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Comparison of Continuous and Intermittent Bolus Infusions of Metoclopramide during 5-day Continuous Intravenous Infusion with Cisplatin

Kiyoshi Mori, Yoshikuni Saitou, Keigo Tominaga, Kohei Yokoi and Naoto Miyazawa

In order to decide the administration method of metoclopramide for prevention or control of chemotherapy-induced nausea and vomiting in multidrug chemotherapy, with cisplatin 5-day continuous intravenous infusion (25 mg/m²/day) for patients with advanced lung cancer, a randomised crossover study of intermittent bolus infusion (1 mg/kg, 30 min, every 8 h, days 1–5) and continuous infusion (3 mg/kg/24 h, 120 h) of metoclopramide was performed. Both regimens included methylprednisolone and diphenhydramine given concurrently. The acute and delayed antiemetic effects were examined. 21 cases could be evaluated. There were 6 and 10 cases ($P = 0.048$), respectively, of no nausea and no vomiting; 14 and 18 cases ($P = 0.048$), respectively, of no vomiting; and vomiting episodes were seen 27 and 9 times, respectively ($P = 0.042$). Thus, metoclopramide continuous infusion was significantly superior in antiemetic effect compared to bolus infusion. Neither method had any serious side-effects and both were safe.
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INTRODUCTION

MULTIDRUG CHEMOTHERAPY, especially with cisplatin, is commonly used in the treatment of advanced cancer. Many ways of administering this therapy have been developed. In some institutes, including our hospital, cisplatin 5-day continuous intravenous infusion (CI) is used and good results have been obtained [1].

Although cisplatin CI causes fewer problems with the digestive system and has less renal toxicity than bolus infusion, the problem of control and prevention of chemotherapy induced nausea and vomiting still remains. No studies have been reported of a comparison of antiemetic agent regimens in cisplatin 5-day CI. Metoclopramide is the most commonly used antiemetic agent [2] and two methods of administration have been reported: intermittent bolus infusion (BI) and CI [2–9]. In our study, we performed a randomised crossover study of continuous and intermittent infusion of metoclopramide in multidrug chemotherapy with cisplatin 5-day CI in order to decide which method is better, examining acute and delayed antiemetic efficacy and side-effects. We also analysed metoclopramide pharmacokinetics.

Correspondence to K. Mori.
The authors are at the Department of Thoracic Disease, Tochigi Cancer Center, 4-9-13, Yonan, Utsunomiya-shi, Tochigi-ken, 320 Japan.
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PATIENTS AND METHODS

Study population

Our subjects were 24 hospitalised patients with primary lung cancer receiving cisplatin alone or multidrug chemotherapy including cisplatin at the Department of Thoracic Disease of the Tochigi Cancer Center. Patients' characteristics are shown in Table 1.

Treatment regimens

Patients with non-small cell lung cancer received cisplatin alone (25 mg/m²/day, 5-day CI) or in combination with vindesine

Table 1. Patients' characteristics

Entered patients	24
Evaluable patients	21
Age (yr)	
Median	54
Range	30–80
Sex (M/F)	17/7
Performance status	
0–1	20
2–3	4
Pathology	
Adenocarcinoma	14
Small cell	7
Squamous cell	3
Treatment regimen	
Cisplatin (CI)	11 (8)
Cisplatin (CI) + vindesine	6
Cisplatin (CI) + etoposide	7
Order of antiemetic therapy	
Infusion first	12 (12)
Bolus first	12 (9)

No. of evaluable patients is given in parentheses.

(3 mg/m^2 intravenously, days 1 and 8). Cisplatin (25 mg/m^2/day, 5-day CI) and etoposide (100 mg/m^2/day intravenously, over 2 h, days 1, 3 and 5) were administered to patients with small cell lung cancer. This was repeated every 4 weeks. In all cases, 25 mg/m^2 of cisplatin was given per day, dissolved in 800 ml physiological saline and administered every 8 h as CI from a peripheral vein.

Antiemetic regimens

After informed consent was obtained, patients were randomised using random numbers to receive one of the two antiemetic regimens. The regimens are shown in Table 2. Regimen A is BI and B is CI of metoclopramide. Both A and B included methylprednisolone and diphenhydramine.

