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SHORT COMMUNICATION

Ting-Chang Chang · Fushing Hsieh · Chyong-Huey Lai
Chih-Jen Tseng · Huei-Hsin Cheng · Chia-Lin Li
Bullard J. Michael · Yoong-Kuei Soong

Comparison of the efficacy of tropisetron versus a metoclopramide cocktail based on the intensity of cisplatin-induced emesis

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Abstract Cisplatin-induced emesis is one of the most feared side effects in cancer treatment. High-dose metoclopramide may prevent only 30–40% of cases of acute emesis. Investigations to test the efficacy of new antiemetics are mandatory. We compared the efficacy, toxicity, and patients' preference for tropisetron, a new 5-hydroxytryptamine$_3$ (HT_3) receptor antagonist, with those of a combination of high-dose metoclopramide, dexamethasone, diphenhydramine, and lorazepam (metoclopramide cocktail) in a randomized crossover study for the control of nausea and vomiting during cisplatin-containing chemotherapy. A total of 62 chemotherapy-naive women were included and followed over 3 consecutive courses. Detailed analysis comparing the incidence of acute emesis for each 4 h period following cisplatin infusion was also performed. Complete protection from acute emesis was obtained in 48% of patients receiving tropisetron and 29% of patients receiving the metoclopramide cocktail over the first two courses of chemotherapy ($P = 0.029$). When the frequency of acute emesis in all patients was compared on a daily basis, no significant difference was found. When emesis frequency was compared over each 4 h period following infusion of cisplatin, tropisetron was superior to the metoclopramide cocktail during the first, the second, and the first and second periods ($P = 0.0001$, $P = 0.01$ and $P = 0.0006$, respectively). This superiority reversed after 12 h but did not reach statistical significance ($P = 0.112$). Tropisetron was more effective in controlling acute nausea, but metoclopramide provided better control of delayed emesis. A drop in efficacy over successive courses was observed in patients receiving metoclopramide first but was not seen in tropisetron-first patients. A tendency for tropisetron preference was observed. Tropisetron is more effective than the metoclopramide cocktail in the control of chemotherapy-induced vomiting within 8 h of the implementation of cisplatin and in the control of nausea on the 1st day. To improve the control of chemotherapy-induced emesis, further investigations on the additional tropisetron dosing at 8 h after cisplatin infusion or the combination use of tropisetron and other antiemetics by a continuous 4 h period of observation and comparison are mandatory.

Key words Tropisetron · Metoclopramide cocktail · Cisplatin-induced emesis

Introduction

Cisplatin, a commonly used chemotherapeutic agent, is one of the most emetogenic agents and frequently induces vomiting [1, 2]. Although chemotherapy-induced emesis is generally self-limited, it is dreaded by patients and represents a major reason for premature termination of treatment. Many agents have been used for the control of this distressing side effect, including phenothiazines [3, 4], the butyrophenones (droperidol, haloperidol) [5, 6], delta-9-tetrahydrocannabinol [7, 8], high-dose metoclopramide [1, 5], and dexamethasone [9, 10].

Unfortunately, despite high doses and/or combinations of the above mentioned agents, complete prevention of cisplatin-induced emesis is achieved in only

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T.-C. Chang (✉) · C.-H. Lai · C.-J. Tseng · H.-H. Cheng · C.-L. Li · Y.-K. Soong
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou, Taoyuan 333, Taiwan

F. Hsieh
Institute of Statistics, National Tsing Hua University, Hsinchu, Taiwan

B.J. Michael
Department of Primary Care Medicine, Chang Gung Medical College, Taoyuan, Taiwan

30–40% of patients [11–13]. Moreover, the toxic effects of antiemetic agents, especially extrapyramidal reactions, which frequently occur in young women treated with high-dose metoclopramide, are upsetting to both patients and clinical personnel [14, 15].

