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FROM THE DEPARTMENT OF ONCOLOGY, HOSPITAL LA PAZ, MADRID, SPAIN.

ANTIEMETIC REGIMENS IN OUTPATIENTS RECEIVING CISPLATIN AND NON-CISPLATIN CHEMOTHERAPY

A randomized trial comparing high-dose metoclopramide plus methylprednisolone with and without lorazepam

M. GONZÁLEZ BARÓN, J. I. CHACÓN, C. GARCÍA GIRÓN, A. ORDÓÑEZ GALLEGO, M. L. GARCÍA DE PAREDES, J. FELIU, P. ZAMORA, C. HERRANZ, P. GARRIDO and A. ARTAL

Abstract

Results of a randomized trial on antiemesis for cisplatin (CDDP) and non-CDDP chemotherapy-induced vomiting are reported. One hundred and sixty-three outpatients received 282 chemotherapy courses (141 with CDDP and 141 without CDDP). Patients were randomly assigned to receive either high-dose metoclopramide plus metylprednisolone (arm A) or the same drugs plus lorazepam (arm B). In both arms a high protection rate for vomiting was obtained, on the whole without statistically significant differences. Patients who received lorazepam had, however, significantly fewer nausea episodes during first day postchemotherapy ($p < 0.05$). Arm B was also superior in anxiety control during the first day of chemotherapy ($p < 0.01$). Both regimens were significantly more effective in patients who had not been given chemotherapy previously ($p < 0.01$). No differences in antiemetic protection were found between CDDP and non-CDDP courses. No significant differences were found in premonitory vomiting control between the two arms of the trial. Toxicity was very mild with both regimens, although sedation was significantly higher in arm B ($p < 0.001$). We conclude that high-dose metoclopramide plus metylprednisolone is a highly effective combination for chemotherapy-induced nausea and vomiting, and that it is quite suitable for outpatient use. Lorazepam did not significantly increase the antiemetic potency of the combination, nor did it improve premonitory vomiting control, although it gave a better control of acute nausea and anxiety.

Key words: Cancer, chemotherapy, cisplatin, nausea, vomiting, high-dose metoclopramide, methylprednisolone, lorazepam.

Control of nausea and vomiting in patients on cytotoxic therapy is still a crucial issue in the management of patients with cancer. Chemotherapy-induced emesis is experienced by more than 75% of patients receiving cisplatin-containing chemotherapy (1). Other authors state that this incidence may be as high as 100% in patients receiving DTIC, doxorubicin or cisplatin-containing regimens (2). This disabling side-effect worsens quality of life and produces a poor compliance with therapy. Penta et al. (3) found that up to 10%–15% of patients refused therapy because of nausea and vomiting at some time during the treatment. Similar figures have been reported by other authors (3). Refusal of therapy due to emesis is particularly serious in potentially curable tumors, such as testicular cancer or malignant lymphoma.

High-dose metoclopramide (MCP) has been shown to be a highly useful antiemetic drug (4–6), but with some limitation due to important side-effects (mainly extrapyramidal symptoms) when used in monotherapy. Several studies have shown that corticosteroids potentiate the antiemetic effect of MCP. The active mechanism of corticosteroids is not known, but they do not seem, like MCP, to exert their effects by primary blockage of dopamine receptors. Despite this, several studies have shown a definite increase of antiemetic action when MCP is associated with high-dose dexamethasone (7, 8) and methylprednisolone (9).

Lorazepam is a benzodiazepine that has been widely used in clinical trials on antiemetic therapy (10, 11). Although it has only limited antiemetic activity in itself (10),

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it has been found to be a quite effective adjuvant to other antiemetic agents (12, 13). It is probable that the amnesic property of lorazepam may contribute to its usefulness in the control of emesis (14).

Diphenhydramine has not shown antiemetic activity in earlier trials. However, several reasons justify its inclusion in an antiemetic trial. First, diphenhydramine is uniformly effective in controlling the acute dystonic reactions produced by MCP (15). Second, it may improve antiemetic control by means of its blocking effect on histamine receptors in the brain stem (16).

Most reported antiemetic trials have been designed on an inpatient base, since this is the way in which chemotherapy courses often are given. In our department, structural, social and demographic reasons make it very difficult to admit a high number of patients for programmed chemotherapy and a large part of the chemotherapy must be given in the outpatient service. Therefore, the present trial was designed as an ambulatory schedule.

