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A randomized trial comparing alizapride alone or with dexamethasone vs a metoclopramide-dexamethasone combination for emesis induced by moderate-dose cisplatin*

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Summary. To evaluate the antiemetic effectiveness and toxicity of a novel congener of metoclopramide (MCP), alizapride (AZP), 29 patients receiving cisplatin (50 mg/m^2) alone or with adriamycin (40 mg/m^2) were entered into a randomized cross-over trial comparing moderate-dose AZP (2 mg/kg for 4 doses) administered alone or with dexamethasone (DXM) (8 mg for five doses) vs a standard combination of MCP (1 mg/kg for four doses) and DXM (as above). With the dosage and schedule used, AZP provided only limited antiemetic protection, with less than 10% of the patients free of emesis. The AZP-DXM combination was significantly more effective than AZP alone in reducing the intensity of the emesis ($P<0.03$). The incidence, however, was statistically unaffected. The additional toxicity of DXM was negligible. Except for the patients' preference for MCP-DXM ($P<0.01$), no differences could be found between the DXM-based regimens, although a trend towards a better antiemetic effect with the MCP combination was evident. The benzamide-related dystonic reactions were equally distributed. Among the 11 patients affected there were 6 who required specific treatments. Unfavourable prognostic factors in the patient population could provide a reasonable explanation for the disappointing antiemetic protection obtained with all the regimens evaluated in this study.

Introduction

In recent years, optimizing the use of drugs already available, given at adequate doses individually or in suitable combinations, has led to improved control of emesis induced by highly emetogenic cytotoxic drugs (e. g. cisplatin). However, the search for new agents with higher therapeutic indexes still remains the principal object of investigation in this field.

Alizapride (AZP), a new benzamide derivative, which showed promising antiemetic activity in preliminary studies with fewer side-effects than metoclopramide (MCP) [7] has recently become available.

Phase I studies have evaluated single doses of AZP ranging from 1 to 5 mg/kg for five doses over an 8-h period. Because of the serious orthostatic hypotension at the highest dose levels, however, lower doses have been selected for further clinical evaluation [2, 4, 6].

Since increasing evidence of a better antiemetic effect with the combination of MCP and high-dose corticosteroids has been reported [1, 3], the present randomized cross-over trial was undertaken to evaluate the effectiveness of moderate-dose AZP alone or in combination with dexamthasone (DXM) vs a standard combination of MCP plus DXM [3].

Patients receiving only intermediate-dose cisplatin (DDP) (50 mg/m^2) were admitted to this study, since recent reports seem to indicate that platinum levels represent a critical factor influencing cisplatin-related emesis [5].

Materials and methods

Between May 1985 and March 1986, 29 cancer patients receiving combination chemotherapy including DDP (50 mg/m^2) were entered in this randomized open cross-over trial (Table 1).

In all but eight cases, adriamycin (40 mg/m^2) was also given on the day of the antiemetic treatment before the 2-h regimen of hydration and diuresis [11] was started for the DDP administration. No other cytotoxic agents were administered until the 3rd day of chemotherapy.

Patients with diabetes mellitus, peptic ulcer and moderate to severe hypertension were excluded. After giving informed consent, patients were randomized to receive one of six possible sequences of the antiemetic regimens currently evaluated (AZP, AZP+DXM and MCP+DXM) during the first three courses of DDP.

Each single dose of either MCP (1 mg/kg) or AZP (2 mg/kg) was diluted in 100 ml saline and infused i. v. over 15 min for four doses, administered 30 min before DDP and 1, 2 and 4 h after. DXM (8 mg) was administered i. m. 24 and 12 h before DDP and 6 and 12 h after; an additional dose was given i. v. over a 5-min period just prior to DDP. Orphenadrine (40 mg) or diazepam (10 mg) was administered only if moderate to severe extrapyramidal symptoms developed.

On the day of the study, the patients were restricted to a clear liquid diet from 12 h before chemotherapy until the evening meal. Prescribed medications with possible antiemetic activity were discontinued 24 h prior to the study.

The patients were asked to complete a self-assessment questionnaire aimed at evaluating the effectiveness of the

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Table 1. Characteristics of the 29 patients

Age	Median	52
	Range	29–72
Sex	Male	5
	Female	24
Performance status	0	19
	1–2	10
Type of cancer	Ovarian	19
	Head and neck	6
	Various	4
Prior non-cisplatin chemotherapy	No	23
	Yes	6
Chemotherapy given on the day of antiemetic treatment	DDP	8
	DDP + adriamycin	21

antiemetic regimens tested. As they occurred, the patients recorded the number of episodes of emesis and retching for 24 h after chemotherapy. The duration of the symptoms was also recorded. The patients also assessed the intensity of the nausea and their subjective opinion, scoring each of these 0–3 on a semantic scale (no nausea, slight nausea, moderate nausea, severe nausea and good, fairly good, bad, very bad). They were also asked whether or not they had eaten on the evening of the study day. On the day after the study, the patients were interviewed, the questionnaire was re-evaluated and side-effects were recorded.

