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Double-Blind Crossover Trial of Single vs. Divided Dose of Metoclopramide in a Combined Regimen for Treatment of Cisplatin-induced Emesis

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In a double-blind crossover antiemetic study in cisplatin-treated cancer patients, metoclopramide 4 mg/kg as a single intravenous dose (regimen A) was compared with 3 mg/kg in two doses (regimen B). In both regimens, metoclopramide was combined with dexamethasone and diphenhydramine. 65 consecutive, chemotherapy-naïve inpatients (45 males and 20 females) treated with high doses (at least 50 mg/m^2) of cisplatin entered the study and 54 completed both treatments. Complete protection from vomiting and nausea, mean number of emetic episodes, mean maximum intensity of nausea and mean duration of emesis or nausea were similar with the two antiemetic regimens. 23 patients (43%) did not express a treatment preference, while 16 (30%) preferred regimen B and 15 (28%) preferred regimen A. Side-effects were similar with the two metoclopramide schedules. A combined antiemetic regimen of a single high dose of metoclopramide (4 mg/kg) can preserve efficacy and tolerability and thus should be preferred.
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INTRODUCTION

METOCLOPRAMIDE administered in two intravenous doses of 3 mg/kg, in combination with dexamethasone and diphenhydramine or lorazepam is probably the most efficacious antiemetic regimen for cancer patients undergoing cisplatin therapy [1, 2]. A pilot study suggested that metoclopramide can be administered in a single intravenous dose of 4 mg/kg with good results [3]. Since a single-dose schedule may offer advantages in terms of cost and less discomfort for the patients, we planned a randomised, double-blind crossover trial to confirm results in the open uncontrolled trial [3].

PATIENTS AND METHODS

From October 1989 to April 1990, all consecutive untreated inpatients undergoing treatment with at least 50 mg/m^2 cisplatin administered on one day alone or combined with other chemotherapeutic agents were included. A Karnofsky performance status of 60 or more was required. Criteria for exclusion were nausea and vomiting from other causes, cerebral metastases, radiotherapy, the use of narcotic analgesics or sedatives, active peptic ulcer, heart failure, severe diabetes mellitus, high blood pressure (diastolic 120 mm Hg or higher) and hypokalaemia (under 3.0 mmol/l).

After obtaining fully informed consent, patients were randomly assigned to receive, 30 min before cisplatin, either regimen A, a single dose of metoclopramide 4 mg/kg or regimen B, 3 mg/kg followed after 1½ h by a second dose of 3 mg/kg. Randomisation was done from a list of computer-generated, random permuted blocks of 12 patients.

Metoclopramide was diluted in 100 ml saline and administered as a 15 min infusion. To assure blinding, 100 ml of saline was administered 1½ h after cisplatin infusion in regimen A. Both groups received diphenhydramine 50 mg over 2 minutes and dexamethasone 20 mg diluted in 100 ml saline 45 min before cisplatin. For the second cycle of chemotherapy, patients were crossed over to receive the alternative antiemetic regimen.

Staff involved in the evaluation of efficacy and tolerability of antiemetic treatment were different from those preparing and administering the drugs. Cisplatin administration (20 min infusion) followed the usual intravenous hydration. The other chemotherapeutic agents were administered immediately after cisplatin infusion. Food intake was not permitted until 8 h after cisplatin. No other antiemetics were administered during the 24 h observation period.