Although not well understood, the mechanism of chemotherapy-induced emesis may include serotonin (5-HT) release from enterochromaffin cells caused by intestinal mucosa damage [16]. This serotonin stimulates vagal and, possibly, splanchnic abdominal nerves and triggers the vomiting center in the central nervous system (CNS) through its binding to 5-hydroxytryptamine$_3$ (5-HT$_3$) and other receptors [17–19]. 5-HT$_3$ antagonists, including ondansetron, tropisetron, granisetron, and dolasetron, are the newest family of antiemetic drugs [20]. A few clinical studies have demonstrated the efficacy of ondansetron (GR 38032F) in controlling cisplatin-induced emesis to be at least comparable with that of high-dose metoclopramide [12, 13, 21, 22], but tropisetron (ICS 205–930) has not yet been extensively investigated. Sorbe et al. [23–25] compared the anti-emetic effects of a single daily dose of 5 mg tropisetron with those of a high-dose metoclopramide-containing cocktail in patients receiving cisplatin-containing chemotherapy. They concluded that tropisetron and the metoclopramide cocktail were almost equipotent in the control of cisplatin-induced emesis, and tropisetron seemed to be both efficacious and safe. To try to evaluate further the efficacy of tropisetron in the control of chemotherapy-induced emesis and compare it with that of the conventional antiemetic regimen of high-dose metoclopramide in women, we undertook a randomized crossover study. For a more detailed analysis and comparison, the timing and frequency of emesis was further divided into 4 h periods starting from the time of cisplatin infusion.

Patients and methods

Patients

Women with genital malignancies were eligible for the study only if they had never received any form of cytotoxic chemotherapy or radiation. They were scheduled to receive at least two courses of chemotherapy that included cisplatin at a dose of 50–100 mg/m^2. Chemotherapy was given as a postoperative adjuvant for various gynecologic malignancies or as a preoperative neoadjuvant for bulky cervical cancer of stage Ib or IIa. Other eligibility criteria included a serum creatinine level of less than 2 mg/dl, a Karnofsky performance status of no less than 60%, an age of over 18 years, and an expected survival of greater than 3 months. Patients were excluded if they had received chemotherapy prior to the study; had nausea or vomiting not caused by chemotherapy, which included but was not limited to gastrointestinal conditions and CNS lesions; or had received an antiemetic agent within 24 h (or steroids during the week) of the start of chemotherapy. The antiemetic agents included metoclopramide, haloperidol, prochlorperazine, and other agents with antiemetic or sedative effects. Patients who received concurrent chemotherapy and radiation therapy were excluded. Patients with a history of diabetes, glaucoma, cataracts, tuberculosis, an active peptic ulcer, or other contraindications to the use of corticosteriods and patients with severe emotional problems or any other indication that would not comply with the conditions of the study protocol were not eligible.

The protocol was approved by the human investigation committee of Chang Gung Memorial Hospital and the Health Bureau, Executive Yuan, Taiwan, Republic of China. This study was conducted according to the Declaration of Helsinki. All subjects agreed to participate in this randomized trial protocol and signed written informed consent forms in the presence of a witness.

Trial design and treatment

Patients were enrolled consecutively and were randomly assigned to receive either tropisetron (experimental regimen) or the high-dose metoclopramide cocktail (standard regimen) during the first course of chemotherapy; they were then crossed over to the other treatment arm for the second course. To investigate the existence of carryover and period effects on chemotherapy-induced vomiting and nausea, as well as the persistence in efficacy of these two antiemetic regimens in different treatment courses on one patient, the regimen that was used at the first course of chemotherapy was again used for the third course. The randomization was carried out by personnel at the Biostatistics Consultation Center, Chang Gung Memorial Hospital. The drugs were prepared by a pharmacist.

