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Efficacy of droperidol in the prevention of cisplatin-induced delayed emesis: a double-blind, randomised parallel study

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Abstract

We conducted a prospective, randomized, double-blind, parallel study comparing the antiemetic activity and tolerability of treatment with droperidol (2.5 mg d.i.v. twice daily for 5 days) and placebo, both combined with granisetron (3 mg d.i.v. on the first day) and dexamethasone (16 mg d.i.v. on the first day, 8 mg d.i.v. on days 2, 3, and 4 mg d.i.v. on days 4, 5). A total of 180 lung cancer patients receiving high-dose cisplatin (80 mg/m^2)-containing chemotherapy were enrolled in the study, and 171 of them were capable of being evaluated. The clinical characteristics of the patients in the two treatment arms were well balanced. Complete protection from nausea and vomiting was recorded in the acute phase in 97% of patients who treated with droperidol versus 98% of patients who given the placebo ($P=0.920$), and in 42% versus 38% in the delayed phase ($P=0.615$). The multiple logistic regression analysis showed that a history of motion sickness was a significant risk factor for cisplatin-induced delayed emesis (odds ratio [OR] = 5.98; 95% CI = 2.15 to 16.7, $P=0.0006$). Droperidol-containing treatment was well tolerated by most patients, however, the incidence of sleepiness in the droperidol group was higher than in the placebo group (69% versus 30%, $P<0.0001$). In conclusion, our data did not support the hypothesis that addition of droperidol to granisetron and dexamethasone reduces the delayed emesis induced by high-dose cisplatin.

Keywords: Delayed emesis; Antiemetics; Droperidol; Dopamine receptor antagonist; Granisetron; 5-HT3 receptor antagonist; Chemotherapy; Cisplatin

1. Introduction

Nausea and vomiting are among the most unpleasant side-effects of lung cancer chemotherapy, and they are particularly severe and prolonged following high-dose cisplatin treatment. Chemotherapeutic agents induce vomiting directly and indirectly at various trigger sites, such as the dopamine D_2 receptor in the chemoreceptor trigger zone (CTZ), neurokinin-1 (NK-1) receptor binding with substance P in the area postrema and 5-hydroxytryptamine (5-HT_3) receptors in the gastrointestinal tract. In the acute emesis that occurs within 24 h after chemotherapy, the several selective 5-HT_3 receptor antagonists (RA) are highly effective, with few significant side-effects [1–3], The 5-HT_3 RA granisetron is highly effective in preventing the acute emesis induced by cisplatin, and some trials have shown that its efficacy against the acute and delayed emesis is enhanced by the addition of a corticosteroid [4–6]. In the delayed emesis that occurs more than 24 h after chemotherapy, no standard medical treatment has been established, and many patients on cisplatin-containing chemotherapy still develop delayed emesis despite administration of 5-HT_3 RA and corticosteroids.

The dopamine D_2 RA droperidol, one of the butyrophenones, has a higher affinity for dopamine D_2 receptors than haloperidol. Before 5-HT_3 RA were developed, some clinical trials of combination therapy containing droperidol showed that it was effective in preventing nausea and vomiting in various anticancer chemotherapy regimens [7–9]. The combination of the 5-HT_3 RA ondansetron and the dopamine D_2 RA metopimazine was superior to ondansetron alone in the prophylaxis of nausea and vomiting induced by chemotherapy [10,11].

To evaluate the additive effect of droperidol in controlling delayed emesis, we conducted a randomised,

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double-blind trial comparing the antiemetic activity and tolerability of droperiol in combination with granisetron and dexamethasone and of granisetron and dexamethasone alone in patients receiving high-dose, cisplatin-containing chemotherapy.

