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Methylprednisolone as an antiemetic drug

A randomised double blind study

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Summary. *To evaluate the antiemetic efficacy of high-dose methylprednisolone (MP) in previously untreated cancer patients receiving cisplatin (CPDD) for the first time, we performed a randomized double blind study. MP or a placebo (PLB) was administered six times during each course of chemotherapy. The first dose was 500 mg and all others, 250 mg. A total of 30 patients were included and studied during three chemotherapy courses. No significant differences were found between the MP- and PLB-treated group with respect to the number of emetic episodes and degree of nausea. There was also no difference for pain, appetite, nausea, vomiting, sleep, weakness, or energy level as analyzed by the use of a Linear Analog Self-Assessment (LASA) scale up to 7 days after chemotherapy. On the other hand, the assessment of well-being, anxiety, and mood favored the PLB group.*

We conclude that high-dose MP used as a single antiemetic medication against CPDD-induced nausea and vomiting is of only limited value or none at all.

Introduction

It was suggested in previous clinical studies [10, 12] that MP possesses a significant antiemetic efficacy when administered in high doses concomitantly with low to moderate emetogenic chemotherapy.

The administration of high-dose dexamethasone (DX) alone or in combination with other antiemetic drugs also improved nausea and vomiting caused by slightly to moderately [4, 5] and highly emetogenic cancer chemotherapy [1–3, 7, 13].

To study the value of high-dose MP as antiemetic medication in CPDD combinations and its possible side effects, a randomized double blind trial was performed in previously untreated cancer patients.

Patients and methods

Thirty previously untreated cancer patients receiving a CPDD-containing regimen entered this trial from January 1983 through September 1983. Criteria for inclusion were:

1. Karnofsky performance status of at least 60
2. Absence of any other cause of nausea and vomiting (e.g., gastrointestinal obstruction, cerebral metastasis)
3. Absence of contraindication for glucocorticoid administration (e.g., diabetes mellitus, peptic ulcer disease, active tuberculosis, or other important infection, previous adverse reactions to glucocorticoids)
4. Absence of contraindications for CPDD treatment (e.g., congestive heart failure, renal failure, peripheral neuropathy, bone marrow depression)

All patients included were expected to be able to receive three cycles of chemotherapy at 3- to 4-week intervals. The combinations used were:

1. CPDD 80 mg/m^2 on day 1; VP16-213 120 mg/m^2 on days 1 and 8; or
2. CPDD 80 mg/m^2 on day 1; vinblastine 6 mg/m^2 on days 2 and 8; bleomycin 15 mg on days 2 and 8.

CPDD was administered by IV infusion over 30 min, with extensive saline hydratation before and after during a 30-h hospitalization.

Patients were randomly assigned to treatment with MP or PLB on day 1 of each cycle. The preparation administered remained the same for each patient during the three courses of chemotherapy. MP or PLB 250 mg was supplied in vials containing sterile powder and was unidentifiable for the research team[1]. The powder was dissolved in 10 ml saline. The 500-mg dose of the study drug was administered by slow IV bolus injection 2 h before the CPDD infusion, and subsequently 250 mg was given IV at the onset of the CPDD administration and every 6 h for four doses afterwards.

The patients were informed about the investigational procedure and allowed to ask for additional antiemetic medication (domperidone 10 mg IV) at any time.

The nursing staff recorded the number of vomiting bouts, the amount of additional domperidone therapy, and possible untoward effects. To obtain information about the overall impression with respect to nausea and gastrointestinal discomfort, patients recorded their symptoms on LASA scales[1] [6] at 5, 11, 17, 23, and 29 h after the first study drug administration. LASA scales for pain, appetite, subjective well-being, nausea, vomiting, sleep, weakness, energy level, anxiety, and mood were completed daily from day 2 through day 7 by the patients, with optional assistance from a member of the family.

Data of all patients, whether or not completing three courses of chemotherapy, were evaluated. All continuous

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1 Study drug and LASA scales were kindly provided by the Upjohn Co. Belgium

Table 1. Patient characteristics

	Methyl-prednisolone	Placebo
Number of patients	15	15
Age (y): – Range	51–76	41–75
– Median	62	62
Sex ratio ♂/♀	12/3	14/1
Tumor origin: – Bronchus	7	11
– Gynecologic system	2	2
– Head and neck	5	2
– Unknown	1	–
Chemotherapy:		
Cisplatin:		
Number of courses	39	40
Dose range (mg)	128–160	120 –160
Median	136	136
VP16–213:		
Number of courses	18	25
Dose range (mg)	100–240	75 –240
Median	200	200
Bleomycine:		
Number of courses	15	10
Dose range (mg)	10– 15	15 –30
Median	15	15
Vinblastine:		
Number of courses	12	10
Dose range (mg)	5– 10	7.5– 10
Median	10	10

Table 2. Anti-emetic effect.