Tropisetron was given intravenously at a dose of 5 mg, at 30 min prior to the cisplatin infusion over 15 min on day 1 and as a 5 mg capsule orally on days 2–4 at least 1 h before breakfast. The metoclopramide cocktail was given on the 1st day beginning at 47 min prior to the cisplatin infusion as: (1) diphenhydramine given at 30 mg intravenously over 2 min, followed immediately by (2) dexamethasone phosphate disodium given at 20 mg intravenously over 15 min, followed by (3) metoclopramide given at 3 mg/kg intravenously over 15 min and at 2 mg/kg intravenously over 15 min at 2 and 4 h after the cisplatin infusion, respectively, and (4) lorazepam given at 1 mg q.i.d. On days 2–4, oral metoclopramide (3 tablets q.i.d.; 1 tablet = 3.84 mg) and lorazepam (1 mg q.i.d.) were given. Patients with cervical cancer received combination chemotherapy consisting of cisplatin given at 50 mg/m^2 on day 1, vincristine given at 1 mg/m^2 on day 2, and bleomycin given at 25 mg/m^2 daily on days 2–4 of each treatment course with a 10-day rest interval. Patients with ovarian cancer received cisplatin at either 50, 75, or 100 mg/m^2 and cyclophosphamide at 500–1,000 mg/m^2 over 1 day every 3 weeks. Patients with germ-cell tumors received cisplatin at 50–100 mg/m^2 on day 1 and etoposide at 100 mg/m^2 on days 1–3. Cisplatin was given intravenously over a 1 h period as the initial chemotherapeutic agent for each treatment course. Prerequisites for administration of chemotherapy were a WBC of $\geq$ 3,000/μl, a platelet count of $\geq$ 10,000/μl, a serum creatinine level of $\leq$ 1.5 mg/ml, and normal serum levels for electrolytes and enzymes. Only light food intake was suggested on the 1st day of chemotherapy.

Assessment of antiemetic effectiveness

The patients stayed in the hospital for at least 24 h after each cisplatin administration. The time at which the cisplatin infusion started was recorded by the nurse in charge. The time of each episode of emesis was recorded by the patient and/or accompanying person(s) who had been given instructions immediately before each treatment course, and each recording confirmed by the investigation nurse. Any vomit or a series of one to five retches within a 5 min period were considered to represent a single emetic episode. On days 2–4 after cisplatin infusion, the patient was also instructed to continue the same recording procedure on a diary sheet. These sheets were collected by the investigation nurse (H.H.C.) and sent to Biostatistic Consulting Center, Chang Gung Memorial Hospital. Episodes of nausea felt before and after chemotherapy were assessed by

the patient according to a graded scale (none, mild, moderate, or severe) and a visual-analogue scale on which a score of 0 indicated no nausea and a score of 100 indicated extremely severe nausea. Adverse effects were observed directly, particularly the presence of extrapyramidal symptoms (dystonic-dyskinetic reaction, parkinsonism, or tardive dyskinesia); the degree of sedation, which was recorded as none, mild, moderate (the patient could be roused easily), or marked (the patient could be roused only with difficulty); headache; and the number of bowel movements per day. After completing the second course of therapy, patients were asked for their preference, if any. Patients who failed to respond (more than five emetic episodes in 1 day) could be additionally treated with prochlorperazine (Novamine) given at 5 mg intramuscularly as a salvage regimen every 4 h if necessary.

Statistical analysis

The severity of vomiting was counted by (1) the real number and (2) ordinal variables of none (no vomiting), mild (vomiting 1–2 times), moderate (vomiting 3–5 times), or severe (vomiting > 5 times) over a specific period. The severity of nausea was classified according to an ordinal scale of none (no nausea), mild (tolerable nausea, no interference with activity), moderate (tolerable nausea, interference with activity), or severe (intolerable nausea, bedridden for over 2 h). Complete control of emesis or nausea was defined as no vomiting or nausea over the specific period and major control, as only a mild reaction, if any, over the specific period.

