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Short communication

Double-blind, randomized crossover study of metoclopramide and batanopride for prevention of cisplatin-induced emesis

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Summary. We conducted a double-blind, randomized crossover study to compare the toxicity and antiemetic efficacy of the 5-hydroxytryptamine$_3$ receptor antagonist batanopride with that of metoclopramide in 21 chemotherapy-naive patients receiving at least 70 mg/m^2 cisplatin. The study was terminated when hypotension was observed following the infusion of batanopride at other institutions testing similar drug schedules. Although we observed no hypotension following treatment with batanopride in this trial, we did note asymptomatic prolongation of the corrected QT interval (QTc), PR interval, and QRS complex on the EKG in the batanopride arm. Of 15 evaluable patients, 8 experienced ≤ 2 episodes of emesis within 24 h of the first batanopride infusion, whereas 9/15 subjects experienced ≤ 2 emetic episodes following the administration of metoclopramide. Overall, the evidence suggests that this dosing schedule for batanopride may be too toxic for clinical use.

Introduction

Cisplatin chemotherapy produces severe nausea and vomiting. Combinations of antiemetics that include high doses of metoclopramide provide only partial protection, and patients may show intolerable extrapyramidal reactions to metoclopramide [6]. Several members of a newer class of drugs, the 5-hydroxytryptamine$_3$ (5-HT$_3$; serotonin) receptor antagonists, have recently shown efficacy against cisplatin-induced emesis that may be comparable or superior to that of metoclopramide, resulting in minimal toxicity [1]. Batanopride (BMY-25801) is a substituted benzamide 5-HT$_3$ receptor antagonist with no significant antidopaminergic properties [5]. Early clinical trials with batanopride have suggested that it is effective against cisplatin-induced emesis [8, 10]; we therefore undertook a double-blind, randomized crossover study to compare batanopride with high-dose metoclopramide in patients receiving cisplatin-based chemotherapy.

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Patients and methods

Patients receiving at least 70 mg/m^2 cisplatin were randomized to infusions of either 2 mg/kg metoclopramide or 6 mg/kg batanopride (both supplied by Bristol-Myers Squibb) given every 2 h for three doses starting at 30 min prior to cisplatin administration. For cycle 2, subjects were crossed over to the alternative therapy. No other antiemetics were given unless the patient experienced three or more episodes of emesis within a 12-h period. An episode of emesis was defined as either vomiting or retching separated by at least 1 min during which no vomiting or retching occurred. In the cisplatin/5-fluorouracil/leucovorin (PFL) regimen (17 patients), cisplatin was given with 18.5 g mannitol in 1,000 ml 5% dextrose/0.9% saline and fluids were adjusted to maintain a urinary output of 150 ml/h for the subsequent 12 h. Fluid orders for the mitomycin/vinblastine/cisplatin (MVP) regimen (4 patients) were not standardized. Vital signs were recorded immediately before and after each dose of drug and at 24 h after the end of the cisplatin infusion. An EKG was obtained within 48 h before each cycle and at 2 and 24 h after the last dose of drug given in each cycle.

Results

The patients' characteristics are listed in Table 1. Five patients were ineligible for efficacy analysis: two subjects were given a dose of prochlorperazine without having qualified for rescue antiemetics, and in three cases the cisplatin infusion was prolonged beyond the prescribed time of 2 h. Two other patients did not receive their crossover cycle, in one case because the subject chose to go off study and in the other due to administrative error.

The efficacy of the two antiemetic regimens is shown in Table 2. Although it seemed that patients receiving metoclopramide in the first course of chemotherapy fared better, there was an imbalance in the treatment groups with respect to prognostic variables. All four women and both evaluable patients receiving the MVP regimen received batanopride in their first course. Six patients preferred

Table 1. Patients' characteristics

Variable	Number of patients (%)
Patients entered	21 (100)
Patients evaluable for efficacy	16 (76)
Patients evaluable for efficacy who received both drugs	14 (76)
Men	16 (81)
Women	4 (19)
Median age (range)	59 (21–74) years
History of alcoholism (>4 drinks/day)	5 (24)
Diagnosis:	
Lung carcinoma	5 (24)
Head and neck cancer	13 (62)
Esophageal carcinoma	2 (10)
Squamous-cell skin cancer	1 (5)
Concomitant chemotherapy:	
5-FU/leucovorin (CDDP @ 100 mg/m^2)	17 (81)
Mitomycin/vinblastine (CDDP @ 120 mg/m^2)	4 (19)

5-FU, 5-Fluorouracil; CDDP, cisplatin

Table 2. Efficacy of treatment with batanopride and metoclopramide in cancer patients

	Batanopride	Metoclopramide
First cycle ($n=16$)	3/ 9	7/ 7
Second cycle ($n=14$)	5/ 6	2/ 8
Total ($n=30$)	8/15	9/15

Data indicate the numbers of patients experiencing ≤ 2 episodes of emesis per cycle over the total number treated

batanopride, five preferred metoclopramide, and three had no preference.

Batanopride was well tolerated. We observed no hypotension, symptomatic or asymptomatic, related to infusion of either drug. Prolongation of EKG intervals was significantly greater for batanopride than for metoclopramide administration (mean increases: in QTc, $10\% \pm 8\%$ vs $1.1\% \pm 7\%$, $P=0.004$; in QRS, $11.7\% \pm 10\%$ vs $1.6\% \pm 6\%$, $P=0.001$; in PR, $15.7\% \pm 10\%$ vs $1.4\% \pm 13\%$, $P=0.014$). The EKG had usually returned to baseline values by 24 h after drug infusion, and no arrhythmias were observed. Toxicity related to dopaminergic blockade occurred only after treatment with metoclopramide and included one acute dystonic reaction and one episode of severe akathisia. Diarrhea, defined as three or more loose stools within 24 h, was seen during one course of batanopride and four courses of metoclopramide; headache occurred during one course of each antiemetic. Transient rises in liver-function values were noted following treatment with both of the drugs. The mean percentage of increase in total bilirubin at 24 h was 73% for batanopride and 100% for metoclopramide ($P=0.3$); the mean percentage of increase in alanine aminotransferase (SGPT) at 24 h was 82% for batanopride and 65% for metoclopramide ($P=0.7$).

Discussion

In this small study, no difference in efficacy between batanopride and high-dose metoclopramide was detected. The suggestion of a period effect is probably explained by the imbalance of risk factors in the two groups. Female sex is a known risk factor for nausea and vomiting during chemotherapy [7], and in our hands the MVP regimen is excessively emetogenic. It is not clear why we did not observe the hypotension previously reported by other institutions [4, 9], although differences in hydration protocols may account for this. Details of hydration in patients suffering hypotension have not been reported. EKG changes have not been reported in patients receiving other 5-HT$_3$ receptor antagonists, although these effects have been seen in those given placebo [2, 3, 9]. However, unlike ondansetron, granisetron, and ICS 205–930, which are serotonin analogues, batanopride is a substituted benzamide, and it may produce some pharmalogical effects that are not accounted for solely by its antagonism toward 5-HT$_3$ receptors. Results of larger dose-ranging studies may prove to be useful in the further delineation of the role of this compound.

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