The efficacy of antiemetic treatment was assessed during the first 24 h after chemotherapy and was based on the count of vomiting episodes, the duration of vomiting and the intensity and the duration of nausea. One vomiting episode was defined as a single vomit or retch (vomit not productive of liquid) separated by vomiting or retching for at least 1 min. The absence of vomiting or of nausea was defined as complete protection from vomiting or nausea. If patients vomited more than 5 times, their treatment was considered a failure. The duration of vomiting was calculated as the time (in min) between the beginning of cisplatin infusion and the last episode of emesis. The intensity of nausea was evaluated at 2, 4, 6, 8 and 24 h after chemotherapy and was scored by the attending staff after questionning of the patients according to the following scale: 0 = none, 1 = slight, 2 = moderate and 3 = severe nausea. The

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Table 1. Characteristics of patients

	Regimen A first (n = 34)	Regimen B first (n = 31)
M/F	24 (71%)/10 (29%)	21 (68%)/10 (32%)
< 60 yr/≥ 60	14 (41%)/20 (59%)	10 (32%)/21 (68%)
Dose of cisplatin (mg/m²)		
Mean	89.2	83.2
< 90	14 (41%)	16 (52%)
≥ 90	20 (59%)	15 (48%)
Performance status		
60–80	16 (47%)	16 (52%)
90–100	18 (53%)	15 (48%)
Neoplasm		
Lung	17	10
Bladder	3	6
Ovary	7	7
Head and neck	3	5
Other	4	3
Chemotherapy		
Cisplatin/etoposide	10	8
M-VAC	3	6
Cisplatin/methotrexate	6	6
Cisplatin/vindesine/mitomycin	5	3
Cisplatin/5-fluorouracil	3	6
PAC	2	2
Other	5	0

M-VAC = methotrexate/vinblastine/doxorubicin/cisplatin, PAC = cisplatin/doxorubicin/cyclophosphamide.

duration of nausea was calculated as the number of minutes in which nausea was felt by the patient during the 24 h observation. Side-effects were also assessed in detail by general questioning and monitoring the patient at the same times. After the second cycle, patients were asked to indicate their preference for either antiemetic regimen.

A log-linear model for binary crossover data [4] was used to analyse complete protection from nausea and vomiting as well as failure of antiemetic treatment. Discrete or ordered variables (mean number of vomiting episodes, mean maximum intensity of nausea, duration of nausea and vomiting) were analysed by the Koch method [5], which extends the non-parametric tests to crossover designs. Preference expressed by the patients was analysed by the Prescott test [6]. All tests were two-tailed and $P \leq 0.05$ was considered significant.

RESULTS

65 patients entered the study (Table 1). 11 patients did not receive the second cycle of chemotherapy because of loss to follow-up (5), death (4) or cisplatin nephrotoxicity (2). Therefore 54 patients received both treatments and were fully evaluable.

Complete protection from vomiting and nausea, the mean number of vomiting episodes, the mean maximum intensity of nausea and the mean duration of nausea and vomiting were not significantly different between regimens A and B (Table 2). The analysis of complete protection from vomiting and nausea by treatment period showed vomiting to be dependent on response in the previous cycle of chemotherapy; 20/31 patients (65%) treated at first cycle with regimen A obtained complete protection and at second cycle, when treated with regimen B, this percentage was 58% (18/31). On the other hand, 19/23 patients (83%) treated at first cycle with regimen B obtained complete protection and at second cycle this percentage was 78% (18/23) (Fig. 1). No carry-over effect was found.

Table 2. Efficacy in 54 patients completing both cycles of chemotherapy

	Regimen A	Regimen B
Complete protection from vomiting	38 (70%)	37 (69%)
Complete protection from nausea	49 (91%)	47 (87%)
No. of patients with failure	3 (6%)	5 (9%)
Mean number of vomiting episodes	1.1	1.1
Mean maximum intensity of nausea	0.2	0.2
Mean duration of vomiting (only patients who vomited) (min)	419.5	553.3
Mean duration of nausea (in patients who had nausea) (min)	458.0	677.5

23 patients (43%) did not express a treatment preference, while 16 (30%) preferred regimen B and 15 (28%) preferred regimen A. This was not statistically significant. However, patients' preference was significantly expressed in favour of the treatment given at the second cycle. When regimen A was administered first, 5/31 patients (16%) preferred A and 14/31 (45%) B. On the other hand, when regimen B was administered first, 2/23 (9%) preferred B and ?/? (43%) treatment A (P = 0.008).