The Mann-Whitney U-test, and Student's t-test for unpaired differences were used to test the presence or absence of period and carryover effects between the first two courses of chemotherapy. The Wilcoxon signed-rank test was used to test the presence of period and carryover effects in one patient treated with the same antiemetic regimen but over different courses of therapy (the first and third courses). These tests were applied to all variables investigated [the frequency of emesis and the severity of nausea on day 1 (acute episodes) and days 2–4 (delayed episodes)]. A two-tailed P value of < 0.10 was considered to denote the presence of period and carryover effects. The mann-Whitney U-test was applied to compare the efficacy of the two antiemetic regimens over the first course of chemotherapy. The chi-square test was used to compare the differences in complete control and in major control of emesis and nausea over the first two courses of therapy. The Wilcoxon signed-rank test for paired data was used to assess differences in the efficacy of treatment on a crossover basis. The signed test was used to assess differences in treatment preference. A two-tailed P value of < 0.05 was considered to indicate statistical significance. Nausea and vomiting were analyzed separately for day 1 (acute episodes) and days 2–4 (delayed episodes). The analysis of delayed episodes was based on the greatest number of daily emetic episodes and the greatest severity of nausea recorded.

For a more detailed comparison, the frequency of acute emesis was further divided into 4 h periods beginning from the time of cisplatin infusion using the same scales mentioned above.

Results

A total of 62 patients were randomly assigned to participate in the first course of chemotherapy. In all, 57 patients completed the scheduled 2 courses of therapy and 43 completed 3 courses of therapy and were evaluated for clinical efficacy. Reasons for nonevaluation during the second course were: a change in the treatment to surgery ($n = 2$), a change in the cisplatin dose ($n = 1$), refusal of further chemotherapy ($n = 1$), and death ($n = 1$). Reasons for patient's not being assessable for the third course were: a change in management to surgery or radiation ($n = 6$), a change in the chemotherapy dose ($n = 6$), and an error in antiemetic administration ($n = 2$). Of the 62 patients, 27 received tropisetron as the antiemetic regimen during the first course of chemotherapy and 35 received the metoclopramide cocktail. The characteristics and cisplatin doses for these 62 patients are shown in Table 1.

No patient experienced nausea or vomiting the day before receiving the first course of chemotherapy. Four patients (three receiving the metoclopramide cocktail and one receiving tropisetron in the first course) experienced mild nausea the day before the second course of chemotherapy, and three patients (two received the metoclopramide cocktail and one received tropisetron in their previous course) experienced mild nausea the day before the third course of therapy. None of these seven patients had received an antiemetic agent within 24 h of the start of chemotherapy. The symptoms disappeared after completion of their treatment course and were believed to be related to the chemotherapy.

Period and carryover effects

Patients who received tropisetron in the first course and the metoclopramide cocktail in the second treatment course experienced more episodes of acute emesis over the second course (emetic episodes recorded during tropisetron administration minus emetic episodes noted during treatment with metoclopramide: mean $= -0.875$, SE $= 0.769$). Patients who received metoclopramide during the first course and tropisetron over the second course also experienced more episodes of acute emesis over the second course (emetic episodes noted during tropisetron administration minus emetic episodes recorded during treatment with metoclopramide:

Table 1 Characteristics and cisplatin doses of the 62 study patients

Characteristic	Value
Age (years):	
Median	52
Range	18–73
Type of primary tumor:	
Cervical cancer	28
Epithelial ovarian cancer	27
Germ-cell tumor	4
Others[a]	3
Cisplatin dose:	
50 mg/m^2	35
75 mg/m^2	9
100 mg/m^2	18

[a]Two patients with endometrial cancer; one received cisplatin and Adriamycin (PA), and one was treated with cisplatin, Adriamycin, and cyclophosphamide (PAC). One patient with uterine sarcoma received PAC

mean = 0.818, SE = 0.548). The difference was marginally statistically significant ($P = 0.07$ by student's t-test; $P = 0.048$ by the Mann-Whitney U-test). Those who had more than five emetic episodes in a single day were additionally treated with prochlorperazine, which may have altered the absolute number of emetic episodes occuring in some patients. It nonetheless indicated the possibility of period and carryover effects in the use of antiemetics with a tendency for more emesis during the second course. The same effect was observed for acute nausea ($P = 0.01$) but was not seen for delayed emesis and nausea.