Each patient in both regimens received the same total dose of metoclopramide, 15 mg/kg, during each course of chemotherapy. Following the initial course of chemotherapy, patients were switched to the other antiemetic regimen for their second course.

Table 2. Antiemetic regimens

Drugs	Dose	
During chemotherapy*		
Diphenhydramine	30 mg orally (10 mg, three times a day), days 1–7	
Methylprednisolone		
Metoclopramide	125 mg intravenous bolus (30 min) every 8 h for 3 doses, days 1–5	
	1 mg/kg intravenous bolus (30 min) every 8 h for 3 doses, days 1–5 (regimen A) or	
	3 mg/kg/day intravenous infusion for 120 h (regimen B)	
After chemotherapy (both regimen A and B)		
Methylprednisolone	125 mg intravenous bolus (30 min)	for 2 doses, day 6 for 1 dose, day 7
Metoclopramide	1 mg/kg intravenous bolus (30 min)	for 1 dose, day 6 for 2 doses, day 7 , 8

* All begun simultaneously starting chemotherapy.

Evaluation

Evaluation of the antiemetic efficacy and the side-effects of the antiemetic treatment was based upon reports maintained by medical staff. Patients were observed from the initial chemotherapy through the second course of chemotherapy and until their side-effects had disappeared. Patients' characteristics, the number of vomiting episodes, the presence or absence of nausea, the duration of nausea and vomiting, extrapyramidal reactions, diarrhoea and nervousness were recorded. Antiemetic efficacy was evaluated by the presence or absence of nausea and the number of vomiting episodes per day. Patients were observed for 28 days. Complete response was defined as no vomiting and no nausea. Major response, minor response and no response were defined as 0–2, 3–4 and 5 or more vomiting episodes, respectively. After the second course of chemotherapy, patients were asked which antiemetic regimen they preferred for further therapy. The following tests were used for determining the statistical significance of the data. Crossover analysis by analysis of variance was used for cases which could be evaluated after the second course. Fisher's exact test was used to compare the presence of digestive system problems, and Student's unpaired t test was used to compare the number of vomiting episodes and duration of emesis after the initial course. In addition, the Wilcoxon matched-pairs signed-rank test was used to compare the patients' choice of antiemetic regimen for futher therapy.

Plasma concentration of metoclopramide

Blood samples were collected before administration and 0, 2, 4 and 8 hours after administration in patients receiving bolus infusion and before and 2, 4, 8, 24, 48, 72, 96, 120, 122, 124 and 128 hours after administration in patients receiving continuous infusion (3 mg/kg/day). Metoclopramide concentrations in the samples were measured.

Furthermore, in order to examine the pharmacokinetics of high-dose metoclopramide (6 mg/kg/day) CI, after informed consent was obtained, high-dose metoclopramide was administered to the patients who requested metoclopramide CI in the third course. Blood concentrations were again analysed. Metoclopramide concentrations were analysed using high performance liquid chromatography [6].

RESULTS

12 patients were randomised to receive regimen A and 12 patients to receive regimen B during the initial course of chemotherapy. 21 out of 24 patients could be evaluated (Table 1). 2 patients required a change of therapy due to progressive disease, and 1 patient refused further chemotherapy after his initial course.

For regimen A, 11 patients experienced nausea during chemotherapy administration (5 days) and 4 during antiemetic administration after chemotherapy (6–8 days). For regimen B, the corresponding figures were 7 and 4 patients. For regimen A, there were 4 patients who experienced vomiting during chemotherapy and 4 during antiemetic administration. For regimen B, the corresponding figures were 1 and 2 patients. There was no difference in the time of occurrence of digestive system problems between the two regimens, and symptoms occurred fairly frequently during chemotherapy administration (Table 3).

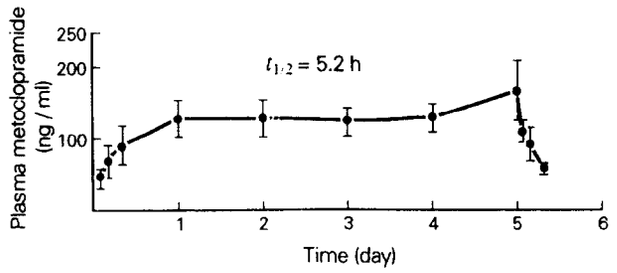

Fig. 1. Peak and trough plasma metoclopramide (mean, S.E.) in 10 patients given 5-day CI (3 mg/kg per day).

