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Activity of a new antiemetic agent: alizapride*

A randomized double-blind crossover controlled trial

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Summary. Alizapride is a methoxy-2-benzamide derivative three times more potent than its parent compound, metoclopramide, as an antagonist of apomorphine-induced emesis in dogs. The antiemetic activity of alizapride plus dexamethasone (DXM) was compared with that of placebo plus DXM in a randomized, double-blind, crossover study in cancer patients receiving cisplatin (DDP). Alizapride, given at the maximally tolerated dose of 4 mg/kg × 5, or placebo was given in a sequence determined by randomization during two successive, identical courses of antitumor chemotherapy. The antiemetic treatment was given 30 min before and 1.5, 3.5, 5.5, and 7.5 h after starting. DXM, in a dose of 12 mg, was given IV with the first administration of alizapride or placebo. A total of 39 patients completed the two courses of chemotherapy. The severity of gastrointestinal symptoms was influenced by previous treatment but not by the treatment sequence. Although our overall results suggest that alizapride does not add to the activity of DXM against DDP-induced amesis, a statistically significant difference favoring alizapride plus DXM was found among patients with the lowest gastrointestinal tolerance to DDP: women, patients under 50 years of age, and patients pretreated with chemotherapy including DDP and non-DDP agents. Side effects consisted of orthostatic hypotension, which was symptomatic in two patients, and a single occurrence of severe extrapyramidal syndrome. We conclude that alizapride is more active than placebo when combined with DXM for DDP-induced emesis in patients at high risk of severe nausea and vomiting. The severity of the side effects in this study indicates that a dose reduction of alizapride might be appropriate for further studies.

Introduction

Cisplatin (DDP)-induced nausea and vomiting may be difficult to control [17]. Few active antiemetics have been identified and severe side effects limit their use [1, 4, 7, 16–18]. Even high-dose metoclopramide, studied mainly in DDP-treated patients, produces only partial relief of these gastrointestinal symptoms [6].

Like metoclopramide, alizapride is a methoxy-2-benzamide derivative [9]. A pharmacologic comparison of these two analogs reveals a threefold greater potency for alizapride as an antagonist of apomorphine- and ergot dihydrogenated alkaloid-induced emesis in dogs. Alizapride exerts mild neuroleptic properties, as shown by catatonigenic reactions in rats and inhibitory effects on the spontaneous motility of mice. It does not produce any antihistaminic reaction. At high doses, a weak sympathicolytic and hypotensive effect has been observed in dogs.

Two double-blind trials have demonstrated the superiority of alizapride over placebo in preventing nausea and vomiting induced by cancer chemotherapy not involving DDP [15, 20]. In both studies, alizapride was given IV at a dosage of 100 mg twice a day with acceptable tolerance.

These results encouraged us to evaluate alizapride in cancer patients who were receiving DDP-containing chemotherapy. The maximally tolerated dose of alizapride was determined in a previous study using a schedule recommended for metoclopramide by Gralla et al. [5]. Alizapride (1–5 mg/kg) was given i.v. in 15-min perfusions repeated every 2 h for five successive perfusions and a total dose of 5–25 mg/kg [12]. No side effects were noted at doses of 1–3 mg/kg × 5. Mild somnolence and diarrhea were observed at doses above 3 mg/kg × 5. Severe orthostatic hypotension was observed in one patient given 5 mg/kg × 5. This study suggested that with this schedule, repeated doses of 4 mg/kg would be appropriate for further studies.

In this randomized, double-blind, crossover study, the antiemetic activity of alizapride was tested vs a placebo in patients receiving DDP-based treatment. As ethical considerations prevented us from using a placebo alone in the control group, a single IV dose of 12 mg dexamethasone (DXM) was added to both treatment regimens [3].

