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Randomized crossover antiemetic study in cisplatin-treated patients

Comparison between high-dose IV metoclorpramide and high-dose IV dexamethasone*

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Summary. This prospective, randomized, nonblind study comparing the antiemetic effectiveness of high-dose IV metoclopramide and high-dose IV dexamthasone was performed in 78 advanced cancer patients. Chemotherapeutic treatment consisted in cisplatin at a high-dose (120 mg/m^2) (HD-CDDP) and at a low-dose (LD-CDDP), either alone (60 mg/m^2) or in combination with other chemotherapeutic agents (50 mg/m^2). The evaluation of the effectiveness of antiemetic therapy was based on three parameters: prevention of vomiting ("major protection"), number of emetic episodes, and subjective preference. Out of 78 study patients, 67 were evaluable. Overall, metoclopramide proved to be statistically superior to dexamethasone in preventing vomiting ($P<0.005$), in reducing the median/mean number of emetic episodes ($P<0.001/0.001$), and in subjective preference ($P<0.01$). The results divided between HD-CDDP and LD-CDDP groups were also in favor of metoclopramide for reduction of the median/mean number of emetic episodes ($P<0.001/0.001$ for the HD-CDDP group and $P<0.001/0.005$ for the LD-CDDP group) and in subjective preference ($P<0.001$ and $P<0.001$ for the HD- and LD-CDDP groups, respectively). No statistical differences were noted when LD-CDDP was used in monochemotherapy, whereas when LD-CDDP was used in combination chemotherapy, statistical differences in favor of metoclopramide were noted again for the median/mean number of emetic episodes ($P<0.01/0.05$) and for subjective preference ($P<0.01$), even though the effectiveness of both antiemetic agents was greatly reduced. The evaluation of previously untreated patients reflected the overall results: for the HD-CDDP group all three parameters demonstrated statistical significance in favor of metoclopramide; for the LD-CDDP group, of all three parameters, prevention of vomiting (major protection) was the only one for which there was no significant difference.

Mild sedation was the only side effect of metoclopramide. No extrapyramidal reactions were noted during this trial, but concomitant orphenadrine treatment was given. Dexamethasone was always well tolerated. In conclusion, high-dose IV metoclopramide demonstrated its superiority over high-dose IV dexamethasone in all subsets of our population except the LD-CDDP monochemotherapy group, in which the two antiemetics were found to be equivalent in effect.

Introduction

Nausea and vomiting are still the most important acute side effects of cisplatin treatment. Moreover, this gastrointestinal toxicity is observed in nearly all patients when high doses of cisplatin are given [16, 24].

In the last few years, an expanding literature has been published regarding this issue, testifying to the importance of the problem and the possible hazard that can result for the patient who refuses further cycles of potentially curative chemotherapy [8, 18, 20, 25].

Because of the ineffectiveness of standard antiemetic treatment [9, 19, 20], new drugs [11, 19, 22, 23] or new schedules for older drugs [1, 4, 6, 9, 12, 15] are now being studied.

Among the different single antiemetics tested with cisplatin-containing regimens, phenothiazines, metoclopramide, cannabinoids, and corticosteroids are the drugs reported so far as effective. Metoclopramide at high-doses was found to be superior to standard phenothiazine treatment and to cannabinoids (THC) when high-doses of cisplatin were used [9, 10]. Cannabinoids were found to be superior to prochlorperazine with low dose cisplatin [11, 23] and equal to prochlorperazine when median to high-doses of cisplatin were given [13, 23]. Therefore, we conclude that metoclopramide at high-doses may be considered the best single antiemetic treatment among those three drugs when high-doses of cisplatin are employed [10].

On the other hand, corticosteroids [5, 14, 17, 20], and particularly dexamethasone [1, 3, 6], have been reported to be very effective in preventing or reducing nausea and vomiting.

However, to our knowledge, no controlled clinical trials have compared IV dexamethasone to IV high-dose metoclopramide in cisplatin-treated patients. It was therefore decided, on the basis of our previous good experience with high-dose metoclopramide [17], to conduct a randomized study comparing the antiemetic activity of these two antiemetic drugs in cisplatin-treated patients.

