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Short communication

Improved control of cisplatin-induced emesis with a metoclopramide-dexamethasone combination

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Summary. *Twenty-four patients receiving combination chemotherapy including cisplatin at a dosage of 50 mg/m² were entered on this antiemetic randomized open cross-over study. High-dose dexamethasone (DXM) (regimen A) was compared with the combination of DXM and high doses of metoclopramide (MCP) (regimen B). Five patients (20%) treated with regimen A and 13 (54%) treated with regimen B suffered neither nausea nor vomiting ($P < 0.05$). Regimen B was found to be significantly more effective than regimen A for all the parameters of evaluation considered. No severe side-effects were observed.*

Introduction

Emesis still remains a very serious problem in cancer chemotherapy, both for patient and for oncologist.

The antiemetic drugs currently in use are of only marginal benefit against most emetogenic drugs such as cisplatin (DDP). Thus, many new antiemetic agents are currently being evaluated [5, 7].

Corticosteroids, given at high doses, are promising as far as their antiemetic effectiveness is concerned. Both methylprednisolone and dexamethasone have been used on the assumption that prostaglandin release is involved in the mechanism of emesis caused by cytotoxic drugs [1, 7]. However, a recent report does not confirm this hypothesis [4].

Several investigators have suggested that the antiemetic combinations affecting the emetic pathway at more than one site might provide improved emesis control [6, 8, 9].

To test this hypothesis, we began a trial in which a combination of metoclopramide (MCP) and dexamethasone (DXM) was compared with DXM administered alone.

Materials and methods

In all 24 patients (17 male and 7 female; median age 61.5, range 36–75 years) were entered on this randomized open cross-over study. Twenty-two patients with head and neck cancer received CABO combination (cisplatin, methotrexate, bleomycin, vincristine) and two patients with cervical carcinoma received BOMP (cisplatin, vincristine, mitomycin C, bleomycin) combination chemotherapy. In both cases DDP was given alone (50 mg/m²) according to Vogl et al. [11] on the day of the study. Patients with diabetes mellitus, peptic ulcer, and moderate to severe hypertension were excluded.

Eligible patients were stratified according to prior chemotherapy. Of the 24 patients, 10 had previously received chemotherapy; four had also been previously treated with DDP. In all cases informed consent was obtained. Two antiemetic regimens were used. *Regimen A:* DXM 8 mg IM 24 and 12 h before and 6 and 12 h after DDP and 10 mg IV immediately before cisplatin. *Regimen B:* DXM as above, plus four injections of MCP 1 mg/kg each IV, at 30 min before and 1, 2, and 4 h after DDP. Each patient completed a questionnaire rating the intensity of emesis on a scale of 0–4 (0 = no side-effect, 1 = only nausea, 2 = less than 5 episodes of vomiting, 3 = 5–15 episodes, 4 = more than 15 episodes). The duration of the symptoms, the patient's overall opinion on a semantic scale (good = 1, fairly good = 2, poor = 3, very poor = 4) and preference between the two antiemetic regimens were also recorded. Details have been presented in a previous report [3].

Results

The results are summarized in Table 1. Five patients (20%) treated with regimen A and 13 (54%) treated with regimen B suffered neither nausea nor vomiting ($P < 0.05$). Regimen B was found to be significantly more effective than regimen A with respect to the mean score for intensity ($P = 0.01$), the mean duration of symptoms ($P < 0.001$), and the mean score for the patients' opinions ($P = 0.01$).

A highly statistically significant difference between the two treatments was found when the products of intensity score and duration were compared ($P < 0.001$). When the patients were asked their opinion of the two treatments 13% had no preference and 66% preferred regimen B ($P < 0.05$).

To evaluate the influence of prior chemotherapy we compared results obtained in previously treated and untreated patients. No significant differences were found in the parameters of evaluation when the sum of the variables obtained with both regimens A and B was considered. When patients were stratified according to previous chemotherapy, statistically significant differences between the two treatments for all parameters of evaluation were found only in the subgroup of untreated patients. Neither treatment caused severe side-effects. Facial erythema occurred in approximately 20% of the patients after both regimens. In 25% of the patients mild to marked sedation was present only after the MCP-DXM combination. Neither extrapyramidal reactions to MCP, nor

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Table 1. Results

Parameters of evaluation		Total patients (n = 24)			Prior chemotherapy					
					No (n = 14)			Yes (n = 10)		
		Reg. A DXM	Reg. B DXM +MCP	P	Reg. A DXM	Reg. B DXM +MCP	P	Reg. A DXM	Reg. B DXM +MCP	P
Patients without nausea or vomiting	No.	5	13	< 0.05[a]	2	9	< 0.05[a]	3	4	> 0.05[a]
	%	20.8	54.1		14.2	64.2		30	40	
Intensity (score)	Mean	2.0	1.1	$= 0.01$[b]	2.3	1.0	< 0.01[a]	1.5	1.3	> 0.05[a]
	SD	1.3	1.2							
Duration of symptoms (h)	Mean	5.5	4.2	< 0.001[c]	7.8	5.9	< 0.05[c]	2.4	1.9	> 0.05[c]
	Range	0–72	0–72							
Intensity (score) × duration (h)	Mean	19.1	11.9	< 0.001[c]	28.9	17.4	< 0.05[c]	54.2	40.8	> 0.05[c]
Patients opinion (score)	Mean	2.3	1.6	$= 0.01$[b]	2.5	1.8	< 0.05[a]	2.1	1.6	> 0.05[a]
	SD	1.0	0.9							
Patients preference	No.	5	16	< 0.05[a]	2	11	< 0.05[d]	3	5	> 0.05[d]

[a] Chi-square test
[b] Student's t-test
[c] Mann-Whitney U-test
[d] Fisher exact test

serious side-effects of the high doses of DXM were observed.

Discussion

Following the first report [1] on the antiemetic activity of high-dose dexamethasone against cisplatin-induced emesis we started a careful investigation of this assertion.

In a previous report [3] we presented results obtained in a randomized open cross-over trial employing MCP vs DXM in patients receiving two combinations of chemotherapy including DDP at a dosage of 50 mg/m^2. The data presented suggest that the two drugs provide a similar degree of protection, both being significantly more active than placebo. Both treatments induced complete relief from emesis in about 25% of patients. No severe side-effects were observed, but patients with serious contraindications to corticosteroids were excluded. However, in approximately one-third of the patients, severe to intolerable emesis was observed with both agents.

In the present study we evaluated the effectiveness of a combination of the two antiemetic drugs. The design of the trial was considered the most reliable for evaluation of the effectiveness of antiemetic agents [10]; in fact the study was planned to rule out several variables that might interfere with correct interpretation of the results.

All the patients received the same emetogenic agent at the same dosage and regimen. The combination of MCP and DXM was able to control emesis completely in more than 50% of patients. We agree with Bruera et al. [2] that this combination does not increase the toxicity of MCP when used alone. Despite these improvements, between 20% and 30% of the patients in our two series were still disappointingly resistant to the antiemetic drugs administered.

Further studies are currently in progress to confirm these preliminary findings, to assess the activity of this antiemetic drug combination in the control of emesis induced by other emetogenic drugs, and to ensure that these same results are maintained in subsequent courses of chemotherapy, as well as to evaluate the long-term toxicity of the MCP-DXM combination.

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