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ALIZAPRIDE ALONE OR ALIZAPRIDE-DEXAMETHASONE COMPARED WITH METOCLOPRAMIDE-DEXAMETHASONE IN PATIENTS AT HIGH RISK OF ACUTE EMESIS AFTER CISPLATIN

A randomized cross-over study

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Abstract

Alizapride (ALZ) is a new benzamide derivative with promising antiemetic activity. In the present study, high-dose ALZ (16 mg/kg) alone or in combination with dexamethasone (DXM, 40 mg) was compared to a combination of DXM (40 mg) and metoclopramide (MCP, 4 mg/kg) in a randomized cross-over trial conducted on 21 out-patients at high emetic risk after moderate-dose cisplatin. All but 3 patients completed the planned cross-over trial for a total of 60 evaluable courses. The patients completed a self assessment questionnaire evaluating the severity and duration of both nausea and vomiting, the toxicity, as well as their subjective opinion of the antiemetic trial. At the dose and schedule employed, ALZ alone or in combination with DXM provided not only a significantly lower rate of complete protection against nausea and vomiting (0 and 4.8%) than MCP + DXM (28.6%) but was also less effective in reducing the number of vomiting episodes and the duration of the vomiting. In addition, the MCP – DXM regimen was the most frequently preferred. Except for one case of orthostatic hypotension following ALZ, benzamide-induced toxicity was mild, whereas that related to DXM was negligible. The results of this study suggest that high-dose ALZ gives no advantage compared to MCP in patients at high risk for emesis after moderate-dose cisplatin.

Key words: Cancer chemotherapy, antiemetics, alizapride, metoclopramide, dexomethasone, cisplatin, high emetic risk.

Some patient characteristics can significantly influence cisplatin-induced emesis (1). Especially for patients at high risk of severe postchemotherapy acute emesis (e.g. females, young patients and those with a good performance status), currently available regimens including metoclopramide (MCP) and dexamenthasone (DXM) are far from satisfactory (1) and more effective agents should be looked for.

Alizapride (ALZ) is a new benzamide derivative with promising antiemetic activity (2). Due to the dose-limiting orthostatic hypotension at ≥ 5 mg/kg for 5 doses over 8 h (3, 4), lower total doses (between 5 and 20 mg/kg) have been selected for further clinical evaluation (3–5).

In a previous report, no significant advantages were observed using moderate-dose ALZ (2 mg/kg for 4 doses) either alone or in combination with DXM as compared to MCP (6). A better effect, however, has been recently reported with higher dose ALZ (4 mg/kg × 5) in combination with DXM in patients at high emetic risk (e.g. women, patients < 50 years of age, and those previously treated with chemotherapy) (7). The aim of the present study was to evaluate:

–the antiemetic efficacy and toxicity of high-dose ALZ alone and in combination with DXM for patients at high risk for severe emesis after cisplatin (e.g. females).

–the therapeutic index of the ALZ-DXM combination as compared to a previously selected reference regimen including MCP and DXM (8) in this subset of patients.

Since the dose level critically influences cisplatin-related emesis (9), only patients receiving moderate-dose cisplatin (50 mg/m^2) were included in this study.

Material and Methods

Patients. Between January 1987 and April 1988, 21 out-patients (median age 55 years, range 26–71 years, median

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WHO performance status 0) consented to enter the study. Eligibility criteria included females with histologically confirmed advanced cancer (ovarian cancer (n = 15); cervical cancer (n = 3); and breast cancer (n = 3)), scheduled to receive cisplatin-based chemotherapy and with adequate bone marrow and normal renal, hepatic and cardiac functions. Patients who had received prior chemotherapy and those with contraindications to corticosteroids (e.g. active peptic ulcer, diabetes mellitus, hypertension) and benzamide derivatives were excluded.

Chemotherapy. Cisplatin (50 mg/m^2) was administered either alone (n = 11) or in combination with doxorubicin 40 mg/m^2 (n = 10), according to the 2-h hydration regimen (10) on an out-patient basis. No other concurrent cytotoxic drugs were administered before the 3rd day of chemotherapy. A total of 60 courses have been administered and evaluated. To maintain the same emetic stimulus throughout the study, no dose-adjustments were allowed during the subsequent chemotherapy courses. In the case of myelotoxicity, chemotherapy was delayed until full hematologic recovery.