Material and Methods

Between October 1988 and January 1989, 167 adult patients with histologically confirmed cancer were entered into the study. Of these patients, 35 had non-small cell lung cancer, 33 urinary tract cancer, 19 small cell lung cancer, 13 breast cancer, 13 head and neck cancer, 11 non-Hodgkin's lymphoma, 9 gastrointestinal cancer, 9 Hodgkin's disease, 6 malignant bone tumors and 15 other types of malignancy. Four patients were excluded from the trial; two died from non-related cancer causes before the protocol was completed, and the other two were lost to follow-up. Eligible patients could have had previous chemotherapy, but this was registered in their medical record. Patients under 14 years of age, pregnant women, patients on psychoactive therapy and with psychiatric disease, and patients with central nervous system metastases were excluded from the study. A basic cultural level was a prerequisite for entering the trial. At inclusion or during the study no therapy with corticosteroids or other antiemetic drugs (not included in the study) was allowed. Because of the outpatient character of the trial, ECOG 0, 1 or 2 performance status was required at inclusion and defined as: ECOG 0 = asymptomatic; ECOG 1 = symptomatic but fully ambulatory; ECOG 2 = symptomatic but less than 50% of day time at bed; ECOG 3 = symptomatic and need of staying more than 50% of daytime at bed but not bedridden; ECOG 4 = bedridden.

In 163 patients, 282 chemotherapy courses were given: 141 with CDDP and 141 without CDDP. Eighty-three patients had received previous chemotherapy (40 with CDDP, 43 without CDDP). During the trial they received 132 chemotherapy courses. Eighty patients had not had previous cytotoxic therapy. They were given 150 chemotherapy courses during the trial.

Table 1

Distribution of patients in the two arms of the trial

	Arm A[1]	Arm B[2]
No. of patients	85	78
Sex (M:F)	65:20	51:27
Age, years (median)	54	50
PS[3]		
0	33 (38%)	32 (42%)
I	40 (48%)	40 (51%)
II	12 (14%)	6 (7%)
No prior therapy	43	37
Previous therapy	42	41
CDDP regimen	20	20
Non-CDDP regimen	22	21
Disease stage		
Early	50	46
Advanced	35	32

[1] Arm A: high-dose metoclopramide + methylprednisolone
[2] Arm B: high-dose metoclopramide + methylprednisolone + lorazepam
[3] PS: performance status according to ECOG scale.

All patients were randomly assigned to receive one of the two antiemetic therapy arms, irrespective of previous therapy or if the patient was programmed to receive a CDDP-containing regimen or not. Each patient was maintained on the same antiemetic therapy during the whole trial. Table 1 summarizes the characteristics of patients and their distribution in each arm of therapy.

Cisplatin was given at our 'day hospital' as a 30-min i.v. infusion, with vigorous hydration and mannitol administration before and after infusion (4). The cisplatin dose range was 80–130 mg/m^2 (median 105 mg/m^2). Other chemotherapeutic agents used in combination with cisplatin included doxorubicin, vindesine, 5-fluorouracil, bleomycin, mitomycin, methotrexate, and ifosfamide. Cytotoxic agents used in courses without cisplatin included doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, dacarbazine, procarbazine, ifosfamide, methotrexate, 5-fluorouracil. No patient stayed more than 6 h in the 'day hospital'.

All patients received metoclopramide 2 mg/kg by i.v. infusion (Primperán, Lab Delagrange S.A., Madrid, Spain), diluted in 50 ml of 0.9% sodium chloride and infused in 15 min, and methylprednisolone 125 mg (Solumoderin, Upjohn Farmoquimica S.A., Madrid, Spain), as i.v. bolus. Both drugs were given 30 min before and 90 min following chemotherapy. All patients also received diphenhydramine 50 mg by oral route (Benadryl, Parke-Davis Lab., Barcelona, Spain) before chemotherapy. Patients in arm A did not receive any other antiemetic therapy. Patients in arm B received in addition lorazepam 0.02 mg/kg by oral route (Orfidal Whyeth, Orfi Farma S.A., Barcelona, Spain) 30 min before chemotherapy and 8 h after the first dose. The patients took this last dose in their

homes. Patients were not told to have any special care concerning meals or life style during the study.