Specifically, significant period and carryover effects were observed in the incidence of acute emesis in the metoclopramide-first patients ($P = 0.0112$ by the Wilcoxon signed-rank test) but were not seen in the tropisetron-first patients ($P = 0.597$, Wilcoxon signed-rank test) when the first and the third courses of therapy were compared. The same tendency was observed in comparisons of acute nausea but not of delayed emesis and nausea. It seems that the metoclopramide cocktail used during the first course of treatment lessened the efficacy of antiemetics during the following courses of therapy but tropisetron did not. This would lead to an underestimation of the efficacy of tropisetron on acute episodes since the first course of metoclopramide lessened the efficacy of tropisetron for the second course. However, when we compared (1) data from the first course only and (2) data from the first two courses on a crossover basis, the results of the two comparisons were similar.

Acute and delayed emesis

Rates of 52% and 45% of complete protection from emesis were observed in patients who received tropisetron in the first and second courses of chemotherapy, respectively, and rates of only 29% and 29%, respectively, were observed in patients receiving the metoclopramide cocktail (Table 2). Pooling of the data revealed that 48% (29/60) of patients receiving tropisetron and 29% (17/50) of those receiving metoclopramide achieved complete protection. Tropisetron appeared superior to the metoclopramide cocktail in providing complete protection from emesis ($P = 0.029$). Mild vomiting was observed in 12 (20%) and 19 (32%) patients; moderate vomiting, in 9 (15%) and 12 (20%) patients; and severe vomiting, in 10 (17%) and 11 (19%) patients receiving tropisetron and metoclopramide, respectively; during the 1st day of therapy. When the responses of all patients were compared, no difference was found over the first, the second, or the first and second courses on a crossover basis.

A more detailed analysis comparing the frequency of acute emesis by 4 h periods beginning from the cisplatin infusion indicated that tropisetron was superior to the metoclopramide cocktail during the first, the second, and the first and second 4 h periods ($P = 0.0001$, $P = 0.01$, and $P = 0.0006$, respectively; Fig. 1). This superiority reversed after 12 h but was not statistically significant ($P = 0.112$). On the basis of the frequency of vomiting encountered on the worst day during oral antiemetic therapy for delayed emesis, only 33% of patients responded completely while taking tropisetron as compared with 58% receiving metoclopramide cocktail therapy. This difference was statistically significant ($P = 0.008$). When the severity of emesis was used for analysis, there was also a significant difference in favor of oral metoclopramide and lorazepam (Fig. 2; $P = 0.0154$). It was noted that the maximal periods of vomiting, either in the acute or the delayed phase, were those that included meal times, whereas the low recordings illustrated during hours 8–16 in Fig. 1 and during hours 12–20 in Fig. 2 reflected the sleeping periods.

Acute and delayed nausea

Rates of 56% and 36% of complete protection from acute nausea were observed in patients who received tropisetron in the first and second courses of chemotherapy, respectively, whereas rates of 34% and 21%, respectively, were noted in metoclopramide courses.

Table 2 Control of acute emesis and nausea in the first (62 patients) and second (57 patients) courses of therapy (*Mod*/Moderate)

Course treatment	Emetic episodes 0	1–2	3–5	> 5	Nausea severity[a] None	Mild	Mod	Severe
	Number of patients				Number of patients			
First:								
Tropisetron	14	5	4	4	15	9	3	0
Metoclopramide	10	9	8	8	12	12	8	3
Second:								
Tropisetron	15	7	5	6	12	14	7	0
Metoclopramide	7	10	4	3	5	9	9	1
Pooled[b]:								
Tropisetron	29[c]	12	9	10	27	23	10	0
Metoclopramide	17[d]	19	12	11	17	21	17	4

[a]Tropisetron versus metoclopramide in pooled data, $P = 0.04$ (Wilcoxon signed-rank test)
[b]First and second courses, [c] versus [d]; $P = 0.029$ (Student's t-test)