Material and methods

Patients. From July 1983 to August 1984, 54 adults with a variety of histologically proven cancers were entered in the study. Eligibility requirements included a Karnofsky performance rating of >50, a life expectancy of at least 8 weeks, WBC count >4.000 mm^3, platelet count

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$>100.000/mm^3$, serum creatinine <1.5 mg/dl, and serum bilirubin <2 mg/dl. Patients were excluded for any of the following reasons: presence of braun metastases, preexisting nausea and vomiting, concomitant radiotherapy or treatment with drugs other than chemotherapeutic agents that might have interfered with our antiemetic evaluation (psychoactive substances, antidepressants, sedatives, tranquilizers, and other antiemetics). Before starting each sequence of treatment, the status of the disease was evaluated and standard biological measurements were obtained.

Chemotherapy. All patients were treated with combination chemotherapy regimens that included DDP at high (100–120 mg/m^2) or low doses (50–60 mg/m^2). The chemotherapeutic agents used in addition to DDP were classified according to their emetogenic potential: *grade O*, bleomycin, vincristine, and methotrexate; *grade 1*, mitomycin C, vindesine, etoposide, 5-fluorouracil, and cyclophosphamide; *grade 2*, doxorubicin, dacarbazine, and lomustine. These drugs were given either simultaneously with DDP or within a maximal interval of 24 h before DDP injection.

DDP was injected i.v. over 15 min. Intravenous pre- and posthydration with 5% dextrose in 0.45% NaCl, supplemented with 1.5 mEq KCl, was given for a total of 2–6 l, depending on the dose of DDP. A 6-h infusion of 20% mannitol was also added in patients receiving DDP in the higher-dose range. Furosemide, 40 mg i.v., was given whenever urinary output fell to less than 100 ml/h.

Antimetic treatment. The trial was conducted during two consecutive and identical courses of DDP chemotherapy. Treatment with alizapride or placebo was randomly allocated for the first course and crossed over for the second course. This treatment was given 30 min before and 1.5, 3.5, 5.5, and 7.5 h after DDP. Alizapride (Delagrange S. A., Paris) was supplied in 2-ml vials, each containing 50 mg active agent. The solvent NaCl 0.9%, packaged in identical vials, was used as placebo. The solution containing alizapride (4 mg/kg) or an identical volume of placebo was diluted in 150 ml 0.9% saline and perfused over 15 min. The total dose of alizapride was 20 mg/kg. Simultaneously with the first dose of alizapride or placebo, 12 mg DXM was given i.v. Patients were kept in bed during the first 10 h of treatment. Neither sedatives nor other antiemetic agents were given within 12 h before the start or during the study.

In case of unusual and/or potentially life-threatening side effects or the persistence of severe gastrointestinal symptoms, the treatment could be stopped and the randomization code, available only to the principal investigator (HB), could be revealed.

Evaluation procedures. Each patient was followed throughout the entire treatment period (i.e., every 2 h, during 10 h, and after 24 h) by a physician (BG) or a registered nurse (NC) from the chemotherapy unit. Nausea and vomiting were considered separate events [10, 11]. The intensity of nausea and of vomiting were graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe) by both the patient and one of the investigators. A global evaluation scale ranging from 0 to 4 and based on the intensity of nausea and of vomiting as well as the number of vomiting episodes was developed prior to data analysis (Table 1). The duration of nausea and vomiting was also recorded.

Table 1. Global evaluation scale of nausea and vomiting

Scale	Criteria
0	No nausea and no vomiting
1	Maximal number of vomiting episodes = 3 Maximal intensity* of nausea and/or vomiting = 1
2	Maximal number of vomiting episodes = 3 Minimal intensity of nausea and/or vomiting = 2
3	Minimal number of vomiting episodes = 4 Maximal intensity of nausea and/or vomiting = 1
4	Minimal number of vomiting episodes = 4 Minimal intensity of nausea and/or vomiting = 2

* The intensity of nausea as well as vomiting were graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe)

After each dose of the antiemetic agent (every 2 h), the patient was also observed for the presence of side effects, particularly headache, shivering, hallucinations, dyskinetic movement, extrapyramidal syndrome, and ataxia. The blood pressure and cardiac rhythm were measured successively with the patient in bed and after 1 min in the upright position following each dose. Changes in blood pressure were expressed as mm Hg above or below the basal blood pressure, which was taken before the start of treatment.