Patients

All consecutive patients with histologically confirmed malignant disease who were considered acceptable for treat-

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Table 1. Characteristics of evaluable patients

No. of patients	67
Performance status = or > 70	67
Age (years)	
Median	58
Range	33–77
Sex	
Men	35
Women	32
Type of cancer	
Head and neck	36
Ovarian	20
Bladder	6
Uterine	2
Prostatic	1
Pulmonary	1
Lacrimal gland	1

ment with cisplatin alone (120 mg/m^2) or in combination (50–60 mg/m^2) were included in this study.

A performance status equal or greater to 70% on the Karnofsky scale was required. According to chemotherapy protocols only patients with normal bone marrow, renal, hepatic, and cardiac functions were eligible. Patients previously treated with chemotherapy and/or cisplatin were also eligible. The antiemetic treatment evaluation was performed while the patients were in the inpatient section of the Medical Oncology Division. Seventy-eight patients entered this randomized crossover study.

Three patients were not eligible (nonadherence to cisplatin dosages established for our study). Eight patients were not evaluable because of failure to complete the crossover therapy (2 due to early deaths, 6 due to progressive disease after the first cycle).

The main characteristics of the remaining 67 evaluable patients are reported in Table 1. Forty-six patients were previously untreated, fourteen pretreated with chemotherapy not including cisplatin, and 7 had previously been treated with cisplatin.

Methods

The chemotherapeutic regimens used consisted in cisplatin only at high doses (HD-CDDP) (120 mg/m^2), and at low doses (50 mg/m^2) with Adriamycin, cyclophosphamide, fluorouracil, VM-26, bleomycin, mitomycin, and vincristine. Pretreatment hydration with fluids (1000–2000 ml) and mannitol (500 ml of 20%) was performed in all treatment schedules, whereas post-therapy hydration (2000 ml) was performed only with high-dose cisplatin or as necessary.

Each patient was randomly assigned to receive either dexamethasone or metoclopramide with the first chemotherapy cycle as antiemetic therapy. Crossover to the other antiemetic agent was timed for the second consecutive and identical chemotherapy treatment.

All patients were also stratified for high and low doses of cisplatin. Metoclopramide at a dose of 2 mg/kg was added to 100 ml 0.9 sodium chloride and infused IV, over 15 min starting 30 min before and 1.5, 3.5, 5.5, and 8.5 h after cisplatin administration. Orphenadrine 50 mg PO b. i. d. was also administered on the day of the therapy to each patient receiving metoclopramide, to prevent extrapyramidal reactions. Dexamethasone at a standard dose of 8 mg was administered IV 30 min before and then every 3 h to give a total of four more doses after cisplatin therapy. The effectiveness and adverse effects of both treatments were evaluated according to three parameters: duration of vomiting, number of episodes of vomiting, and subjective preference.

The onset and the termination of vomiting were reported on a special flowsheet and then, according to the duration, a score from 0 to 4 was attributed as follows: 0, no symptoms; 1, only nausea; 2, vomiting for less than 4 h; 3, vomiting for longer than 4 but less than 12 h; 4, vomiting for more than 12 h. Scores 0 and 1 correspond to our classification of "major protection."

The number of episodes of vomiting was recorded by nursing staff during the patients' hospitalization. The adverse effects were investigated by the medical staff and reported on a special flowsheet. The subjective preference of those patients expressing any preference was determined upon completion of the crossover therapy through a personal interview by one of the researchers.

The study was not blind; because of the crossover trial design, we performed a paired analysis to remove interpatient variability, calculating the one-tailed probability. We used the Wilcoxon matched-pairs signed-rank test [21] to compare the median number of emetic episodes and the paired *t*-test [2] to compare the mean number of emetic episodes. We also compared matched proportions of patients with scores 0–1 by an exact method [2], because the number of nonconcomitant pairs was too small to apply non-exact methods such as the MC Nemar test. We applied X^2 to test differences between subjective preferences.

Results

Of the 67 evaluable patients, 42 received the LD-CDDP and 25 the HD-CDDP regimens. After randomization, 33 patients completed the treatment with the sequence dexamethasone-metoclopramide and 34 with the metoclopramide-dexamethasone sequence.

Overall (Table 2), metoclopramide was statistically superior to dexamethasone for all three parameters considered (major protection, number of emetic episodes, subjective preference). Major protection (scores 0–1) was evident in 43.3% of patients receiving metoclopramide, as against only 29.8% for those receiving dexamethasone ($P<0.005$). The median/mean number of emetic episodes was greatly reduced with metoclopramide (2/5.1 vs 8/9.4; $P<0.001/0.001$).

