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Original Paper

Comparison of Granisetron Alone and Granisetron Plus Hydroxyzine Hydrochloride for Prophylactic Treatment of Emesis Induced by Cisplatin Chemotherapy

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The efficacy and safety of granisetron alone (group G) and granisetron plus hydroxyzine hydrochloride (group G/H) as prophylactic therapy for acute and delayed nausea and vomiting were evaluated in an open trial in head and neck cancer patients undergoing chemotherapy with cisplatin. The severity of nausea was significantly reduced on days 1 and 4 in patients receiving combination therapy, but the frequency of vomiting was not significantly different between the two groups. The only side-effect observed was headache in 1 patient from group G, and no drug-related laboratory test abnormalities were observed. These results suggest that the anti-emetic efficacy of granisetron can be augmented by hydroxyzine hydrochloride.

Key words: granisetron, hydroxyzine hydrochloride, anti-emetic efficacy, cisplatin
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INTRODUCTION

CISPLATIN CHEMOTHERAPY is effective in head and neck cancer [1]. However, the side-effects of this treatment include potentially debilitating nausea and vomiting [2, 3]. Successful anti-emetic therapy can enable patients receiving chemotherapy to maintain nutritional intake and improve their quality of life.

Recently, a number of new anti-emetics, the 5-hydroxytryptamine 3 receptor (5-HT_3 receptor) antagonists, have been developed [4]. These drugs were initially found to prevent vomiting due to cisplatin, a chemotherapeutic drug with strong emetic effects [5], but subsequent clinical studies have shown that 5-HT_3 receptor antagonists are also effective in controlling vomiting due to other anticancer drugs and radiotherapy [6, 7]. Studies have shown that the 5-HT_3 receptor antagonist ondansetron is more effective than high-dose metoclopramide in controlling acute cisplatin-induced nausea and vomiting [8]. However, only limited data are available on the efficacy of the 5-HT_3 receptor antagonists in the treatment of delayed nausea and vomiting due to cisplatin chemotherapy [9]. We investigated the anti-emetic efficacy of granisetron alone versus that of a combination therapy comprising granisetron and the antihistamine hydroxyzine hydrochloride (hydroxyzine) in patients undergoing cisplatin treatment.

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PATIENTS AND METHODS

Patients

Previously untreated head and neck cancer patients admitted to Yokohama City University School of Medicine or Kanagawa Cancer Center, Kanagawa, Japan between September 1992 and August 1993 were enrolled in a randomised, open study. Patients were treated with intravenous (i.v.) cisplatin 60 mg/m^2 on day 1 of the study, followed by a 120 h continuous i.v. infusion of 5-fluorouracil 1000 mg/m^2/day.

Patients who met any of the following criteria were excluded from the study: younger than 16 years of age; concomitant severe cardiac, renal, or hepatic disease; confirmed or suspected pregnancy; concomitant cerebral tumour or epilepsy; and other conditions deemed by attending physicians to make entry into the study inappropriate.

A total of 50 patients were enrolled: 25 were randomly assigned to receive granisetron alone (group G) and 25 to receive granisetron and hydroxyzine (group G/H). No significant differences with respect to sex, age, original tumour site and performance status existed as determined according to World Health Organization (WHO) criteria (Table 1); 1 patient in each

Table 1. Patients' characteristics

Characteristic	Granisetron alone	Granisetron plus hydroxyzine
No. of patients	25	25
Male/Female	23/2	22/3
Age (years)		
Median	57	58
Range	37–77	19–76
Original tumour site		
Pharynx	16	20
Nose	3	1
Oral cavity	6	4
Performance status		
0	20	17
1	5	8

group had an average alcohol intake of > 30 units/week as determined using a questionnaire on alcohol consumption. Informed consent was obtained from all patients entered into the study, which was approved by the ethics committee of the participating institutions.

Anti-emetic treatment

Patients in group G received granisetron 40 μg/kg every 12 h during the first 3 days after administration of cisplatin, and granisetron 40 μg/kg/day from days 4 to 7. Patients in group G/H received granisetron on the same schedule as patients in group G from days 1 to 7, and also received hydroxyzine 25 mg every 12 h during the first 3 days after cisplatin administration.

Both granisetron and hydroxyzine were dissolved in 100 ml of physiological saline and administered by i.v. infusion.

Assessment of anti-emetic effectiveness

Effectiveness was evaluated based on patient and physician assessments of the degree of nausea and frequency of vomiting, including dry retching. Patients' and physicians' subjective assessments of nausea and vomiting were recorded before treatment, 6, 12, 18, and 24 h after the start of cisplatin infusion, and three times daily for the next 13 days. Both patient and physician made global assessments of nausea and treatment effectiveness. The degree of nausea was graded: none; mild (no interference with normal daily life); moderate (interference with normal daily life); and severe (confinement to bed due to nausea). The clinical effectiveness was expressed as the percentage of patients who experienced no or mild nausea.