2. Patients and methods

2.1. Design of the study

The study was designed as a prospective, randomised, double-blind, parallel study. Sample size was calculated on the assumption that complete protection against delayed emesis would be achieved in at least 40% of the patients given droperidol and in at most 20% of those given the placebo. The complete protection rate expected was computed from past reports [3,16,17] and experience at our hospital. A total of 162 patients (81 patients each) had to be enrolled to demonstrate a 20% advantage for droperidol at an overall *P*-value (two-sided) of $\leqslant 0.05$, which was considered to indicate statistical significance with a power of 80%. Patients were stratified according to sex and randomly assigned to receive one of the two combinations in a blinded fashion. The primary objective of this study was to compare antiemetic prophylaxis with droperidol and placebo in terms of complete protection rate against delayed emesis from day 2 to day 5 in patients receiving high-dose cisplatin. The secondary objective was to evaluate the role of droperidol in the grade of nausea, the number of times patients vomited, and its safety in this setting.

A questionnaire was used to assess degree of motion sickness and habitual alcohol consumption before chemotherapy.

2.2. Patients

Patients with histologically or cytologically confirmed lung cancer who were receiving high-dose cisplatin ($\geqslant 80$ mg/m^2)-containing chemotherapy were enrolled in this study. All of the following eligibility requirements had to be met: no previous chemotherapy; an ECOG performance status of 2 or less; over 20 years old; no liver or renal failure, and no other serious concomitant illnesses; written informed consent was obtained. The exclusion criteria were: presence of clinically uncontrolled brain metastasis; active gastric ulcer; concomitant treatment with other antiemetic drugs, including steroids or antipsychotropic drugs; active infectious disease; and concurrent radiotherapy.

2.3. Clinical assessment

Episodes of nausea and retching or vomiting were recorded by patients on diary cards for the 5 days after chemotherapy. Nausea was graded on the following categorical scale: 1, none; 2, mild (able to eat some foods and drink beverages); 3, moderate (unable to eat any food, but able to drink some beverages, and interference with normal daily life); 4, severe (unable to eat any foods or beverages, and requires bedrest). A 'complete response' in regard to delayed emesis was defined as the absence of vomiting episodes and a rating of 1 on the categorical scale from day 2 to day 5. The following adverse events were recorded by each patient on diary cards: sleepiness, restlessness, tremor, staggering, headache, hiccups, and constipation, with episodes of other events being recorded freely.

Patients who experienced one or more episodes of vomiting could receive additional granisetron (3 mg) intravenously during the first 24 h after chemotherapy, and those who experienced two or more vomiting episodes after the first 24 h were defined as treatment failure.

2.4. Antiemetic regimen

All patients were admitted to the hospital to administer cisplatin at 80 mg/m^2 by 60-min intravenous infusion. Granisetron (3 mg) was diluted in 100 ml of saline and administered intravenously for 30 min on day 1. Dexamethasone (8 mg on day 1, 4 mg on days 2 and 3, 2 mg on days 4 and 5) was diluted in 50 ml of saline and intravenously administered twice daily. Droperidol (2.5 mg) was diluted in 50 ml of saline and administered intravenously over 20 min twice daily on days 1–5. The bottle containing the placebo (50 ml of saline) was indistinguishable from the bottle containing droperidol.

2.5. Statistical analysis

Nausea and vomiting in the acute phase (on day 1) and delayed phase (on days 2 to 5) were analysed separately. The χ^2 test was used to evaluate the balance of prognostic factors and to compare the proportion of patients with a complete response and each adverse event between the two groups. The toxicity grades of vomiting and nausea were compared by the Mann–Whitney U-test. Student's *t*-test was used to compare the total numbers of vomiting episodes.

3. Results

A total of 180 lung cancer patients were enrolled in this study between July 1998 and September 2001, and 87 (96%) of the 91 patients in the droperidol treatment arm and 82 (92%) of the 89 patients in the placebo treatment arm were capable of being fully evaluated. Nine patients could not be evaluated, six because of protocol violations and three because they did not receive cisplatin-based chemotherapy. Two of the

patients enrolled in the droperidol arm were evaluated for adverse events alone, because one patient's general condition worsened by pneumothorax and the other patient refused to continue the protocol. Both were considered ineffective cases. The clinical characteristics of the patients in the two treatment arms were well balanced (Table 1).