A subjective preference for metoclopramide was expressed by 55% of the patients, while only 13.4% expressed a preference for dexamethasone ($P<0.001$).

The analysis of our results referred to HD- and LD-CDDP is reported in Table 2. A statistical difference between the two antiemetics, in favor of metoclopramide, was found with both cisplatin dosages for median/mean number of emetic episodes (HD-CDDP; 2/2.8 versus 6/9.4, $P<0.001/0.001$; LD-CDDP: 3/8 versus 6.5/9.5, $P<0.005/0.01$) and again in the subjective preference of the patients (HD-CDDP $P<0.001$; LD-CDDP $P<0.001$).

Major protection obtained with metoclopramide was similar with both HD-CDDP and LD-CDDP (44% and 42%) and reflected the overall results (43.3%). The same

Table 2. Antiemetic efficacy

Characteristics	Overall results ($n = 67$)			HD-CDDP ($n = 25$)			LD-CDDP ($n = 42$)		
	Metoclopramide	*P*	Dexamethasone	Metoclopramide	*P*	Dexamethasone	Metoclopramide	*P*	Dexamethasone
Patients with score 0–1 (major protection)									
No.	29/67	0.05	20/67	11/25	NS[a]	7/25	18/42	NS[a]	13/42
Percentage	43.3		29.8	44.0		28.0	42.8		30.9
Median score	2	–	2	2	–	2	2	–	2
Range	0–3		0–4	0–3		0–4	0–3		0–4
No. of emetic episodes									
Median	2	0.001	8	2	0.001	6	3	0.005	8
Mean	5.1	0.001	9.4	2.8	0.001	9.4	6.5	0.01	9.5
Range	0–30		0–30	0–11		0–27	0–30		0–30
Subjective preference									
No.	37/67	0.01	9/67	15/25	0.01	4/25	22/42	0.001	5/42
Percentage	55.2		13.4	60.0		16.0	52.4		11.9

[a] NS signifies no statistical differences

was observed with the use of dexamethasone, but the percentage of patients protected against vomiting was lower, i.e. 28.0% and 30.9% for both cisplatin levels (overall 29.8%).

In these subgroups the *P*-values were not significant, perhaps because of the low number of cases collected per group.

Analysis of median scores and ranges obtained overall and in the HD- and LD-CDDP groups reveals no differences except that score 4 was observed only in patients treated with dexamethasone.

The influence of concomitant chemotherapy during LD-CDDP treatment is analyzed in Table 3. No statistical differences were found between the two antiemetics when LD-CDDP was used in monochemotherapy. This fact is confirmed by a high percentage of patients who did not express any subjective preference (76.5%) between the two antiemetics. Moreover, the effectiveness of both drugs in this particular subset of patients is clearly superior to the overall results in the percentage of patients experiencing major protection (64% for both antiemetics) and in the median/mean number of emetic episodes (0/2.3 versus 0/4.1).

On the other hand, during combination chemotherapy (Table 4) the effectiveness of both antiemetics was greatly reduced. Major protection was limited to only 28% of the patients treated with metoclopramide, as against 8% treated with dexamethasone (difference not significant). The median observed score was 3 for both antiemetics, whereas score 4 was observed again only during dexamethasone treatment. The median/mean number of emetic episodes was the highest encountered in this trial (10/9.3 versus 11/13.2 for metoclopramide and dexamethasone, respectively), yet the differences were statistically significant ($P < 0.01/0.05$). The subjective preference was in favor of metoclopramide and was statistically significant ($P < 0.01$).