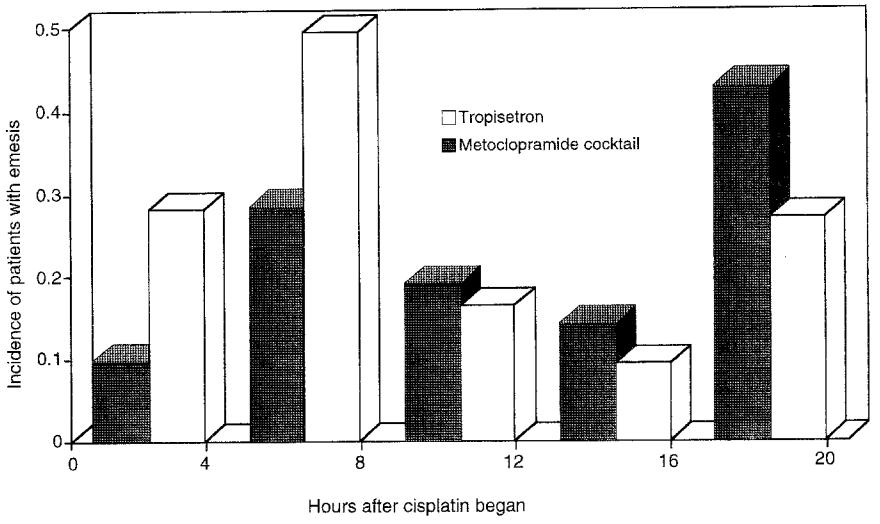

Fig. 1 Incidence of emesis beginning from the cisplatin infusion as determined by 4 h periods. The incidences were calculated by pooled data from 80 courses with tropisetron and 82 with the metoclopramide cocktail

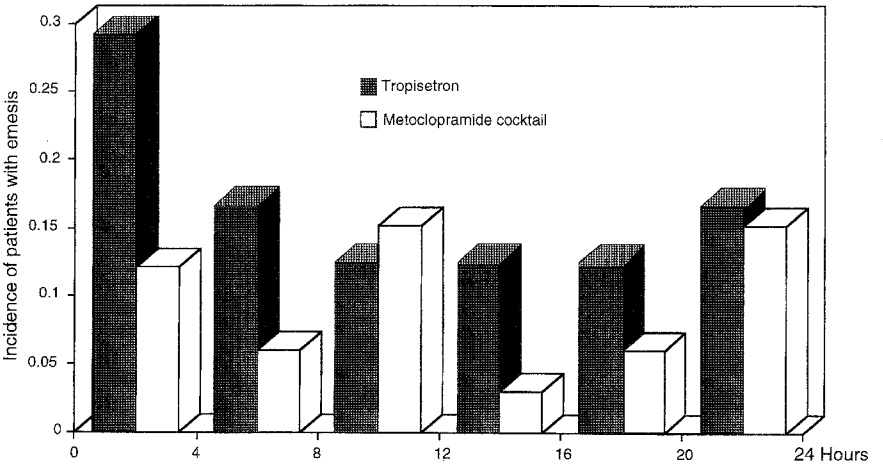

Fig. 2 Incidence of delayed emesis on the worst day as determined by 4 h periods. The incidences were calculated by pooled data from 80 courses with tropisetron and 82 with the metoclopramide cocktail

The use of tropisetron resulted in better control of the acute nausea following chemotherapy ($P = 0.04$, Wilcoxon signed-rank test). Tropisetron was also found to be more effective in controlling acute nausea when the evaluation was based on scores on the visual-analogue scale. In the prevention of delayed nausea, no difference was found.

Patients' preference

Of the 24 patients given tropisetron first, 17 preferred tropisetron, 5 preferred metoclopramide, and 2 expressed no preference. Of the 33 patients given metoclopramide first, 21 preferred tropisetron, 9 preferred metoclopramide, and 3 expressed no preference. The overall preferrence was 67% for tropisetron and 25% for metoclopramide (chi-square = 10.1, $P < 0.01$).