		Number (N°) of emetic episodes Methyl-prednisolone	Placebo
1st cycle:	N° of courses	15	15
	Range	0– 8	0– 8
	Median	2	3
	Total	33*	45
2nd cycle:	N° of courses	12	14
	Range	0–20	0–12
	Median	2– 3	4
	Total	51*	62
3rd cycle:	N° of courses	12	11
	Range	0–20	1–11
	Median	3– 4	4
	Total	52*	57
		Additional domperidone (mg)	
		Methyl-prednisolone	Placebo
1st cycle:	Range	0–40	0–40
	Median	10	10
	Total	170	180
2nd cycle:	Range	0–50	0–40
	Median	10	10–20
	Total	170	210
3rd cycle:	Range	0–40	0–40
	Median	10	20
	Total	180	190

* Not significantly different

variables were analyzed by analysis of variance; categorical variables were analyzed by a chi-square test.

Results

Patient characteristics are summarized in Table 1. There was an equal distribution with respect to age, sex, tumor type and number and amount of chemotherapy. Three patients in the MP group withdrew from the study after one cycle of chemotherapy (tumor progression 2; compliance 1). One patient in the PLB group discontinued the chemotherapy because of gastrointestinal toxicity after one cycle; three patients in the PLB group withdrew after two cycles (tumor progression 2; compliance 1). A total of 39 courses was given in the MP group and 40 in the PLB group. All six doses of study medication were administered in each course of chemotherapy. There was no statistically significant difference between the two groups in the total number of vomiting episodes (Table 2) and the degree of nausea, as represented by the amount of domperidone administered (Table 2).

In both groups, 20% of patients were free of vomiting during the first course: 16.7% in the MP group and 7.1% in the PLB group during the 2nd course; and 25% and 0%, respectively, during the 3rd course. These percentages, however, are not statistically different. The analysis of LASA scales from day 2 through 7 did not show any statistical difference for nausea, vomiting, sleep, weakness, energy level, pain, or appetite. Statistically significant differences were found for anxiety during the 3rd course of chemotherapy (days 2 and 7); for mood during the 1st course (days 5 and 6) and the 2nd course (day 6 only); and for subjective well-being during the 1st course (day 3). All these differences were in favor of the PLB-treated group.

In the MP group one patient presented a sinus bradycardia during the 1st course. No other adverse reactions were recorded.

Discussion

The present study is the first randomized double blind trial examining the efficacy of high-dose MP as sole antiemetic agent during CPDD combination chemotherapy. In contrast to what could have been expected from previous studies [1, 2], no significant antiemetic activity of this corticosteroid in the given schedule was observed. This lack of significant antiemetic efficacy is also in contrast with the favorable results with high-dose DX, showing that high-dose DX possesses similar antiemetic efficacy to high-dose metoclopramide (MCP) [3, 7, 13]; is better than PLB [7] inCPDD-containing chemotherapy; or is better than PLB in slightly to moderately emetogenic chemotherapy [4, 5]. Nevertheless, these favorable results for high-dose DX were not consistently observed. In one study [9], which was well designed and involved a relatively large number of untreated patients [4, 6], high-dose MCP was more effective than high-dose DX as an antiemetic in low-dose CPDD (50–60 mg/m^2) chemotherapy, reaching statistically significant superiority in the high-dose CPDD (120 mg/m^2)-treated patients. Furthermore, the results of the only randomized double blind study in CPDD combination chemotherapy with high-dose DX and PLB [8] suggested that high-dose DX was no better than PLB in reducing the incidence of vomiting and only reduced the severity of vomiting, an aspect we did not

look for. In a third study [11], the antiemetic efficacy of high-dose DX in non-CPDD-containing chemotherapy was comparable to that of high-dose MCP only in patients treated with slightly to moderately emetogenic chemotherapy, but was significantly worse with highly emetogenic combinations (including dacarbazine, nitrosurea, nitrogen mustard).

These discrepancies between the results of the favorable high-dose DX studies [1–3, 7, 13] and the unfavorable studies [8, 9, 11], including the present observations might possibly, however, be explained partly by differences in study design (randomization, double blind procedure) and patient characteristics (type of cancer, previous treatment, number of patients). In our study, for example, a small but not significant superiority of high-dose MP was observed with respect to the number of vomiting episodes in each of the three cycles and to the number of patients not affected by vomiting. It is conceivable that with a larger sample small antiemetic effects could have led to significant differences.

Although some of the results of the high-dose DX trials in CPDD chemotherapy may be contradictory, our results with high-dose MP contribute to the general impression that high-dose corticosteroids have only limited clinical value or none at all as antiemetics if used as a single antiemetic modality in CPDD-related nausea and vomiting.

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