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Dose-ranging evaluation of the substituted benzamide dazopride when used as an antiemetic in patients receiving anticancer chemotherapy**

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Summary. Dazopride, a substituted benzamide structurally related to metoclopramide, is a potent gastric prokinetic agent that prevents cisplatin-induced emesis in animals. Unlike metoclopramide, dazopride has no effect on dopamine receptors and therefore should not produce extrapyramidal side effects. In this dose-ranging trial, 23 patients with cancer receiving chemotherapy known to produce nausea and vomiting received three i.v. infusions of dazopride every 2 h beginning 30 min before the chemotherapy. Seven dose levels were explored ranging from 0.5 to 4.0 mg/kg in each of the three infusions. Toxicities were mild and included sedation, dizziness, visual disturbances, and headaches. All side effects were transient and were not dose-related. Antiemetic effects were observed. Dazopride can be safely given on this schedule at doses of up to 4.0 mg/kg to patients receiving chemotherapy. On the basis of the results of this trial, further studies of this agent are warranted.

Introduction

Dazopride [AHR-5531; 4-amino-5-chloro-*N*-(1,2-diethyl-4-pyrazolidinyl)-2-methoxy-benzamide] is a substituted benzamide structurally related to metoclopramide (Fig. 1). In animal studies, dazopride is a gastric prokinetic agent that is equally if not more potent than metoclopramide [4]. It has been shown to antagonize cisplatin-induced emesis in ferrets [4, 6], an animal model that has confirmed the antiemetic effectiveness of metoclopramide in controlling cisplatin-induced emesis in humans [5]. Unlike metoclopramide, dazopride does not antagonize peripheral or central nervous system dopamine receptors [3, 4]. Its action is thought to be mediated by antagonism of 5-hydroxytryptamine (5-HT_3) receptors, which in turn may act to increase cholinergic function [15]. Single doses of dazopride (1.0 mg/kg i.v.) have prevented or attenuated the vomiting caused by cisplatin (10 mg/kg i.v.) in ferrets, and doses of 5 mg/kg given before cisplatin have abolished cisplatin-induced emesis completely [4]. Toleration studies in human volunteers have revealed only minor, transient elevations in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and minor changes in leukocyte counts (A. H. Robins Co., data on file). On the basis of this information, we conducted a dose-ranging evaluation of dazopride given i.v. for three doses in patients receiving anticancer therapy known to cause nausea and vomiting.

Patients and methods

From December 1983 to November 1984, 23 cancer patients receiving emesis-causing chemotherapy were entered into the present study. Eligibility required a Karnofsky performance status of $\geq 60\%$, a leukocyte count of $\geq 4000/\mu l$, a platelet count of $\geq 100{,}000/\mu l$, a serum bilirubin level of ≤ 1.5 mg/100 ml, a creatinine value of ≤ 1.5 mg/100 ml, and stable cardiovascular status. Pretreatment evaluation included a complete history and physical examination, a complete blood count, a serum biochemical profile, and an ECG. Written informed consent was obtained from all participants and the protocol was reviewed by the institutional review board of Memorial Sloan-Kettering Cancer Center.

Dazopride was given as a 15- or 30-min infusion every 2 h for a total of three doses, with the first dose being infused 30 min before chemotherapy. Dose escalation was made through seven levels (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 mg/kg) for each of these doses per treatment course. A minimum of three patients were entered at each level. A total of 23 patients received 25 treatment courses. Two patients receiving cyclophosphamide/doxorubicin/vincristine (CAV) chemotherapy had a minor and equivocal antiemetic response and were retreated, at a higher dose of dazopride, with their next cycle of chemotherapy. All patients were directly observed in hospital during the 24-h study period following chemotherapy administration. The number of episodes of emesis was recorded for each patient. Any vomiting productive of liquid was recorded as an emetic episode. In addition, one to five "dry heaves" (vomiting not productive of liquid) within any 5-min period were also

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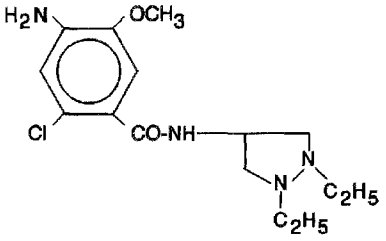

Fig. 1. Chemical structure of dazopride

Table 1. Patients' characteristics

Number of patients entered (evaluable)	23 (23)
Number of courses	25
Median age (range)	56 (23–76) years
Men: women	14:9
Median Karnofsky performance status (range)	80 (60–90)
Primary site of cancer:	
Lung	19
Breast	1
Testes	2
Acute leukemia	1
Received chemotherapy previously	12
Chemotherapy given:	
Mitomycin and vinblastine	9
Cyclophosphamide + doxorubicin + vincristine	8
Lomustine and methotrexate	2
Other anthracycline combinations	2
Cisplatin at ≥ 60 mg/m^2	2
Cisplatin at <60 mg/m^2	1
Actinomycin and cyclophosphamide	1

counted as a single emetic episode. Side effects of dazopride were also directly observed, including assessments of sedation, numbers of bowel movements, and the occurrence of akathisia (restlessness) or acute dystonic reactions. Sedation was graded as follows: none, mild (patient lethargic but aroused by verbal stimuli and completely oriented to time, place, and person when awakened), moderate (patient aroused only by physical stimuli but oriented when awakened), and marked (patient aroused only by physical stimuli and disoriented when awakened). Diarrhea was defined as more than three loose bowel movements during the 24-h observation period. Patients were awakened if necessary and side effects were assessed before each dose of study medication, at the conclusion of the 24-h observation period, and at least every 3 h during the trial. The heart and respiratory rate as well as the supine and/or erect blood pressure were obtained before each dose of study medication.