As shown in Table 3, antiemetic responses were as follows: 6 and 10 cases showed complete response, no nausea and no vomiting for regimens A and B, respectively ($P = 0.048$). 14 and 18 cases showed no vomiting in regimens A and B, respectively ($P = 0.048$). There were 2 cases of no response in regimen A. Vomiting episodes were seen 27 and 9 times in regimens A and B, respectively. The average number of episodes was 1.28 and 0.43, respectively ($P = 0.042$). There was no difference in the average duration of nausea or vomiting.

When 24 cases were evaluated after the initial course, vomiting episodes were seen 21 and 4 times in regimens A and B, respectively ($P = 0.048$). Thus, there was a significant difference. No significant difference was obtained for any other observation. For both regimens, side-effects such as diarrhoea, extrapyramidal reactions and nervousness were reported. However, these were not serious and treatment was not required. Thus it was possible to continue administering metoclopramide.

When patients were interviewed after the second course of chemotherapy, 15 patients chose CI and one patient chose BI as the antiemetic regimen for further therapy. The remaining 5 patients said either regimen was acceptable. This shows that CI was preferable ($P < 0.001$). Most patients who chose CI said that CI resulted in less serious digestive system problems than BI.

With regard to metoclopramide pharmacokinetics, the peak concentrations were 268 ng/ml for BI, 169 ng/ml for 3 mg/kg/day CI and 488 ng/ml for 6 mg/kg/day CI.

The average half-lives ($t_{1/2}$) were 5.1, 5.2 and 7.0 h, respectively, and the areas under the curve (AUC) were 13 552, 15 792 and 49 607 ng·hr/ml, respectively (Fig. 1).

Table 3. Results of antiemetic therapy

	Regimen		
	A	B	*P*
Mean occurrence of emesis (day)			
Nausea	4.7 (n = 18)	4.7 (n = 11)	
Vomiting	5.9 (n = 9)	5.3 (n = 3)	
Antiemetic response			
Complete	6 (3)	10 (5)	0.048
Major	10 (4)	10 (6)	
Minor	3 (4)	1 (1)	
No response	2 (1)		
No. of vomiting episodes			
Mean	1.28 (1.75)	0.43 (0.33)	0.042
Range	0–9 (0–6)	0–4 (0–4)	(0.048)
Length of nausea (day)			
Mean	4.5 (3.3)	2.2 (2.8)	NS
Range	0–14 (0–9)	0–8 (0–7)	
Length of vomiting (day)			
Mean	0.76 (1.3)	0.38 (0.25)	NS
Range	0–5 (0–5)	0–4 (0–3)	
Diarrhoea	5	3	NS
Extrapyramidal reaction	2	1	NS
Nervousness	1	1	NS

NS = not significant at $P = 0.05$.
Values for first course are shown in parentheses.

DISCUSSION

We performed a randomised crossover study to compare CI and BI of metoclopramide in multidrug therapy including 5-day CI of cisplatin. The result of this study showed that CI of metoclopramide was superior in antiemetic effect. In particular, the number of cases showing complete response (no nausea and no vomiting) and the number showing no vomiting was significantly higher for continuous infusion, and that of vomiting episodes was significantly lower ($P < 0.05$). A higher number of patients preferred continuous infusion as the antiemetic regimen for further therapy ($P < 0.001$). Our results show that CI has superior antiemetic effect on acute and delayed nausea and vomiting.

The peak concentration of metoclopramide in the blood for BI was higher by 1.58 than that for CI. The AUC in CI was higher by 1.16. Compared with other reports, the peak concentrations were lower. This is because the total amount of metoclopramide administered per day was 3 mg/kg, which is lower than other reports [9]. According to Meyer *et al.* [6], if the peak metoclopramide concentration is 850 ng/ml or more in cisplatin high-dose BI, good antiemetic effect can be obtained. In our study, on the other hand, cisplatin was administered in small amounts, repeatedly. Therefore, it is considered that a lower metoclopramide peak concentration gives adequate results. We compared 3 mg/kg/day metoclopramide CI with 6 mg/kg/day CI. The latter had higher peak concentration by a factor of 2.9, and higher AUC by a factor of 3.1. Therefore, metoclopramide kinetics in CI were linear with dose. There was no difference in half-life, and no evidence of accumulation [9].