Statistics. The nonparametric Wilcoxon test for paired observations was used to compare the activity of the two treatment options in relation to the different parameters evaluated. Patient evaluation of the treatment was analyzed using the McNemar test. For the analysis of pronostic factors, the Mann-Whitney U-test was used [19].

Results

Of the 54 entries, 39 were evaluable: 2 patients did not meet the eligibility requirements, and 13 did not complete the two courses of chemotherapy. Of the latter, eight died between the two cycles of treatment (3, alizapride; 5, placebo), two had changes in chemotherapy, one refused chemotherapy, one had hypotension before starting the

Table 2. Patient characteristics

Number of evaluable patients:	39	(21/18)*
Sex: male:	24	(14/10)
female:	15	(7/ 8)
Age: median:	55	
range:	18–76	
No prior chemotherapy:	21	(11/10)
Prior chemotherapy:		
without DDP:	12	(7/ 5)
with DDP:	6	(3/ 3)
High-dose DDP	16	(9/ 7)
Low-dose DDP	23	(13/10)
Concomitant chemotherapy:		
grade 0:	14	(8/ 6)
grade 1:	15	(9/ 6)
grade 2:	10	(4/ 6)

* Number of patient by therapeutic sequence (A-P/P-A)

Table 3. Antiemetic effect of alizapride + DXM and placebo + DXM

Parameters	Alizapride + DXM median (range)	Placebo + DXM median (range)
Nausea		
intensity*	0 (0– 3)	0 (0– 3)
duration (h)	0 (0– 9)	0 (0– 9)
Vomiting		
number of episodes	4 (0–19)	5 (0–21)
intensity*	1 (0– 3)	1 (0– 3)
duration (h)	4 (0– 8)	4 (0– 9)

* Results were identical for patients' and investigators' estimates. The intensity of nausea as well as were graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe)

second treatment cycle, and another antiemetic agent was given to one patient inadvertently. No patient was excluded because of emesis or antiemetic therapy.

The patient characteristics are given in Table 2. Initial antiemetic therapy consisted of alizapride in 21 patients and placebo in 18. Between these two groups, there was no imbalance in terms of age or sex distribution, nor of the emetogenic potential of current chemotherapy. Anticipatory vomiting occurred in two patients, both of whom had received chemotherapy with an emetogenic potential of grade 2 prior to the study.

Overall, with both alizapride and placebo the incidence of nausea was relatively low, and when it occurred it was generally of mild intensity and short duration (Table 3). Estimates of the intensity of nausea and vomiting were comparable whether made by the patients or the investigators. Neither the intensity nor our global evaluation was affected by the treatment sequence. However, both parameters were strongly influenced by sex, age, and pretreatment status including DDP and non-DDP agents. For example, in the placebo-DXM group, men were asymptomatic more often than women (no nausea, 58% vs 47%; no vomiting episodes, 25% vs 7%). Patients 50 years of age or older were more often asymptomatic than those under the age of 50 (no nausea, 62% vs 38%; no vomiting episodes, 23% vs 8%). Similarly, non-pretreated patients were asymptomatic more often than pretreated ones (no nausea, 67% vs 38%; no vomiting episodes, 28% vs 5%). Our global evaluation was also affected by sex, age, and pretreatment status. Ratings of 2–4 severity on our global evaluation scale were given to 13/15 women (87%) compared with 11/24 men (46%), to 9/13 patients under 50 years old (69%) compared with 15/26 patients over 50 years of age (58%), and to 14/18 pretreated patients (77%) compared with 8/21 non-pretreated patients (38%) (Table 4).