Each patient was issued with a form before the chemotherapy infusion started and was asked to fill it in at home. All the items in the form referred to the day of the chemotherapy and to the two following days. The following items were included: time when nausea and vomiting started, their frequency and intensity and the time when they abated; nervousness or anxiety; somnolence or sedation; occurrence of abnormal reactions (tremor, dystonic movements, diarrhea, etc.). Vomiting protection was evaluated on the following scale: complete protection (CP) = no vomiting; major protection (MP) = 1–2 vomiting episodes; minor protection (mP) = 3–4 vomiting episodes; failure (F) = 5, or more than 5 vomiting episodes. Similarly, the following scale was used for the evaluation of nausea protection: complete protection (CP) = no nausea; major protection (MP) = 1–4 nausea episodes; minor protection (mP) = 5–9 nausea episodes; failure (F) = 10 or more nausea episodes. On both scales, global protection (GP) was used as a common term for complete protection (CP) and major protection (MP).

Anxiety or nervousness was graded as none, slight, moderate and severe. Sedation was graded as none, mild (patient lethargic but woken up by verbal stimulation), moderate (only woken up by physical stimulation (face clapping) and completely oriented when awake), and severe (only woken up by physical stimulation and confused when awake). The form was collected at the next visit by one of the investigators, and a new form was provided for the following course. Telephone surveillance was provided for each patient during the two days following chemotherapy, in order to ensure optimal data collection.

Informed consent was obtained from each patient before entering the trial.

Statistical analysis was performed using the χ^2-test, Fisher's exact test and Yates' correction for small samples.

Results

Vomiting. Of the patients in arm A, 76% obtained CP and 16% MP during the first day of therapy. During the second day, 78% obtained CP and 13% MP. Global protection (GP = CP + MP) was 92% for the first day and 91% for the second day respectively. Patients in arm B obtained 82% CP and 10% MP during the first day of therapy, and 84% CP and 10% MP during second day of therapy. GP was 92% and 94% for first and second day respectively. The differences between the two arms were not significant for any the first, second and third days. In arm A, CP was achieved in 86% of the patients, and MP in 8%. In arm B, CP was obtained in 85% and MP in 10%.

Table 2 shows the results in both arms, also comparing patients who received CDDP with those who were given non-CDDP regimens. There were no significant differences between the two arms, regardless of whether CDDP was used or not; nor were any significant differences revealed by stratification for low-dose CDDP (< 100 mg/m^2) and high-dose CDDP (> 100 mg/m^2). Antiemetic therapy was less effective in both arms in patients previously treated ($p < 0.01$). This was true of both CDDP and non-CDDP regimens (Table 3).

Table 2

Results in the two arms of antiemetic therapy during CDDP and non-CDDP courses

	Arm A				Arm B			
	CDDP (n = 73)		Non-CDDP (n = 72)		CDDP (n = 68)		Non-CDDP (n = 69)	
	n	(%)	n	(%)	n	(%)	n	(%)
CP	53	(73)	58	(80)	51	(75)	62	(90)
MP	14	(19)	9	(12)	11	(16)	2	(3)
mP	2	(3)	3	(4)	4	(6)	4	(6)
F	4	(5)	2	(3)	2	(3)	1	(1)
				NS				

CP = complete protection; MP = major protection; mP = minor protection; F = failure.

Table 3

Results of antiemetic treatment in patients who received or not chemotherapy before entering the trial (global results for both arms of the trial)

	No previous therapy (n = 150)		Previous therapy (n = 132)	
	n	(%)	n	(%)
CP	127	(85)	94	(71)
MP	16	(11)	24	(18)
mP	5	(3)	6	(4)
F	2	(1)	8	(6)

CP = complete protection; MP = major protection; mP = minor protection; F = failure

Occurrence of delayed vomiting (third day post-chemotherapy) was not modified in the two arms. As expected, delayed vomiting episodes were significantly more frequent in CDDP courses than in non-CDDP courses (with CDDP: CP = 79%, MP 12%; without CDDP: CP = 92%, MP = 6%. $p < 0.01$).

Nausea. Nausea control was significantly more effective in arm B than in arm A during the first day of chemotherapy (arm A: CP = 68%; MP = 22%; GP = 90%; mP = 3%; F = 6% and arm B: CP = 79%; MP = 13%; GP = 92%; mP = 6%; F = 0.8%; $p < 0.05$). However, no differences were found between the two arms during days 2 and 3 post-chemotherapy. Stratification for CDDP/non-CDDP regimens and for previously treated/previously untreated

Table 4

Toxic effects

	Arm A	Arm B	p-value
Dystonia	5.4%	3.4%	NS
Sedation			
Grade 0	49.0%	8.4%	<0.01
Grade 1	40.0%	43.7%	NS
Grade 2	7.3%	26.0%	<0.01
Grade 3	2.4%	21.8%	<0.01

patients revealed no significant differences between the two arms.