A statistical analysis to evaluate the differences in the antiemetic protection was carried out by means of Fisher's exact test. The Mann-Whitney U non-parametric test was used to examine the differences in both the duration and in the number of episodes of vomiting. Both the severity of emesis and the patients' opinions were evaluated by means of a contingency table.

Results

All but five patients completed the study, having received the assigned sequences of three antiemetic regimens. Reasons for discontinuing the study prior the third regimen were: progressive disease (3 patients), prior severe dystonic reaction (1 patient) and refusal (1 patient). In all these cases the expected antiemetic regimen assigned by randomization in the third course of DDP was AZP alone. In all, 29 evaluable courses for each regimen including DXM and 24 courses for AZP alone were therefore administered.

Table 2 summarized the antiemetic results regardless of the sequence of administration.

The combination of MCP+DXM provided the best

Table 2. Results

		A[a] $N = 24$	AD[a] $N = 29$	MD[a] $N = 29$	*P*-value[b]	
No vomiting						
No symptoms	No.	0	3	6	A/MD[a]	0.02[c]
	%	–	10.3	20.7		
Only nausea	No.	2	3	6		
	%	8.3	10.3	20.7		
Total	No.	2	6	12	A/MD	0.007[c]
	%	8.3	20.6	41.4		
Vomiting						
Episodes (no.)						
1–2	No.	2	4	1	A/AD/MD	0.01[d]
	%	8.3	13.8	3.4	A/AD	0.05[d]
3–10	No.	10	15	15	A/MD	0.01[d]
	%	41.7	51.7	51.7		
>10	No.	10	4	1		
	%	41.7	13.8	3.4		
Number	Median	9	6	3	A/AD	0.03[e]
	Range	0–30	0–24	0–24	A/MD	0.0008[e]
Duration (hours)	Median	3.5	2.6	2.1	A/MD	0.014[e]
	Range	0–24	0–21	0–21		
Patients' opinion						
Good	No.	2	3	4	A/AD/MD	0.0025[f]
	%	8.3	10.3	13.8	A/AD	0.05[f]
Fairly good	No.	7	14	16	A/MD	0.001[f]
	%	29.2	48.3	55.2	AD/MD	0.01[f]
Bad	No.	10	9	8		
	%	41.7	31.0	27.5		
Very bad	No.	5	3	1		
	%	20.8	10.3	3.4		

[a] A, AZP; M, MCP; D, DXM; /, versus
[b] Only significant differences are reported
[c] Fisher's exact test: *P* equal to value shown
[d] 3 × 3 contingency table: *P* smaller than value shown
[e] Mann Whitney U test: *P* smaller than value shown
[f] 3 × 4 contingency table: *P* smaller than value shown

antiemetic effect, with as many as 20% of patients presenting no symptoms and another 20% experiencing no emesis (only nausea or retching), with an overall protection rate that was approximately fivefold higher and twofold higher than AZP alone and AZP+DXM, respectively.

Statistically significant differences, however, were found only between MCP+DXM and AZP as far as patients presenting no vomiting ($P=0.007$) and those experiencing no symptoms ($P=0.02$) were concerned.

Evaluation of the duration (first to last episode interval) and the intensity (median number of episodes) of emesis showed the MCP-DXM combination to be significantly more effective than AZP alone ($P<0.014$ and $P<0.0008$, respectively). The combination of AZP+DXM also provided a better antiemetic effect than AZP alone as far as the intensity of emesis was concerned ($P<0.03$). No differences were observed between the DXM-based antiemetic combinations.

Considering the severity of emesis, evaluated as the numbers of patients presenting fewer than 3, 3–10 and more than 10 episodes of vomiting over a 24-h period, a P-value lower than <0.01 was found with the aid of a 3×3 contigency table. Both the DXM-based antiemetic regimens showed greater activity than AZP alone, whether the patients experiencing no vomiting were included or not ($P<0.001$ or $P<0.01$ for MCP+DXM and $P<0.025$ or $P<0.05$ for AZP+DXM).

Furthermore, highly statistically significant differences were found between both the DXM-based combinations and AZP alone in the incidence of high-degree emesis (more than 10 episodes): $P=0.007$ and $P=0.043$ for MCP+DXM and AZP+DXM, respectively, but not when patients with a lower degree of emesis (1–2 or 1–5 episodes) were evaluated. As regards the intensity and duration of nausea and retching, no significant differences were observed among the antiemetic regimens studied.