Overall, no statistically significant differences were detected between the two regimens (Table 5). The analysis of the number of vomiting episodes favored the alizapride regimen, with a difference that approached statistical significance ($P = 0.06$). Further analysis by subgroups revealed the superiority of alizapride, with significant differences in the number of vomiting episodes among patients less than 50 years old ($P = 0.04$), and the global evaluation among women ($P = 0.04$). Alizapride was also significantly superior in terms of the number of vomiting episodes and the global evaluation in patients who had prior chemotherapy including DDP and non-DDP agents ($P = 0.03$). No statistically significant differences could be found among males, patients older than 50 years of age, those with no prior exposure to chemotherapy, or those treated with high- or low-dose DDP.

Toxicity

Extrapyramidal syndrome and orthostatic hypotension, with and without clinical symptoms, were the only adverse reactions during the study. During alizapride administration, a 30-year-old patient developed a severe extrapyra midal syndrome, which responded to 10 mg pocicli-dine i.v.

Orthostatic hypotention was defined as a fall of 20 mm Hg or more in systolic blood pressure and an unchanging pulse (variation of $<10\%$), with or without a fall in diastolic blood pressure, 1 min after rising from bed to an up-

Table 4. Gastrointestinal intolerance by age and sex with placebo-DXM therapy

	Male $N = 24$ (%)	Female $N = 15$ (%)	>50 $N = 26$ (%)	<50 $N = 13$ (%)	Nonpretreated $N = 21$ (%)	Pretreated $N = 18$ (%)
Intensity of nausea (grade)						
none (0)	14 (58)	7 (47)	16 (62)	5 (38)	14 (67)	7 (38)
mild (1)	6 (25)	6 (40)	7 (27)	5 (38)	6 (28)	6 (33)
moderate (2)	3 (13)	2 (13)	3 (11)	2 (15)	1 (5)	4 (22)
severe (3)	1 (4)	0 (0)	0 (0)	1 (8)	0 (0)	1 (5)
Intensity of vomiting						
none (0)	6 (25)	1 (7)	6 (23)	1 (8)	6 (28)	1 (5)
mild (1)	13 (54)	6 (40)	12 (46)	7 (54)	12 (57)	7 (39)
moderate (2)	3 (13)	7 (47)	7 (27)	3 (23)	3 (14)	9 (50)
severe (3)	2 (8)	1 (7)	1 (4)	2 (15)	0 (0)	1 (5)
Global evaluation scale						
0	5 (21)	0 (0)	5 (19)	0 (0)	6 (28)	0 (0)
1	8 (33)	2 (13)	6 (23)	4 (31)	7 (33)	3 (17)
2	6 (25)	5 (33)	7 (27)	4 (31)	0 (0)	1 (5)
3	1 (4)	6 (40)	5 (19)	2 (15)	6 (28)	4 (22)
4	4 (17)	2 (13)	3 (12)	3 (23)	2 (9)	10 (55)

Table 5. Comparative efficacy of alizapride-DXM vs placebo-DXM

	Superiority of alizapride	Superiority of placebo	No difference	
Nausea				
intensity (patient)	8	6	25	NS
intensity (investigator)[a]	6	6	25	NS
duration	10	11	18	NS
Vomiting				
Number of episodes	21	11	7	NS[b]
intensity (patient)	10	8	21	NS
intensity (investigator)[a]	11	8	18	NS
duration	17	9	13	NS[c]
Global evaluation	13	8	18	NS[c]
Patients' preference +	11	8	10	NS

[a] Data were not recorded in all cases
[b] Superiority of alizapride among patients pretreated and younger than 50 ($P = 0.03$)
[c] Superiority of alizapride among patients pretreated and female ($P = 0.04$)

right position. No patient exhibited orthostatic hypotension before the start of the study. During the study, it was observed in a total of eight patients: in one during the placebo regimen, in six during the alizapride regimen, and in one during both. The median fall in systolic/diastolic pressure was $-60/-20$ mg Hg (range, -20 to $-100/0$ to -30) during the alizapride regimen. For the two hypotension episodes occurring during the placebo regimen, the fall was $-50/-10$ and $-20/-10$ mm Hg.