We evaluated acute nausea and vomiting (Table 2) in 171 patients. No patients in either group vomited within 24 h after administration of cisplatin. Complete protection from nausea was achieved in 86 of the 89 patients receiving droperidol (97%) and 80 of the 82 patients receiving placebo (98%), and the difference was not significant. Table 3 shows the antiemetic effect of droperidol on the incidence of delayed emesis. A complete response was recorded in 37 (42%) of the 89 patients given droperidol and in 31 (38%) of the 82 patients given the placebo. The difference in complete response rates between the two groups was not significant. Table 4 shows the effect of droperidol on the incidence of vomiting and dry retching reported on the worst day and total number of episodes of vomiting from day 2 to day 5 after cisplatin-containing chemotherapy. There was no significant difference in toxicity grade of nausea and vomiting between the droperidol group and placebo group. The average total number of vomiting episodes was lower in the droperidol group (1.09) than in the placebo group (1.99), but the difference was not significant.

Among the toxicities, sleepiness was only significantly more frequent among the patients receiving droperidol (61 of 89 patients) than placebo (25 of 82 patients; $P < 0.0001$).

We used multiple logistic regression analysis to determine the simultaneous effect of sex, performance status, antiemetic treatment, and history of motion sickness, and habitual alcohol consumption (Table 5). Motion sickness was associated with a higher risk of cisplatin-induced delayed emesis than in patients who had never experienced motion sickness (odds ratio = 5.98; 95%

Table 1
Clinical characteristics of 171 lung cancer patients receiving antiemetic treatment with droperidol and placebo who were capable of being evaluated

Characteristics	Antiemetic treatment		*P*
	Droperidol (%)	Placebo (%)	
No. of patients evaluated	89	82	
Sex			0.935
Male	71 (80)	65 (79)	
Female	18 (20)	17 (21)	
Age (years)			0.770
Median	61	62	
Range	35–74	28–73	
Performance status (ECOG)			0.718
0–1	86 (96)	80 (98)	
2	3 (4)	2 (2)	

Table 2
Effect of droperidol less than 24 h after cisplatin administration in the acute period

	Droperidol $n = 89$ (%)	Placebo $n = 82$ (%)	*P*
Toxicity grade of nausea (categorical scale)			0.920
Grade			
0 [1]	86 (97)	80 (98)	
1 [2]	3 (3)	1 (1)	
2 [3]	0 (0)	1 (1)	
3 [4]	0 (0)	0 (0)	
No. of vomiting episodes			
0	89 (100)	82 (100)	
1⩽	0 (0)	0 (0)	

The toxicity grade is based on the National Cancer Institute Common Toxicity Criteria version 2.0.

Table 3
Effect of droperidol on the incidence of CDDP-related delayed emesis

Response	Treatment groups		*P*
	Droperidol	Placebo	
No. of patients capable of evaluation	89	82	
Complete response	37 (42%)	31 (38%)	0.615

Table 4
Effect of droperidol on the incidence of vomiting and dry retching, and the toxicity grade of nausea reported on the worst day and total number of vomiting episodes from day 2 to day 5 after administration of cisplatin

	Droperidol $n = 87$ (%)	Placebo $n = 82$ (%)	*P*
Toxicity grade of nausea (Categorical scale)			0.369
Grade			
0: [1]	38 (44)	32 (39)	
1: [2]	32 (37)	28 (34)	
2: [3]	9 (10)	11 (14)	
3: [4]	8 (9)	11 (14)	
Toxicity grade of vomiting (number of days)			0.547
Grade			
0 (0)	64 (74)	56 (68)	
1 (1)	8 (9)	10 (12)	
2 (2–5)	15 (17)	13 (16)	
3 (6⩽)	0 (0)	3 (4)	
Total number of vomiting episodes			
Average	1.99	1.09	0.471

The toxicity grades are based on National Cancer Institute Common Toxicity Criteria version 2.0.

