

A Randomized, Multicenter Study Comparing the Efficacy and Tolerability of Tropisetron, a New 5-HT₃ Receptor Antagonist, with a Metoclopramide-Containing Antiemetic Cocktail in the Prevention of Cisplatin-Induced Emesis

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Background. Chemotherapy-induced emesis is one of the most disturbing side effects in cancer therapy. Thus, antiemetic treatment is a mandatory adjunct in emetogenic chemotherapy.

Methods. Tropisetron (Navoban, Sandoz Pharma Ltd., Basel, Switzerland), a new 5-HT₃ receptor antagonist, was compared in a randomized multicenter trial with a high-dose metoclopramide-dexamethasone cocktail for the prevention of nausea and emesis during cisplatin-containing chemotherapy. Two hundred fifty-nine chemotherapy-naïve patients were included and followed during two consecutive courses. The main cancer types were gynecologic tumors, followed by lung cancer, head and neck cancer, and bladder cancer. The cisplatin dose usually was in the range of 50–89 mg/m². The efficacy and quality of life assessments and the safety record-

ings were done during the first 6 days of both courses of chemotherapy.

Results. Acute vomiting was prevented in 63–64% of patients by both antiemetic regimens. The total rate of control of vomiting increased from 63% on day 1 to 93% on day 6 in the group receiving tropisetron. Acute nausea was prevented in 40% of the patients with tropisetron monotherapy and in 61% of patients receiving the antiemetic cocktail. With regard to delayed nausea, there were no significant differences between the two antiemetic regimens. Mild headache and constipation were more frequently associated with tropisetron, and extrapyramidal side effects and sedation were associated with the antiemetic cocktail.

Conclusions. Tropisetron was easier to administer and better tolerated than the cocktail, and it seems to be a highly efficacious and safe new antiemetic drug. *Cancer* 1994; 73:445–54.

Key words: antiemetics, emesis, chemotherapy, tropisetron, 5-HT₃ receptor antagonists, metoclopramide cocktails.

Nausea and emesis are symptoms frequently associated with cancer chemotherapy. These adverse events generally belong to the category of less well-tolerated side effects,¹ and for some patients, the problems presented may prejudice the completion of effective treatment. The problem of nausea and vomiting is not new, but the increased use of cisplatin, alone or in combinations, has focused interest on antiemetics during the past decade.

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All patients vomit after the administration of high doses of cisplatin unless antiemetic drugs are given.² None of the previously used antiemetic regimens is entirely effective. High-dose metoclopramide, alone or in combination with a steroid and an anxiolytic agent, has been found to be most promising regimen. However, 40% of the patients still experience emesis.³⁻⁵ Approximately 20% of patients treated with metoclopramide have disturbing extrapyramidal reactions.⁶ The extrapyramidal reactions and the sedation associated with metoclopramide are caused by the agent's dopamine antagonistic activity,^{2,7} whereas the antiemetic activity of the drug probably is associated with its blocking effect on the 5-HT₃ receptors.⁸⁻¹⁰

During the last few years highly selective antagonists of these serotonin receptors have been synthesized.^{11,12} 5-HT₃ binding sites are present in the peripheral (the vagus nerve and splanchnic afferent neurons) and central nervous systems. In human brain tissue the highest densities of binding sites are found in the area postrema and the nuclei of the solitary tract in the brain stem.¹³ The mechanism of action of 5-HT₃ receptor antagonists in preventing nausea and vomiting induced by cancer chemotherapy probably involves antagonism of the actions of serotonin at both of these sites,¹⁴ but the exact mechanisms of action are not fully understood. Direct chemical stimulation of the chemoreceptor trigger zone leads to triggering of the vomiting center. It also is possible that chemotherapeutic agents cause cellular damage to the intestinal mucosa, eliciting the release of serotonin from enterochromaffin cells in the proximal gut. Serotonin probably activates vagal and splanchnic afferent neurons, thus initiating the vomiting reflex.¹⁴

