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Short communication

A randomised cross-over trial comparing low-dose metoclopramide and chlorpromazine with high-dose metoclopramide in Chinese patients with advanced cancer receiving cisplatinum and 5-fluorouracil

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Summary. Nineteen Chinese patients receiving chemotherapy for advanced cancer were studied for chemotherapy-induced acute nausea and vomiting. The chemotherapy consisted of cisplatinum 100 mg/m^2 i.v. infusion over 4 h on day 1 and 5-fluorouracil (5-FU) 1000 mg/m^2 120-h continuous infusion from day 2 to day 6, repeated every 3 weeks. At the first course of chemotherapy the patients were randomized to receive either low-dose metoclopramide and chlorpromazine or high-dose metoclopramide, and then crossed over for the second course. In the high-dose metoclopramide group there was a suggestion of an earlier onset of emesis, with slightly more frequent retching and vomiting and less food consumed. However, the duration of emesis was shorter in the high-dose group. These differences were not statistically significant. There were no major side effects. Mild salutary drowsiness was noticed in patients receiving low-dose metoclopramide and chlorpromazine. This trial suggests that, in the dosage, route and schedule described, high-dose metoclopramide is no more effective than low-dose metoclopramide together with chlorpromazine in preventing cisplatinum-induced nausea and vomiting. The low-dose scheme is more economic and suitable for patients with advanced cancer.

Introduction

Nausea and vomiting continues to be the most frequent and debilitating acute side effect of cancer chemotherapy and steadily escalates as higher doses of anti-cancer drugs are used. Hence optimal control of nausea and vomiting in these patients has become an important objective of supportive care.

Several studies have helped to identify useful agents and indicate directions for further improvement. Recent trials have examined phenothiazines, cannabinoids, substituted benzamides, butyrophenones and corticosteroids [11]. These studies provide a rationale for new combinations. At present high-dose metoclopramide appears to be the most effective single-agent anti-emetic in patients receiving cisplatinum [5, 8]; in low dosage, this agent has produced conflicting results in the hands of different workers [4, 7, 10].

The present study compares the efficacy of high-dose single-agent metoclopramide with that of low-dose metoclopramide combined with chlorpromazine to control cisplatinum-induced emesis in patients with advanced cancer. In addition the side effects of each anti-emetic regime were observed and compared.

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Materials and methods

Patients and chemotherapeutic regimes. Nineteen consecutive patients referred to an oncology department in whom treatment with cisplatinum and 5-FU was planned were entered into this study. Of these, 17 had advanced head and neck cancer, one oesophageal carcinoma and one advanced carcinoma of ovary. Of the 17 patients with advanced head and neck cancer, 11 had nasopharyngeal carcinoma (NPC) (Table 1). The NPCs were staged using Ho's classification [6]. Other tumours were staged using the UICC classification.

The regime consisted of cisplatinum 100 mg/m^2 i.v. infusion over 4 h on day 1 followed by 5-FU 1000 mg/m^2 120-h continuous infusion on days 2–6. This regime was repeated every 3 weeks. No patient received any sedative or other anti-emetic during this study. No patient had biochemical evidence of renal or hepatic impairment prior to chemotherapy.

Table 1. Patient and tumour characteristics

Patient no.	Age	Sex	Site of carcinoma	Stage
1	51	F	Nasopharynx	II
2	58	F	Ovary	IV
3	71	F	Larynx	IV
4	50	M	Nasopharynx	IV
5	62	M	Oesophagus	II
6	47	F	Nasopharynx	IV
7	29	M	Nasopharynx	III
8	54	F	Left nasal fossa	III
9	52	M	Larynx	IV
10	43	F	Nasopharynx	III
11	54	M	Nasopharynx	IV
12	57	M	Soft palate	III
13	38	M	Nasopharynx	IV
14	55	M	Larynx	II
15	50	M	Nasopharynx	III
16	53	M	Tonsil	III
17	34	M	Nasopharynx	II
18	59	M	Nasopharynx	III
19	59	M	Nasopharynx	III

Study design. Patients were randomly assigned to receive either high-dose single-agent metoclopramide or low-dose metoclopramide with chlorpromazine in their first course of cytotoxic therapy. They then crossed over to the opposite arm for their second course of chemotherapy.

Anti-emetic treatment. The low-dose group received metoclopramide 10 mg and chlorpromazine 50 mg i.v. half an hour before cisplatinum infusion. This was followed by oral metoclopramide 10 mg every 4 h and oral chlorpromazine 50 mg every 6 h for 24 h, then oral metoclopramide 10 mg every 6 h and oral chlorpromazine 25 mg every 8 h until emesis stopped. The high-dose group received metoclopramide 1 mg/kg body weight i.v. half an hour before cisplatinum infusion and then every 4 h for a total of six doses. This was followed by metoclopramide 10 mg i.v. every 6 h until emesis stopped.