In two patients, orthostatic hypotension was severe and symptomatic, occurring during both treatment regimens in one case. The fall in orthostatic pressure was greater during the alizapride sequence for the first patient ($-90/-20$ compared with $-50/-10$ for the placebo) and was $-100/-100$ for the second patient during the alizapride sequence. The lowest blood pressure values were recorded at the end of the fourth alizapride and the fifth placebo infusion in the first patient and at the end of the second alizapride infusion in the second patient.

Discussion

A randomized crossover design is an attractive approach to antiemetic studies. Using the patients has their own controls minimizes the variance in results for a given sample size [2, 14]. A fundamental assumption, however, is that the clinical status remains unchanged during the study period, which in patients with advanced cancer is difficult to achieve. In our study, 13 of the 52 eligible patients failed to complete the crossover. On the other hand, the results were independent of the treatment sequence.

As do other workers [10], we consider nausea and vomiting as two different events. They are separate phenomena; nausea without vomiting, nausea with vomiting, and vomiting without nausea have been reported [11] and were observed in our series. The intensity of the symptoms were estimated by the patient and the investigator; overall, the results were comparable. Global or composite assessment of chemotherapy is of paramount importance. We conceived a scale based on the intensity of nausea and vomiting as they were estimated by the patient [10, 14] and on the number of vomiting episodes, which represent more objective data. Based on our experience, the cutoff point of severity was fixed at 2 for the intensity of nausea and vomiting and at 3 for the number of vomiting episodes.

The presence of gastrointestinal symptoms in this study was not universal. Of the 39 patients, 22 did not have nausea and 7 (20%) did not have vomiting episodes during the placebo regimen. The development of gastrointestinal symptoms during DDP therapy is not constant, and patients may have few symptoms even at high doses [13]. The difference between placebo and an active agent may be difficult to distinguish in patients with mild to moderate symptoms and, presumably, may become more apparent in patients with severe symptoms. When our entire group of patients is analyzed, there is a trend favoring alizapride in the control of the number of vomiting episodes ($P = 0.06$). When the analysis is restricted to patients with the highest gastrointestinal intolerance (women, patients under 50 years of age, and pretreated patients), the superiority of the alizapride regimen becomes statistically significant.

Age and sex have never been identified as important prognostic factors. Considering the relatively small number of patients in each group and the fact that 50 years was a cutoff point that was arbitrarily selected, these results should be confirmed prospectively. Pretreated patients are universally recognized to have more severe gastrointestinal symptoms than non-pretreated patients; therefore, they are usually excluded from antiemetic studies. The superiority of alizapride in this group of patients reinforces the significance of our results.

Orthostatic hypotension was observed during both the alizapride and placebo regimens but was seen more often with alizapride. The other important side effect was the development of a single case of severe extrapyramidal syndrome in a 30-year-old man. This complication has been reported in patients under 30 years of age given high doses of metoclopramide [8]. While alizapride appears to be less neurotoxic than metoclopramide in animals [9], the dose of alizapride used in this study (4 mg/kg $\times 5$) might have comparable neurotoxicity.

Overall, alizapride at a dose of 4 mg/kg $\times 5$ does not add to the activity of DXM against cisplatin-induced emesis. However, it appeared more active in a subgroup of patients with severe gastrointestinal symptoms (i.e., in pa-

tients who had prior chemotherapy, women, and patients under 50 years old). These data suggest that alizapride would be a useful new drug for cytotoxically induced emesis. Our results warrant further investigation of this antiemetic by its comparison with standard treatments in patients at high risk of severe nausea and vomiting.

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