Study design. According to a randomized 3-period cross-over design and after having obtained informed consent, the eligible patients were randomized to receive 1 of 6 possible sequences of ALZ, ALZ + DXM and MCP + DXM during the first 3 cisplatin courses. The following sequences were employed 1) ALZ→ALZ+DXM→MCP + DXM; 2) ALZ→MCP+DXM→ALZ+DXM; 3) ALZ+DXM→ALZ→MCP+DXM; 4) ALZ+DXM→MCP+DXM→ALZ; 5) MCP + DXM→ALZ→ALZ+DXM; 6) MCP + DXM→ALZ + DXM→ALZ. In this way, regardless of the sequence considered, each of these 3 antiemetic regimens was tested on up to 7 patients during their first, second and third cisplatin course respectively.

Antiemetic regimens. Each single dose of ALZ (4 mg/kg single dose) and MCP (1 mg/kg single dose) was administered in 100 ml saline over a 15-min period, 30 min before and 1, 2 and 4 h after cisplatin (total dose 16 and 4 mg/kg respectively). DXM was administered at a dose of 24 mg i.v. in 100 ml saline just prior to cisplatin, followed by two additional 8 mg doses i.m. after 6 and 12 h (total dose 40 mg).

Assessment. The patients were requested to fill in a self-assessment questionnaire in order to evaluate the endpoints of this study during a 24-h period: duration and severity (absent, slight, moderate and severe) of the nausea, the number and the duration (interval from the first to the last) of vomiting episodes, subjective opinion (good, fairly good, poor and very poor effect) and side-effects. Details have been provided elsewhere (6). The antiemetic effect was defined as follows: complete protection (CP) i.e. no nausea and no vomiting; partial protection (PP) i.e. only nausea; no protection (NP) i.e. vomiting.

Statistical analysis. The χ^2-test on a 3 × 4 contingency table and the Fisher's exact test, when appropriate, were employed to evaluate differences in the prevalence of antiemetic protection and patient opinion between the regimens considered. The non-parametric Wilcoxon's matched paired signed rank test compared the antiemetic control of the regimens, evaluated in relation to both the duration and number of vomiting episodes.

Results

With the exception of 3 patients who discontinued the study before the third cisplatin course (all had been randomized to receive ALZ at that time) because of progressive disease (n = 2) and refusal (n = 1), all the patients received the planned regimen during the first 3 courses of cisplatin for a total of 60 evaluable courses (18 with ALZ and 21 for each of the DXM-regimens). Table 1 summarizes the results, regardless of the administration sequence.

By means of the χ^2-test on a 3 × 4 contingency table, significant differences in the antiemetic protection were observed between the three regimens evaluated ($p < 0.01$). As compared to the MCP-DXM combination, the ALZ-including regimens were significantly less effective in controlling emesis. The MCP-DXM combination provided a CP rate 6-fold higher than that with ALZ + DXM (4.8%) ($p = 0.05$), whereas no CP was observed in the 18 patients receiving ALZ alone ($p = 0.02$) (Table 1). Furthermore, ALZ was significantly less effective than both ALZ+DXM ($p = 0.03$) and MCP + DXM ($p = 0.01$) in reducing the prevalence of severe vomiting ($\geqslant 3$ episodes over 24 h). As compared to MCP + DXM, the ALZ-including regimens were also less effective in reducing the median number and the median duration of the vomiting episodes. The addition of DXM to ALZ led to a significant reduction in the number of vomiting episodes ($p = 0.003$) but had little effect on the duration of the emesis during the 24-h study period (Table 1). The patients preferred the MCP + DXM combination to the ALZ regimen ($p = 0.02$). No relationship could be found between the sequence of administration and the antiemetic effect for each of the regimens evaluated.

As shown in Table 2, toxicity was mild with the exception of one case of ALZ-related orthostatic hypotension. The incidence and the severity of dystonic reactions were similar after the two benzamide derivatives, whereas DXM-related toxicity was negligible in this sample of patients with no contraindications to corticosteroids. In particular, no perineal discomfort was reported during the i.v. DXM administration.

