for a minimal period of 4 hrs. Other drugs were associated according to tumor types and included either fluorouracil, doxorubicin, etoposide, methotrexate, bleomycine, vindesine or cyclophosphamide. Patients were well balanced for the different chemotherapy regimens used. None of the patients received any other specific treatment at the same time.

Table 1. Characteristics of the 47 patients entered in the trial

Characteristics	High dose MCP	High dose MCP + MPN
No. of patients	23	24
Age (year)		
Mean	51.1	52.4
Range	26–75	21–72
Sex (No. of patients)		
Men	13	17
Women	10	7
ECOG scale		
0	19	19
1–2	4	5
Type of tumor		
sarcoma	5	4
head and neck cancer	4	8
testis cancer	3	2
gastric cancer	4	3
ovarian cancer	0	1
adenocarcinoma of unknown primary	2	2
others	5	4
Cisplatin dose		
75–80 mg/m^2	15	15
100 mg/m^2	8	9

MCP = Metoclopramide; MPN = Methylprednisolone

Antiemetic treatment

Before receiving their first course of chemotherapy, patients were randomly assigned to receive as antiemetic treatment, either high dose intravenous MCP alone, or a combination of high dose MCP and high dose methylprednisolone. MCP treatment consisted of three infusions of 1 mg/kg of the drug diluted in 125 ml of 0.9% sodium chloride solution; every dose was infused over 15 min, and given half an hour, 2 hr and 4 hr after initiation of cisplatin. In patients randomised to receive MPN also, the latter was given in three intravenous push injections of 1 mg/kg (total dose 3 mg/kg) with the same time schedule as metoclopramide. No other sedative or potentially antiemetic medications were allowed during the 24 hr post-treatment period.

Evaluation

All patients were kept in hospital for at least 24 hr after chemotherapy administration. Assessment of nausea, vomiting and adverse effects of antiemetic treatment was recorded by a medical oncologist who did not participate in the care of the patients and who was unaware of what antiemetic treatment had been given. The assessment was done according to an antiemetic response scale. Grade III was no nausea or emesis; grade II, nausea for less than 3 hr, and/or a single episode of vomiting; grade I, nausea for more than 3 hr, and/or two to four episodes of vomiting; grade 0, continuous nausea for more than 3 hr, and/or five or more episodes of vomiting. The side-effects attributable to antiemetic treatment were also recorded with particular reference to sedation, diarrhoea, trismus or acute dystonic reactions. The toxicity scale utilized was 0, no toxicity; 1, mild toxicity; 2, moderate toxicity; 3, severe toxicity leading to interruption of antiemetic treatment.

Statistical analysis

The results of quantitative analysis are expressed as mean and standard deviations. After control of normal distribution of the data and equality of variances, means were compared using Student's *t*-test. For qualitative analysis, frequencies were compared with the chi square test. The chi square test of Yates (chi-square corrected) was used when one of the expected frequencies was less than 5.

This antiemetic trial has been carried out according to Pater and Willan's methodologic issues [16].

RESULTS

Efficacy

All patients completed their chemotherapy course with the antiemetic regimen allocated, and were evaluable for antiemetic response. Patients treated with the combination of MCP and methylprednisolone had significantly fewer episodes of nausea or vomiting than patients receiving metoclopramide alone ($P = 0.03$). Among patients who received high dose metoclopramide alone, only two had no nausea or vomiting (8.6%), six had a single episode of vomiting or nausea in a period not exceeding 3 hr, four had either nausea for 3 hr or more, or two to four episodes of vomiting; 11 (47.8%) had digestive toxicity which was considered as unaffected by the antiemetic treatment. Among patients who received the combination of high dose MCP and high dose MPN, eight (33%) had no nausea or vomiting, eight had only one vomiting episode or nausea in a period not exceeding 3 hr, five had nausea for more than 3 hr or two to four episodes of vomiting, and only two presented marked nausea and/or vomiting.

The number of patients who experienced no emetic episodes was significantly higher in the MCP + MPN group (Table 2) ($P < 0.01$). Likewise, in this group, the mean number of emetic episodes is significantly decreased ($P = 0.01$) (Table 2). When nausea is considered, it appears that 23/24 patients treated with MCP and MPN presented no or only mild nausea for less than 3 hr, compared with 15/23 patients treated with MCP alone ($P = 0.025$) (Table 2). Further analy-

Table 2. Antiemetic observed effects

	MCP No. of patients	MCP + MPN No. of patients	
No of emetic episodes			
0	3	12	$P < 0.01$
1, 2 or more	20	12	
Mean of vomiting episodes	5.4	2.1	$P = 0.01$
Nauseas duration			
No nausea or < 3 hr duration	15	23	$P = 0.025$
Nausea > 3 hr duration	8	1	

MCP = Metoclopramide; MPN = Methylprednisolone

sis of this series was performed to determine the patients, features which could be correlated with poor response to antiemetic therapy. No difference appeared owing to treatment characteristics such as drug associations employed, cisplatin dosage of 75–80 mg/m^2 or 100 mg/m^2, patient's age, sites of the primary. The only characteristic which affected the response was sex, with women presenting more nausea and vomiting than did men ($P < 0.05$).

Tolerance

Both antiemetic regimens were tolerated well and no important side-effects, especially extrapyramidal reactions, were recorded. Only mild sedation in four patients, and mild (four patients) or moderate (5 patients) diarrhoea were noted. No special toxicity due to methylprednisolone such as facial blush, headache or epigastric pains was noted.

DISCUSSION

Metoclopramide has been shown to be really useful as an antiemetic drug in patients receiving cisplatin chemotherapy [17, 18]. When given in high intravenous doses, MCP has proved to be superior to placebo or other antiemetic agents such as prochlorperazine and Delta-9-tetrahydrocannabinol [19]. While very high doses of MCP up to 10 mg/mg were initially used by Gralla *et al.* [4], similar antiemetic efficacy was later obtained with only a 3 mg/kg total dose [5, 20]. Corticosteroids used alone have been previously reported to have also antiemetic effects [9, 11]; a few trials have recently shown that combination regimens adding metoclopramide to corticosteroids were of interest to prevent CDDP-induced nausea and vomiting [13, 20, 21]. A randomized trial published by Strum *et al.* [21] did not show better efficacy of the MCP + Dexamethasone combination over MCP alone, but patients subjectively preferred the combination treatment. Our trial shows that high dose methylprednisolone added to high dose metoclopramide constitutes a more effective antiemetic regimen than metoclopramide given alone at the doses and schedules tested, with improved control of the number of vomiting episodes as well as decreased nausea. Both regimens were well tolerated, without dystonic reactions.

Differences in efficacy of antiemetic treatment have been reported to depend on the dose of CDDP used [22, 23]. No such difference was observed in our series although the CDDP-doses only varied from 75 to 100 mg/m^2 which may constitute a bias to assess this statement. Likewise the combination of antineoplastic drugs did not result in poorer digestive tolerance. However, sex appeared to affect the incidence of nausea and vomiting, with women presenting more nausea and vomiting than did men ($P < 0.05$), irrespective of both chemotherapy regimen and cancer primary site. This has been recently reported for cancer chemotherapy-induced nausea and vomiting [23] whereas poorer digestive tolerance to morphine in terminal cancer patients has been observed in female patients [24].

Finally, the use of corticosteroids deserves some caution. If they do not modify the antineoplastic properties of such drugs as cisplatin [25], the additional doses given as antiemetics may overlap with chemotherapy regimens using glucocorticoids [26] and may induce adverse effects such as osteonecrosis (as has occurred, for example, during treatment for lymphomas) or cataracts [27].

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