Results

Side effects

Characteristics of the 23 patients (who received 25 courses) entered into this trial are presented in Table 1. All patients were adequate for both toxicity and antiemetic response assessment, with each patient receiving the full planned dose of the study drug. All patients receiving cisplatin, doxorubicin, and cyclophosphamide had received chemotherapy previously.

The observed side effects for each of the seven dose levels examined are shown in Table 2. Overall, dazopride was well tolerated and no dose-limiting toxicity was observed. Mild sedation was seen in 28% of courses, as was dizziness in 20%. In neither case was a clear dose-response

Table 2. Observed side effects of dazopride

Dose level (mg/kg)	Courses (*n*)	Mild sedation	Dizziness	"Bright lights"	Diarrhea	Mild headache	Akathisia
0.5	3	1	0	0	0	0	0
1.0	3	0	0	0	1	0	0
1.5	3	2	2	0	0	0	0
2.0	3	0	0	0	1	0	0
2.5	3	2	0	1	1	0	0
3.0	3	0	3	2	1	1	0
4.0	7	2	0	2	0	1	1
Totals	25 (100%)	7 (28%)	5 (20%)	5 (20%)	4 (16%)	2 (8%)	1 (4%)

Table 3. Antiemetic results obtained for dazopride by chemotherapy regimen

Chemotherapy	Complete response (no emetic episodes)	Major response (0–2 emetic episodes)
Mitomycin (8–10 mg/m^2) + vinblastine (4–5 mg/m^2)	8/9	8/9
Cyclophosphamide (600–1000 mg/m^2) + doxorubicin (40 mg/m^2) + vincristine (1.4 mg/m^2)	3/8	3/8
Methotrexate (30 mg/m^2) + lomustine (40 mg/m^2)	2/2	2/2
Other anthracycline combinations	0/2	1/2
Cisplatin (20–120 mg/m^2)	0/3	0/3
Actinomycin (1 mg/m^2) + cyclophosphamide (600 mg/m^2) + bleomycin (30 IU)	0/1	0/1
Totals	52%	56%

Chemotherapy doses given are shown in parentheses

relationship apparent. Patients reported a transient sensation of seeing bright flashing lights during five courses given at a dose of ≥ 2.5 mg/kg. Diarrhea occurred during 16% of courses, two patients experienced mild headache, and one patient manifested akathisia. No change in heart rate or blood pressure caused by dazopride was observed. Three patients reported a burning sensation at the infusion site, one at the 1.0-mg/kg dose level and two at the 4.0-mg/kg dose level.

Antiemetic effects

The antiemetic effects of dazopride are depicted in Table 3. Overall, no emesis was observed in 52% of courses. No vomiting was observed in a substantial fraction of patients receiving mitomycin plus vinblastine or methotrexate plus lomustine.

Discussion

Dazopride was given safely at individual doses ranging from 0.5 to 4.0 mg/kg as a 15- to 30-min i.v. infusion every 2 h for three doses. Although a number of patients described a sensation of perceiving flashing lights, this effect was transient and no dose-limiting toxicity was identified. Antiemetic effects were observed.

Major progress in the control of chemotherapy-induced emesis has been achieved, with drugs such as metoclopramide [7] dexamethasone [14], and ondansetron [9, 12, 13] being identified as useful agents for this indication. The development of antiemetic combinations have reduced treatment-related side effects, improved antiemetic efficacy [1, 11, 16], and reduced the duration of treatment. Despite these developments, chemotherapy-induced emesis remains a problem for many patients, even with the development of specific serotonin antagonists such as ondansetron. The extrapyramidal effects associated with dopamine antagonists make the use of these agents difficult in younger patients [2, 10] and in individuals receiving chemotherapy on successive days [2, 8]. New antiemetics and antiemetic combinations are needed to improve further the management of chemotherapy-induced vomiting. Although dazopride is a substituted benzamide structurally related to metoclopramide, it does not appear to exert its action via dopamine receptors. As such, it has the potential to permit administration to younger patients or to patients receiving emetogenic chemotherapy for several days without the development of the extrapyramidal side effects that limit the use of metoclopramide. Its effects have been proposed to be mediated by antagonism of 5-HT_3 receptors.

Dazopride is a substituted benzamide that can be given to adults receiving anticancer chemotherapy without producing any significant acute adverse reactions. The results of this trial suggest that i.v. dazopride merits further study in single-agent trials using higher doses, and different schedules and routes of administration to define a dose appropriate for phase II trials.

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