Premonitory vomiting. There were 39 episodes of anticipatory vomiting in the 282 courses administrated (14%) with no significant difference between arm A (16%) and arm B (9%). Several variables were explored for prognostic value in anticipatory vomiting (sex, age, performance status, tumor extension, chemotherapy schedule, antiemetic therapy). The only factor that seemed to influence anticipatory vomiting was age. Its rate was significantly higher in patients with age between 15 and 35 years compared to older patients ($p < 0.05$).

Anxiety. Anxiety control was significantly more effective in arm B than in arm A during first day chemotherapy (no anxiety in 60% of courses in arm B vs 44% of courses in arm A, $p < 0.05$). Surprisingly, anxiety was significantly higher in arm B during the third day post-chemotherapy than in arm A (arm A: no anxiety 80%, slight anxiety 13%; arm B: no anxiety 69%, slight anxiety 7%, $p < 0.001$).

The toxicity was low. Mild dystonic reactions occurred in 8 patients (5%) and during 13 courses (4.6%). They occurred in 5% of the courses in arm A and in 3% of the courses in arm B. This difference was not significant. Sedation occurred more frequently in arm B, and the difference was significant ($p < 0.001$) (Table 4). No other toxic effects were recorded.

Discussion

Since Gralla et al. (4) published their paper, high-dose MCP has become nearly a standard schedule for prevention of chemotherapy-induced nausea and vomiting. However, corticosteroids have shown a high synergistic and potentiating action when given with MCP. Diphenhydramine and lorazepam are useful as adjuncts to other antiemetic drugs (10).

The purpose of the present trial was to test in a randomized way the efficacy of two antiemetic combinations, to compare their effectiveness in CDDP and non-CDDP chemotherapy regimens and to explore their use on an outpatient basis. The combination of MCP and methylprednisolone has previously only rarely been reported on in the literature, in contrast to the combination with dexamethasone (17).

The results are quite encouraging. Global protection (complete protection plus major protection) from nausea and vomiting was obtained in more than 90% of the courses for CDDP and non-CDDP regimens with both types of antiemetic therapy. No important differences between the effect of MCP plus methylprednisolone and the same regimen plus lorazepam were observed. Addition of lorazepam seemed to condition a lesser anxiety level during the first day of chemotherapy, which is in agreement with the literature (10). Surprisingly, the patients reported a significantly higher anxiety level during the third day post-chemotherapy when lorazepam was used. This paradoxical effect is difficult to explain although the sedation effect of lorazepam has been reported as a desired effect in patients on chemotherapy (18). We feel that our patients experienced the pharmacological sedation as uncomfortable. Efforts to keep awake might be the reason for the late anxiety reported. This explanation is contradicted by lorazepam being a short-action benzodiazepine, and thus unlikely to produce sommnolence two days after its administration. Another possible explanation is that the 'anxiety' reported by the patients could have been self-limited episodes of akathisia and other mild extrapyramidal reactions. This might also account for the absence of mild dyskinesia from toxic effects recorded.

Patients who had previously received chemotherapy experienced significantly poorer vomiting control. Psychologic predisposition in patients who had had severe vomiting during chemotherapy courses given with less powerful antiemesis might play a role (17).

Quality of life in cancer patients is a diffuse concept that is influenced by a large number of factors. Provided that a symptomatic relief is obtained with anticancer therapy, we think that the time spent in hospital could be a very important factor conditioning quality of life. For this reason and also for some practical reasons already mentioned, our group is very interested in outpatient chemotherapy. Very few antiemetic randomized trials with this specific aim have been previously reported (19). To our knowledge, this is the first high-dose MCP randomized trial in which CDDP and non-CDDP regimens have been used on an outpatient basis. A trial of this type has some limitations. The patients' compliance with therapy, the results of therapy and its side-effects cannot be as reliably evaluated as is possible when the patients are observed in hospital. However, we think that these drawbacks are outweighed by the advantages to be gained, namely more comfort for the patients and less dependence on the hospital.

We conclude that high-dose MCP combined with methylprednisolone is highly effective for control of emesis during CDDP and non-CDDP chemotherapy. The addition of lorazepam improves anxiety control, but it does not increase the antiemetic efficacy or improve control of anticipatory and delayed vomiting. The two regimens tested are quite suitable for outpatient use.

Corresponding author: Dr José Ignacio Chacón, Servicio de Oncología (5a. Planta), Hospital La Paz, Pasèo de la Castellana 261, E-28046 Madrid, Spain.

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