Side-effects were not significantly different between the two schedules (Table 3).

DISCUSSION

This study showed that a single high dose of metoclopramide (4 mg/kg) in a combination antiemetic regimen can preserve efficacy and safety in protecting patients from acute emesis due to cisplatin chemotherapy. This regimen has been shown to give complete protection from emesis similar to that obtained with a widely used regimen giving a higher total dose of metoclopramide divided in two doses with similar toxicity [2]. The therapeutic equivalence of the two antiemetic regimens was confirmed by the fact that our patients expressed a similar treatment preference.

Not unexpectedly, the complete protection from vomiting found at the second cycle of chemotherapy was dependent on the response obtained in the first cycle, irrespective of anti-

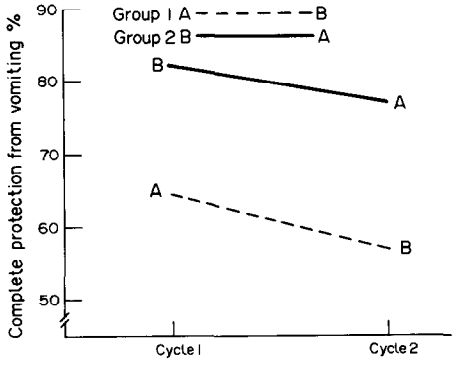

Fig. 1. Complete protection from vomiting, by regimen.

Table 3. Side-effects

	Regimen A	Regimen B
No. of evaluable patients	57	62
Slight sedation	30 (53%)	26 (42%)
Diarrhoea	3 (5%)	1 (2%)
Extrapyramidal reactions	3 (5%)	4 (6%)
Excitability	4 (7%)	2 (3%)
Epigastric and abdominal pain	2 (4%)	0
Other (headache, dry mouth)	9 (16%)	8 (13%)

emetic treatment. This effect was probably due to a slight imbalance between the two groups of patients of some important prognostic factors favouring emesis, such as age and cisplatin dose. Indeed, the group of patients treated first with regimen A had a slightly lower complete protection from vomiting with both antiemetic treatments and were also younger and treated with doses of cisplatin over 90 mg/m^2. We cannot explain the period effect on treatment preference since patients favoured the last antiemetic treatment given irrespective of the regimen they were receiving.

The single-dose regimen seems to be preferable on the basis of its therapeutic equivalence, simpler schedule of administration and lower cost.

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Effect of Intraperitoneal Recombinant Human Tumour Necrosis Factor Alpha on Malignant Ascites

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29 patients with refractory malignant ascites due to metastatic peritoneal spread of adenocarcinomas originating from the ovary, gastrointestinal tract, liver, breast and uterus were treated in a phase I trial of intraperitoneal infusions of recombinant human tumour necrosis factor alpha (rhTNF-α). Patients received 40–350 μg/m^2 rhTNF-α intraperitoneally once weekly for 2 months or for a shorter period in case of early resolution of ascites. Systemic side-effects resembled those reported for rhTNF-α given intravenously. No dose-limiting toxicities were found and thus a maximum tolerated dose of intraperitoneal rhTNF-α was not established. Out of 29 patients, 22 responded with a complete (16) or partial (6) resolution of their ascites. There was a less than 50% reduction in 4, and no increase in ascites in 1. 1 patient showed progressive ascites formation, and another patient was not eligible because of early death unrelated to treatment. Trials in patients with smaller tumour burden are warranted.
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INTRODUCTION

IN PRECLINICAL studies recombinant human tumour necrosis factor alpha (rhTNF-α) induced *in vivo* tumour regression in various models [1–3]. Phase I trials with intravenous bolus or long-term infusion (up to 5 days) or intratumoral injection gave dose recommendations for phase II studies. However, except after direct intratumoral injection, objective tumour response was minimal [4–6]. Since intraperitoneal administration of rhTNF-α in patients with malignant ascites in many aspects resembles direct intratumoral application, we started a phase I trial of short-term intraperitoneal infusion. All patients had