As described above, metoclopramide continuous infusion was significantly superior to bolus infusion in antiemetic effect for control and prevention of chemotherapy-induced acute and delayed nausea and vomiting in cisplatin 5-day continuous intravenous infusion. Side-effects were minimal in both methods, and both could be used safely.

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Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma

Lodewijk Th. Vlasveld, Maarten P.W. Gallee, Sjoerd Rodenhuis and Babs G. Taal

4 patients with malignant peritoneal mesothelioma have been treated with intraperitoneal chemotherapy in the Netherlands Cancer Institute in the recent years. 1 patient achieved a complete remission for 36+ months and another patient had a partial remission that lasted for 10 months. Intraperitoneal chemotherapy alone or in combination with other treatment modalities may yield a response rate of 58% with 24% complete remissions in 70 patients reviewed in the literature. Although these data should be considered wtih caution because of the heterogenicity of the patient group treated, cisplatin-based intraperitoneal chemotherapy seems to be the best available treatment for malignant peritoneal mesothelioma at present.
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INTRODUCTION

PRIMARY MALIGNANCIES of the mesothelium, the lining of the pleura, peritoneum, pericardium and tunica vaginalis are rare. Malignant mesothelioma commonly involves the pleura, but in 10–20% of cases the disease is confined to the peritoneal cavity [1, 2]. The observed increased incidence of malignant mesothelioma in the past decades is most likely the result of the widespread exposure to industrial products such as asbestos [1, 3–5]. The reported percentage of asbestos exposure in patients with malignant mesothelioma varies highly depending on the demographic variables of the patient groups studied. Cohort studies in asbestos workers demonstrate a calculated death risk due to mesothelioma of up to 10%, with a latency of 30–40 years after exposure [6].

For malignant peritoneal mesothelioma other risk factors such as abdominal irradiation, exposure to a variety of toxic agents or recurrent peritonitis have occasionally been implied [4, 5]. Usually, malignant peritoneal mesothelioma presents with vague abdominal complaints, abdominal swelling, pain, weight loss and fever of unknown origin [1, 3]. Since conventional radiological examination and computed tomography are non-specific, laparoscopy or laparotomy is often needed to establish the diagnosis. The histological pattern of malignant mesothelioma ranges from the most frequently encountered epithelial type to more sarcomatous forms [1, 3, 5]. Therefore immunohistochemical assays, demonstrating the co-expression of vimentin, keratins and epithelial membrane antigens are often necessary to establish the diagnosis [7].

The prognosis of malignant peritoneal mesothelioma is even worse than that of pleural mesothelioma with a mean reported survival of less than 12 months [4]. The response rates to single agent or combination chemotherapy do not exceed 30% in most reported series [4]. Combination of the various treatment modalities with intracavitary application of radioactive or cytostatic agents may yield significant response rates in patients with malignant peritoneal mesothelioma with long-term survival in some cases [4, 8, 9]. In this paper we present data of 4 patients with malignant peritoneal mesothelioma treated with intraperitoneal chemotherapy in our institute over the recent years, with a review of the literature.

CASE REPORTS

Case 1 (55 years, male). He had previous short-term asbestos exposure, and malignant epithelial mesothelioma was diagnosed at exploratory laparotomy for unexplained right upper abdominal pain and 5 kg weight loss. After cholecystectomy for tumour infiltration in the wall of the gallbladder, diffuse peritoneal involvement remained. Because of rapidly progressive ascites 25 mg/m^2 mitoxantrone was intraperitoneally administered through a Tenckhoff catheter, despite the presence of pleural thickening on the chest X-ray. After three 3-weekly courses that were complicated by transient peritoneal irritation, the treatment was discontinued because of rapid progression. 8 weeks later the patient died, 6 months after the initial diagnosis.

Correspondence to L. Th. Vlasveld.
L. Th. Vlasveld, S. Rodenhuis and B.G. Taal are at the Department of Medical Oncology and M.P.W. Gallee is at the Department of Pathology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
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