The antiemetic effectiveness in the previously untreated patient group is reported in Table 4. These results, when divided for HD- and LD-CDDP groups, agree with the overall results, but at a slightly superior level. Statistical differences in favor of metoclopramide were reached at HD-CDDP for all three parameters: major protection

Table 3. Results for LD-CDDP alone or in combination

Characteristics	LD-CDDP alone ($n = 17$)			LD-CDDP in combination ($n = 25$)		
	Metoclopramide	*P*	Dexamethasone	Metoclopramide	*P*	Dexamethasone
Patients with score 0–1 (major protection)						
No.	11/17	NS	11/17	7/25	NS	2/25
Percentage	64.7		64.7	28.0		8.0
Median score	0	–	0	3	–	3
Range	0–3		0–3	0–3		1–4
No. of emetic episodes						
Median	0	NS	0	10	0.01	11
Mean	2.3	NS	4.1	9.3	0.05	13.2
Range	0–11		0–20	0–30		0–30
Subjective preference						
No.	4/17	NS	0/17	16/25	0.01	5/25
Percentage	23.5		0.0	64.0		20.0

Table 4. Results for untreated patients

Characteristics	HD-CDDP ($n = 19$)			LD-CDDP ($n = 27$)		
	Metoclopramide	P	Dexamethasone	Metoclopramide	P	Dexamethasone
Patient with score 0–1 (major protection)						
No.	11/19	0.05	6/19	14/27	NS	10/27
Percentage	57.9		31.6	51.8		37.0
Median score	1	–	2	2	–	2
Range	0–2		0–3	0–3		0–4
No. of emetic episodes						
Median	0	0.05	4	1	0.01	7
Mean	1.8	0.005	7.5	5.4	0.05	9.0
Range	0–7		0–30	0–24		0–28
Subjective preference						
No.	12/19	0.01	2/19	15/27	0.01	2/27
Percentage	69.1		10.5	55.5		7.1

($P<0.05$), median/mean number of emetic episodes ($P<0.05/0.005$) and subjective preference ($P<0.01$).

For the LD-CDDP group, the parameter major protection was the only one for which the difference was not statistically significant whereas median/mean number of emetic episodes and subjective preference again demonstrated the superiority of metoclopramide ($P<0.01/0.05$ and $P<0.01$, respectivley). Metoclopramide toxicity was mild, and in no case was the treatment discontinued. Four patients (5.9% developed diarrhea (more than three bowel movements/24 h); mild sedation was encountered in the majority of patients; and no extrapyramidal reactions were noted during this trial.

Mild diarrhea was also encountered in three patients (4.5%) during dexamethasone treatment. No other toxicity was noted, and most patients reported a good state of general wellbeing.

Discussion

The results of this study confirm the effectiveness of high-dose metoclopramide and dexamethasone as antiemetics. In fact, our overall results of 43.3% and 29.8% of patients experiencing major protection (no vomiting) for metoclopramide and dexamethasone, respectively (Table 2), demonstrate an improvement over the results reported in the literature during cisplatin treatment with concomitant placebo or prochlorperazine administration.

During HD-CDDP therapy and in previously untreated patients (Table 4), we obtained major protection in 57.9% with high-dose metoclopramide, which is superior to the percentage found by Gralla et al. (38% of asymptomatic patients) with the same antiemetic schedule administered to previously untreated patients [9]. We do not have any particular explanation for this difference, except that in our group of patients who experienced major protection we included one who had only nausea (score 1).

On the other hand, when the number of emetic episodes is compared, our results are in accordance with those of Gralla et al. We found a median number of emetic episodes of 0 (range 0–7) while Gralla et al. found a median number of 1 (range 0–9).

Our results with dexamethasone during LD-CDDP in combination with other drugs are not in agreement with those obtained in Aapro's study. The 30.9% (overall group) (Table 2) and the 37% (untreated patients) (Table 4) of patients achieving major protection are different from the 47% with excellent response (no symptoms or slight nausea) in the total group and the 54% with excellent response in the untreated patient group of Aapro's trial [1]. The explanation for these differences may lie in the different dexamethasone schedules (administration IV vs PO), in the different combination chemotherapy, or in the different types of data sampling (inpatients vs outpatients).

Both antiemetic drugs were well tolerated and safe. No extrapyramidal reactions were noted during metoclopromide treatment, but the concomitant administration of orphenadrine could have prevented their onset. The absence of a control arm and the reported low incidence of this side effect do not permit us to draw any conclusions.

We underline the importance of the "emetogenic stimulus" and pretreatment for the response to any antiemetic therapy. In fact, both drugs gave the best results in the untreated patient group, whereas the worst results were recorded during combination chemotherapy. Nevertheless, metoclopramide clearly demonstrated its superiority over dexamethasone, and particularly in the HD-CDDP group, the LD-CDDP group during combination chemotherapy, and the previously untreated patient group.

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