Safety

Monitoring of side-effects was initiated upon the start of chemotherapy. Blood pressure, pulse rate and temperature were recorded when the patients were screened for entry into the trial, immediately before treatment and after the start of cisplatin infusion. An electrocardiogram (ECG) recording was made, and alertness and general health were assessed by the physician when patients were screened. Blood and urine samples were taken for laboratory tests at screening and twice weekly for 3 weeks after completion of anti-emetic therapy.

Statistics

Results were analysed using the χ^2 test, Fisher's exact test and the Mann–Whitney U-test with a level of significance of 5%.

RESULTS

All 50 patients who entered the trial completed it and tolerated the anti-emetic treatments.

The incidence of nausea and vomiting was recorded daily for 2 weeks after cisplatin administration. The data recorded during the first 7 days are shown in Table 2; neither nausea nor vomiting occurred after day 8 in any patient. The combination anti-emetic therapy significantly reduced the intensity of nausea on day 1 (none or mild nausea in 84/48%, combination/granisetron alone; $P < 0.05$) and day 4 (92/60%; $P < 0.05$) compared with granisetron alone, whereas no significant difference was seen on days 2, 3, 5, 6 and 7 with respect to nausea.

The percentage of patients who did not experience vomiting on days 1, 2, and 3, respectively, was 68, 68 and 72% in group G and 84, 84 and 96% in group G/H. However, the differences between these values were not statistically significant.

Side-effects (moderate headache and heavy headedness) occurred in only 1 patient in group G. This symptom disappeared spontaneously after 3 days. No laboratory test or ECG abnormalities were observed in any patient during the study.

DISCUSSION

Among the various side-effects of cisplatin chemotherapy, nausea and vomiting are the most unpleasant for patients. Recently, the efficacy of anti-emetic therapy in controlling these side-effects has been studied, and 5-HT_3 receptor antagonists have been found to be very effective in controlling those caused by cisplatin [10–13]. 5-HT_3 receptor antagonists can also be used as monotherapy, making them more acceptable than the anti-emetic drug combinations used previously [14, 15]. However, several studies have shown that dexamethasone significantly improves the efficacy of a 5-HT_3 receptor antagonist in the treatment of cisplatin-induced emesis [16–20].

Although the combination of a 5-HT_3 receptor antagonist and a steroid is more effective than a 5-HT_3 receptor antagonist alone, steroids cannot be administered to patients with complications such as peptic ulcer or diabetes mellitus. Therefore, it is necessary to develop a combination therapy regimen with greater

Table 2. Distribution of patients according to the degree of nausea, frequency of vomiting and efficacy

	Degree of nausea			Frequency of vomiting			
Day	None or mild	Moderate	Severe	0	1–2	3–4	5+
Granisetron alone (n = 25)							
1	12	10	3	17	4	3	1
2	13	8	4	17	7	1	0
3	14	7	4	18	6	1	0
4	15	8	2	23	1	1	0
5	18	6	1	24	0	1	0
6	23	2	0	24	1	0	0
7	24	1	0	25	0	0	0
Granisetron plus hydroxyzine (n = 25)							
1	21	3	1	21	3	1	0
2	17	8	0	21	4	0	0
3	20	5	0	24	1	0	0
4	23	2	0	24	1	0	0
5	25	0	0	25	0	0	0
6	25	0	0	25	0	0	0
7	25	0	0	25	0	0	0

efficacy than 5-HT_3 receptor antagonist monotherapy for use in these patients. Furthermore, the efficacy of the 5-HT_3 receptor antagonist–steroid combination therapy regimen is not 100% in patients with cisplatin-induced nausea. This justifies the investigation of further 5-HT_3 antagonist-based combinations.

In this study, combination therapy with the 5-HT_3 antagonist granisetron and the histamine H_1 receptor antagonist hydroxyzine significantly reduced the intensity of nausea compared with granisetron alone. However, no significant difference between these regimens was observed in relation to vomiting.

Side-effects were not seen in any patient who received granisetron and hydroxyzine. In our experience, hydroxyzine can cause drowsiness and other adverse effects. However, drowsiness was not observed in this study, although the sedative effect may contribute to the greater anti-emetic efficacy of the combination regimen. These results suggest that the anti-emetic combination therapy presents no significant problem with respect to safety.

In conclusion, this is the first randomised study to use an anti-emetic combination therapy consisting of a 5-HT_3 antagonist and a histamine H_1 receptor antagonist. This combination could be useful in the treatment of chemotherapy-induced emesis in patients with a contraindication for the use of steroids. In addition, an anti-emetic combination therapy regimen consisting of a 5-HT_3 receptor antagonist, a steroid and hydroxyzine may be more effective than a 5-HT_3 receptor antagonist plus a steroid. We are currently conducting a randomised, blind study to compare the anti-emetic effects of a 5-HT_3 receptor antagonist, dexamethasone, plus hydroxyzine with those of a 5-HT_3 receptor antagonist plus dexamethasone in patients with cisplatin-induced nausea and vomiting.

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