Assessment of anti-emetic response. A flow chart was constructed to record the onset of emesis, duration of emesis, number of retchings, number of vomitings, volume of vomitus and amount of food consumed. Nursing staff trained in the investigation questioned patients every 4 h and the results were checked by medical staff. Other toxicities resulting from the anti-emetics were also noted at the same time.

Statistical analysis. With the crossover design applied in this trial, it was first determined that the period effect and the carry-over effect were both absent, so that proper statistical methods could be employed to compare the efficacy of the two anti-emetic regimes [9]. The analysis used the Wilcoxon signed rank test [1] examining the difference in each parameter in a patient's response to the two treatments. The association of the two regimens and food consumption was also analysed by the χ^2 test [1].

When no emesis occurred during the study period of 144 h, for practical purposes the patient was unlikely to develop this symptom as a result of the treatment. For statistical analysis the value of 144 h was assigned (censored observation). Similarly, if a patient did not stop emesis during the study period of a treatment, the duration of emesis was again assigned as 144 h (Table 2). To analyse this type of censored data, the Wilcoxon test was modified [3]. The emesis onset distribution (or emesis-free rate) and the emesis duration rate of each treatment in the presence of censored observations were further calculated using survival analysis.

Results

Onset of emesis

Time 0 was taken as the beginning of the cisplatinum infusion. Table 2 shows the differences in time to onset of emesis in the 19 patients (combined − high-dose treatment). For simplicity the actual time of onset of emesis during each treatment is not shown in the table. There were four censored differences (patients 9, 11, 12 and 14). Patients 9 and 11 had more than 72 h and 128 h difference, respectively in development of emesis. Patients 12 and 14 had no emesis during either high-dose or low-dose metoclopramide therapy.

Ignoring the censored differences, the average difference of the time to start of emesis for the two treatments was 0.17 h. The combined anti-emetic regime thus caused a slightly later onset of emesis, but this difference was not significant ($P = 0.53$) using the modified Wilcoxon test. This situation is illustrated graphically in Fig. 1, which shows the emesis-free rate as a function of time.

Table 2. Difference of responses between the high-dose metoclopramide and combined anti-emetic regimens (Combined anti-emetic regimen) − (high-dose metoclopramide)

Patient no.	Onset of emesis (h)	Duration of emesis (h)	No. of retchings	No. of vomitings	Volume of vomitus (ml)
1	0	136	5	13	1445
2	2	1	1	0	385
3	0	0*	−34	−16	−1014
4	0	−137*	−45	−19	−1555
5	−9	0*	−8	−8	−490
6	1	0*	11	9	515
7	8	0*	−4	6	715
8	1.5	63*	12	4	930
9	−72*	8	0	2	700
10	9	137*	47	14	1090
11	−128*	84	1	4	820
12	0*	0	0	0	0
13	−10.5	−27	−5	−8	−530
14	0*	0	0	0	0
15	0	−96*	−7	2	−415
16	−5.5	105*	−1	0	−50
17	0	−76*	−6	−6	−935
18	5	−4	0	−3	−420
19	1	−4	0	−1	−300
Mean			−1.7	−0.4	46.9

* Censored observations: see "Materials and methods", subsection "Statistical analysis"

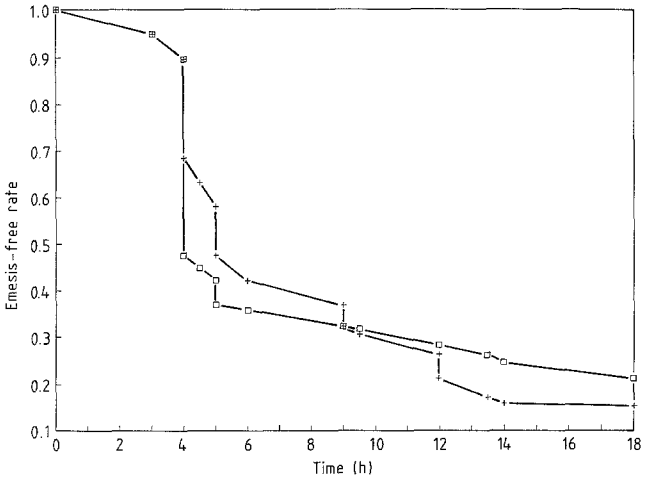

Fig. 1. Proportion of patients remaining free of emesis, as function of time. □, high dose; +, combined