Discussion

ALZ is a second-generation benzamide derivative (methoxy-2-benzamide) with promising antiemetic activity

Table 1

Antiemetic effect of alizapride (ALZ), alizaparide + dexamethasone (DXM), and metoclopramide (MCP) + dexamethasone

	Antiemetic regimens		
	ALZ (18)	ALZ + DXM (21)	MCP + DXM (21)
Complete protection			
No.	0	1	6
%	0	4.8	28.6
		* —— p = 0.05 —— *	
	* —— p = 0.02 —— *		
Partial protection			
No.	2	2	4
%	11.0	9.5	19.0
No protection			
1–2 episodes No.	0	6	0
≥3 episodes No.	16	12	11
Total No.	16	18	11
%	89.0	85.7	52.4
		* —— p = 0.02 —— *	
	* —— p = 0.02 —— *		
Nausea			
Severity: absent	3	7	8
slight	3	7	6
moderate	6	4	7
severe	6	3	0
Duration (h)			
median	4.5	8.75	0
range	0–48	0–60	0–24
Vomiting			
Episodes (No.)			
median	10	6	3
range	0–21	0–16	0–13
		§ —— p = 0.001 —— §	
	§ —— p = 0.003 —— §		
	§ —— p < 0.0001 —— §		
Duration (h)			
median	4	3	1
range	0–21	0–17	0–8
		§ —— p = 0.003 —— §	
	§ —— p = 0.02 —— §		
Patient opinion (No.)			
Good effect	0	1	3
Fairly good effect	5	8	11
Total positive (%)	27.8	42.9	66.7
Poor effect	11	10	6
Very poor effect	2	2	1
Total negative (%)	72.2	57.1	33.3
	* —— p = 0.02 —— *		

3 × 4 contingency table: $p < 0.01$
Fisher's exact test: * —— p —— *
Wilcoxon's test: § —— p —— §
Only significant differences are reported

Table 2

Benzamide-related toxicity

	Antiemetic regimens		
	ALZ (18)	ALZ + DXM (21)	MCP + DXM (21)
Drowsiness	–	1	3
Akathisia	1	3	4
Tremor	3	3	1
Trismus	1	1	1
Diarrhea	3	1	1
Orthostatic hypotension	1	–	–

in both experimental and preliminary clinical studies (2, 5). Further evaluation, however, has provided conflicting results (4, 11), showing limited toxicity for total doses $\geqslant 25$ mg/kg (3, 4). Using moderate-dose ALZ (2 mg/kg × 4 doses) alone or with DXM (40 mg total dose), no significant advantages over MCP (1 mg/kg × 4 doses) combined with DXM (as above) were observed in patients receiving moderate-dose cisplatin (6). Similar conclusions, though with slightly better results, were obtained in another study evaluating higher ALZ doses (3.5 mg/kg for 4 doses) combined with methylprednisolone (12), whereas no differences were found comparing single agent ALZ (at the same total dose) to prochlorperazine (13). In a recent phase I study on patients who did not receive cisplatin, no limiting toxicity was observed for total ALZ doses between 5 and 20 mg/kg (14).

The present report indicates that at the dose and schedule employed, ALZ provides a limited antiemetic activity in patients at high emetic risk receiving moderate-dose cisplatin. No CP and only 11% PP were observed with ALZ alone. In combination with DXM, ALZ was significantly less effective that MCP in reducing the incidence and severity of emesis, although a lower intensity of vomiting was observed than with ALZ alone. Confirming previous observations, the MCP + DXM combination provided greater antiemetic protection and appeared more effective in completely protecting against both nausea and vomiting. In addition, most patients preferred this regimen.

Unfavorable prognostic factors concerning risk of acute emesis (such as female gender and good performance status) could provide a reasonable explanation for the disappointing antiemetic protection obtained with all the regimens employed and a further demonstration of the important role of some patient characteristics for the risk of cisplatin-related emesis (1).

The present study suggests that there are no advantages in administering high-dose ALZ for patients at high risk of acute emesis after moderate-dose cisplatin. New agents, such as the 5-HT3 receptor antagonists should urgently be tested in these high-risk patients using the MCP + DXM combination as a reference regimen.

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