Table 5
Results of multiple logistic regression analysis of potential predictors of cisplatin-induced delayed emesis

	OR	95% CI	*P* value
Sex male	1.02	0.40–2.61	0.967
PS $\geqslant$ 1	1.12	0.56–2.22	0.757
Droperidol	0.89	0.45–1.75	0.728
Motion sickness	5.98	2.15–16.7	$<$0.001
Habitual drinker	0.57	0.28–1.17	0.126

OR, odds ratio; CI, confidence interval. Performance status (ECOG): 0 versus $\geqslant$1. Motion sickness: never versus mild or more severe. Habitual drinker is defined as a person who consumes alcohol $\geqslant$4 times a week.

confidence interval = 2.15–16.66, $P = 0.0006$). The percentage of patients who had never experienced motion sickness was the same in both groups (both 24%). There were no significant differences between any of the other factors.

4. Discussion

This randomised, controlled study compared the widely accepted current standard treatment for cisplatin-induced emesis, i.e. a combination of a 5-HT_3 RA and dexamethasone, with the same combination plus low-dose droperidol in terms of prevention of delayed vomiting and nausea and the safety of treatment.

Because treatment with a single antiemetic agent that acts on one trigger site often fails during cisplatin-containing chemotherapy in the delayed phase, it may be necessary to combine antiemetics that differ in their ability to block the emetogenicity of chemotherapeutic agents to obtain a synergistic or additive effect. The rationale behind the antiemetic combination consisting of granisetron, dexamethasone and droperidol is that they have different mechanisms of action.

The combinations of 5-HT_3 RA and previously available antiemetics, such as a corticosteroid and dopamine D_2 RA, are less effective during the delayed period than during the acute period [12–15]. 5-HT_3 receptors on the afferent vagal fibres are thought to have a major role in acute emesis, but probably to be of only minor importance in delayed emesis. In the trials by the Italian Group for Antiemetic Research and the National Cancer Institute of Canada Clinical Trial Group, the investigators concluded that dexamethasone alone is as effective in the control of delayed emesis as any other regimen containing 5-HT_3 RA [16,17].

Dopamine D_2 receptors and NK-1 receptors are thought to drive the central pattern generator for vomiting and to have a major role in the delayed emesis. In the recent trials of NK-1 RA, it has been shown that addition of the NK-1 RA to a standard therapy provided superior protection in the delayed phase compared with standard therapy alone [18,19].

In this study, all participants received a high dose of cisplatin, 80 mg/m^2. During the initial 24 h, our result shows a high rate of complete protection in both groups and indicate that a 5-HT_3 RA and corticosteroids are highly effective (Table 2). On days 2-5, droperidol was as effective as the placebo in terms of rates of complete protection from vomiting, nausea and from both nausea and vomiting, and total number of vomiting episodes (Tables 3, 4). These results were the same as for the efficacy in previous studies in similar settings without droperidol.

In two Danish randomised trials by Herrstedt and colleagues [10,11], the combination of ondansetron plus metopimazine was superior to ondansetron alone in the prophylaxis of nausea and vomiting induced by chemotherapy. However, the first of these trials differed from our own in that the chemotherapies were based on non-cisplatin-containing regimens, the participants were younger, and the vast majority were women [10]. Furthermore, neither trial of metopimazine in combination conducted by the Danish investigators included the use of a corticosteroid as antiemetic. Because dexamethasone was used with granisetron in both groups, in our trial, the complete response rate of the placebo group rose from 24.1% (ondansetron alone [11]) to 38% (granisetron plus dexamethasone). Treatment with a 5-HT_3 RA alone is not enough as a preventative for delayed emesis.

Tolerability of the droperidol-containing regimen was good, and there were no severe side-effects. However, the percentage of patients receiving droperidol who reported sleepiness was significantly higher than the number of patients receiving placebo (69% versus 30%, $P \leqslant 0.05$).

Variability of the antiemetic response among patients is a common and familiar experience, and some patient-related prognostic factors have been identified. In the present study, complete protection from nausea and vomiting was significantly better in the patients who had never experienced motion sickness.

In conclusion, our data do not support the hypothesis that the addition of droperidol to combination therapy with granisetron and dexamethasone enhances its efficacy in preventing delayed nausea and vomiting induced by high-dose cisplatin. This finding suggests that at least when patients are receiving a corticosteroid in delayed phase, there is no rationale for the additional use of dopamine D_2 RA.

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