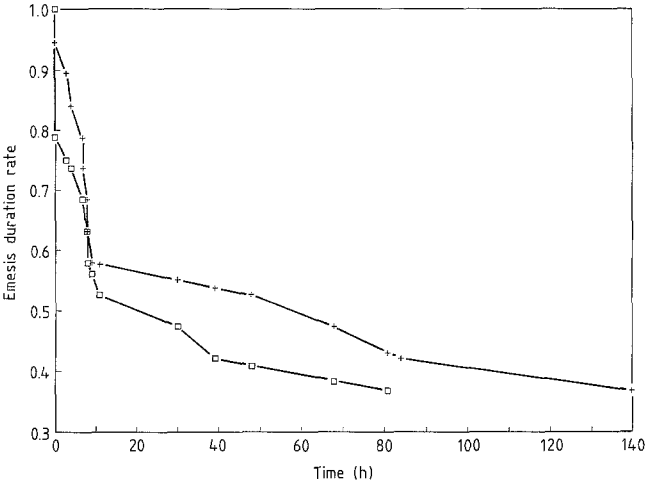

Fig. 2. Duration of emesis, as function of time. □, high dose; +, combined

Duration of emesis

The differences in duration of emesis were censored for 10 of the 19 patients. Four patients displayed persistent emesis for at least 144 h during both regimens (Table 2). Three negative censored values show that these three patients had emesis persisting at least 144 h during the high-dose treatment, while the remaining four positive censored differences come from the patients with emesis persisting during the whole period of the low-dose combined treatment. Overall the duration of emesis was shorter in the high-dose group, but this difference was not statistically significant ($0.28 < P < 0.86$). This is illustrated graphically in Fig. 2, which shows the emesis duration rate for the two treatments.

Number of retchings and vomitings

As Table 2 shows, the mean difference in number of retchings between high-dose and combined treatment was -1.7, indicating that the combined treatment induced less frequent retching; the difference, however, is not significant ($P = 0.617$). There was also no significant difference between the two arms in the number of vomitings (mean difference -0.4, $P = 0.976$).

Volume of vomitus

Although the volume of vomitus in the high-dose group was less than that in the combined group, this difference was not significant ($P = 0.757$) (Table 2).

Food consumption

In order to study food consumption as a function of anti-emetic regime, patients were grouped according to their ability to consume normal hospital meals. Table 3 shows that seven patients completely abstained from food during the high-dose therapy while only two out of these seven patients did not consume any food during the low-dose combined treatment. On the other hand, five patients abstained completely during the combined treatment yet three of them could consume some food during high-dose treatment. This suggests that individual factors play an important role.

Table 3 shows that there was slightly better food consumption in the combined group but this difference was not significant ($P = 0.75$). The statistical test was performed by regrouping the patients according to whether they were able or unable to consume food.

Table 3. Food consumption in high-dose metoclopramide and combined anti-emetic regimens

		Combined anti-emetic regimen			
		Consumed all supplied meals	Consumed some but not all meals	Abstained completely	Total
High-dose metoclopramide	Consumed all supplied meals	1	1	0	2
	Consumed some but not all meals	1	6	3	10
	Abstained completely	1	4	2	7
	Total	3	11	5	19

Discussion

This randomized crossover trial showed that the mean time to onset of emesis was longer with the combined anti-emetic regime than with high-dose single-agent metoclopramide (Table 2), but the difference was not significant. However, the duration of emesis was shorter in the high-dose group, but again this was not statistically significant. There was no significant difference in the number of retchings or vomitings or in the volume of vomitus. Table 3 suggests that there was better food consumption in the combined group, but again this is not statistically significant. There was more sedation in the combined group due to chlorpromazine, but this can be regarded as therapeutic for patients undergoing cytotoxic therapy.

Two patients experienced no vomiting on either regimen. This underlines the individual variation in tolerance to chemotherapeutic drugs. Of the 19 patients, 16 were over 40 years of age (Table 1). This may explain the absence of dystonic reactions in both groups, since these have been shown to be commoner in younger patients [2]. One patient had transient hypotension attributable to chlorpromazine. There were no other serious side effects.

This study suggests that in the dosage, route and schedule described above, low-dose metoclopramide combined with chlorpromazine is as effective as high-dose metoclopramide as an anti-emetic regimen in patients receiving cisplatinum chemotherapy. The combined regimen is more economic and also has the action of salutary sedation. We find that the combined therapy is therefore more appropriate, at least in developing areas, as an anti-emetic regimen in patients receiving cisplatinum chemotherapy for advanced head and neck cancer.

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