Side effects

Side effects related to tropisetron included headache (9.5%); fatigue, sedation, lethargy, or drowsiness (8.3%); constipation (8.3%); and diarrhea (2.3%). Side effects related to the metoclopramide cocktail comprised fatigue, sedation, lethargy, or drowsiness (21.2%); restlessness or hyperactivity (14.1%); extrapyramidal reaction (11.7%); and constipation (7.1%). Two patients who received the metoclopramide cocktail during their first chemotherapy course refused further metoclopramide because of extrapyramidal reactions.

Discussion

Our investigation addressed the question as to whether the efficacy of tropisetron might be better than that of a high-dose metoclopramide cocktail in the control of chemotherapy-induced nausea and vomiting by a new 5-HT_3 antagonist, tropisetron. In our study, no significant difference was observed between a single dose of intravenous tropisetron and multiple doses of the metoclopramide cocktail in the control of acute emesis, but tropisetron showed a better control of acute

nausea. In a comparison of the frequency of emesis for each 4 h period starting from the cisplatin infusion, tropisetron was significantly superior to the metoclopramide cocktail during the first, the second, and the first and second periods. This superiority disappeared thereafter. From 12 h after the cisplatin infusion and onward, a tendency for better emesis control, although not statistically significant, was observed in the metoclopramide users. One possible explanation for this phenomenon is that by 8 h the serum level of tropisetron becomes subtherapeutic. Tropisetron is purported to have a serum half-life of 7.2 h [26], and in some studies, better emetic control has been achieved by using a multidose regimen or a continuous infusion of ondansetron, another 5-HT_3 antagonist [12, 27]. The possibility that a 5-HT_3 antagonist is efficacious for only a few hours after cisplatin infusion cannot be completely ruled out.

Carryover and period effects, or the decline in the efficacy of antiemetic regimens over time, have not been demonstrated in some studies [12, 27]. We observed these effects in patients who received metoclopramide during their first course of chemotherapy but did not see them in those who received tropisetron during their first course when we compared the first and third courses of therapy. These findings were consistent with the results of a large-scale study consisting of 287 patients randomized to receive ondansetron or metoclopramide, dexamethasone, and diphenhydramine as an antiemetic regimen for cisplatin-induced acute emesis [28]. In that study, a significant reduction in the efficacy of vomiting prevention was detected when the first to the third cycles of metoclopramide courses, but not those of ondansetron courses, were compared. In our study, we noted that following the initial use of the metoclopramide cocktail the efficacy of antiemetics given during subsequent courses of chemotherapy treatment decreased, whereas when tropisetron was used first, no such decrease occurred.

In the control of delayed emesis, oral metoclopramide and lorazepam were more effective than oral tropisetron in each of the 4 h periods as well as over the 24 h duration of the worst day, but no significant difference was found in the control of delayed nausea. One study comparing the efficacy of ondansetron with high-dose metoclopramide noted no difference in the prevention of delayed vomiting, but nausea was better controlled with metoclopramide [12]. A single dose of oral tropisetron afforded no additional benefit in the management of delayed nausea and vomiting. This might suggest that delayed emesis is mediated by 5-HT_3-independent mechanisms and is poorly responsive to 5-HT_3 antagonists; however, investigation of the effectiveness of absorption of tropisetron and other 5-HT_3 antagonists by the gastrointestinal tract in patients receiving chemotherapy is also mandatory to ensure that serum concentrations are reaching therapeutic levels.

In conclusion, tropisetron given as a 5-mg single loading dose by intravenous infusion, was significantly more effective than the metoclopramide cocktail in preventing vomiting in the first 8 h following cisplatin infusion as well as in the control of acute nausea. In the management of delayed nausea and vomiting the results of both regimens were unsatisfactory, although metoclopramide and lorazepam were better at controlling delayed emesis. When used during the initial chemotherapy course, the metoclopramide cocktail tends to reduce the efficacy of antiemetics given during the following courses. The observed side effects of tropisetron were minimal and acceptable, and patients preferred tropisetron. These findings verify the value of tropisetron in the prevention of chemotherapy-induced nausea and vomiting. Investigations to determine the value of additional doses of tropisetron or of combining tropisetron with other antiemetics are necessary for further improvement of our treatment regimens.

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