Chemotherapy-induced interference with the evening meal on the day of the study affected more than 50% of patients, regardless of the antiemetic regimens they were receiving.

When the score system for evaluation of the patients' opinion on a 0–3 scale was considered a P-value lower than 0.025 was found by means of a 3×4 contingency table. Significantly better opinions were expressed by patients receiving both the antiemetic combinations than by those receiving AZP alone ($P<0.001$ and $P<0.05$ for MCP+DXM and AZP+DXM, respectively) and by those receiving the MCP-based regimen than by those receiving the AZP-DXM combination ($P<0.01$).

A highly significant correlation ($P<0.00003$ using Spearman's coefficient) between the patients' opinions and the severity of emesis (both evaluated on a 0–3 scale of a scoring system) was found for the antiemetic regimens studied. On the basis of subjective opinions, however, the patients underscored their emesis more often than they overrated it (24% vs 7% for MCP+DXM, 21% vs 4% for AZP+DXM, and 17% vs 8% for AZP).

Table 3 summarizes the toxicity observed with each of the regimens.

Acute dystonic reactions (ADR) were the most prominent side-effects, requiring specific treatments in six cases (20.7%) and early discontinuation in one (oculogyric crisis with MCP-DXM).

Regardless of the type and severity of the symptoms, 3 of 11 patients (27.3%) experienced ADR with all the antiemetic regimens, whereas the remaining patients developed dystonic symptoms with either MCP+DXM (3 cases, 27.3%) or AZP regimens (5 cases, 46.4%).

No definite relationship could be found between the sequence of administration and the onset of dystonia. Other side effects, expecially those related to high-dose DXM, were usually mild, requiring no specific treatment. No hypotensive reactions were observed.

As many as 13 of 29 patients (44.8%) presented no side-effects related to antiemetic treatments administered sequentially throughout the study.

Table 3. Toxicity

Type	A[a] $N=24$	AD[a] $N=29$	MD[a] $N=29$
Oculogyric crisis	–	–	1
Trismus	–	2	1
Tremors	4	6	5
Akathisia	1	2	3
Sedation	2	3	4
Flushing	–	6	5
Perineal irritation	–	2	2
Diarrhoea	1	1	–
Pyrosis	–	1	1
Dry mouth	–	–	2
Headache	–	–	1

[a] A, AZP; M, MCP; D, DXM

Discussion

Neither preliminary nor subsequent studies evaluating total doses ranging from 5 to 15 mg/kg for five administrations [2] and 24-h infusion [10] have revealed any close dose-antiemetic effect relationship for AZP. A higher incidence of side-effects has been clearly demonstrated for single doses exceeding 3 mg/kg, however, orthostatic hypotension being dose-limiting at 5 mg/kg for five doses over 8 h [4, 6].

Based on these findings, moderate-dose AZP (2 mg/kg for four administrations) given alone or in combination with high-dose DXM was selected for a comparative trial against a standard regimen combining moderate-dose MCP and high-dose DXM [3].

At the dose and schedule used, AZP showed only limited antiemetic activity, with less than 10% of patients free of emesis when AZP was administered alone to patients receiving intermediate-dose DDP.

In combination with DXM, however, AZP appeared to provide a greater antiemetic effect, significantly reducing the severity of vomiting whether patients free of emesis were considered or not ($P=0.03$ and $P<0.05$, respectively). The incidence of emesis remained statistically unaffected, though reduced.

Compared with AZP alone (but not with the AZP-DXM combination), MCP+DXM provides a significantly higher, complete antiemetic protection rate ($P=0.02$) with an activity five times greater in reducing the incidence of emesis ($P=0.007$). The severity ($P<0.0008$) and duration ($P<0.014$) of the vomiting were also markedly reduced.

Major differences in both the patient population (lower male-to-female ratio and lower median age) [9] and the

DDP-based regimens (concurrent treatment with ADM in the majority of cases) [8] should be considered to explain the disappointing complete antiemetic protection rate obtained with the MCP-DXM combination in the present report (20.7%) compared with previous data (54.1%) [3].

Except for the patients' preference for MCP+DXM ($P<0.01$) no statistically significant differences could be found between the DXM-based regimens, though a trend towards a better antiemetic effect with MCP+DXM was evident.

At the dose and schedule used in the present study, the side-effects induced by the two benzamide derivatives (AZP and MCP) were comparable in terms of type and severity, whereas those related to DXM were not significant in patients with no contraindications to corticosteroids.

Even though some unfavourable prognostic factors in the patient population could be detrimental to the attainment of a good antiemetic control with the regimens evaluated, the data presented suggest that at the selected dose and schedule AZP does not provide a higher therapeutic index than MCP. The search for new antiemetics still needs to be continued.

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