Tropisetron (Navoban, Sandoz Pharma Ltd., Basel, Switzerland), a selective 5-HT₃ receptor antagonist, has shown promising antiemetic properties in pilot studies.¹⁵ To evaluate this drug in the prevention of cisplatin-induced nausea and vomiting, an open, randomized, multicenter study was conducted, and a comparison was made with a metoclopramide-containing antiemetic cocktail.¹⁶ This antiemetic cocktail had been used routinely at one of the participating centers (Linköping). The aim was to make the comparison with the best treatment available.¹⁷ Metoclopramide alone is not an optimal antiemetic treatment⁴⁻⁶ and thus was not used in the comparison with the new 5-HT₃ receptor antagonist.

Patients and Methods

Study Design

A randomized, multicenter study with two parallel groups was conducted at nine trial centers to compare

Table 1. Cytostatic Agents Given on Days 2-6

	Tropisetron	Antiemetic cocktail
Etoposide (days 3-6)	13	19
5-fluorouracil (days 1-5)	12	15
Methotrexate (day 2)	7	6
Doxorubicin (day 2)	0	1
Total	32	41

the clinical efficacy and safety of tropisetron, a single agent antiemetic, with a commonly used metoclopramide-containing antiemetic cocktail for the prevention of cisplatin-induced nausea and vomiting. The study was conducted in an open fashion for logistic reasons. It was approved by the Ethics Committees of the hospitals involved and the National Health Boards, as applicable. Informed consent of all patients was obtained.

Patient Selection

Patients with a histologically or cytologically confirmed malignant tumor who were receiving chemotherapy for the first time were included in the study. All patients received at least 50 mg/m² of cisplatin, administered intravenously during a maximum of 3 hours on the first day of chemotherapy. Two hours was the most commonly used infusion time. Administration of other cytostatic agents (etoposide, 5-fluorouracil, methotrexate, and doxorubicin) was allowed on days 1-6 of each course of chemotherapy (Table 1). There were no significant differences in the distribution of additional emetogenic agents, besides cisplatin, in the two treatment groups. Patients were scheduled to be evaluated during two identical courses of chemotherapy. Patients experiencing nausea or vomiting before the start of chemotherapy were not included. Treatment of nausea and vomiting with other drugs than the study medication was not allowed, except when patients vomited more than four times within the 24 hours after the start of chemotherapy or experienced severe nausea for more than 12 hours (treatment failure). Small doses of benzodiazepines given as required as sleeping medication were permitted.

Study Population

The study population consisted of 259 chemotherapy-naïve patients scheduled to receive at least two courses of a cisplatin-containing chemotherapy regimen. The patients, consisting of men (21%) and women (79%) with various cancer diagnoses, were recruited consecutively at nine different cancer clinics in Sweden, Fin-

Table 2. Characteristics of the Treatment Groups

	Tropisetron (%)	Antiemetic cocktail (%)
No. of patients	131	128
Females	104 (79)	102 (80)
Males	28 (21)	26 (20)
Mean age (yr)	61	62
Mean weight (kg)	66.7	66.0
Mean height (cm)	166	166
Coexistent diseases	45 (34)	53 (41)
Prior medication*	88 (67)	92 (72)
Concomitant medication	94 (74)	90 (75)
Gynecologic cancer	98 (74)	94 (73)
Urologic cancer	11 (8)	3 (2)
Lung cancer	12 (9)	12 (9)
Head & neck cancer	4 (3)	7 (6)
Other cancer	7 (5)	12 (9)

* All kinds of medication used before the start of chemotherapy.

land, Denmark, and Belgium. The period of recruitment was from November 1, 1988, to September 15, 1989. Of the enrolled patients, 132 were allocated to the tropisetron treatment group and 128 to the antiemetic cocktail group. The ages of the patients ranged from 25 to 81 years, with a mean of 61 years. There were no statistically significant differences between the treatment groups with respect to sex, age, weight, or height. Because a reliable history of alcohol intake is difficult to obtain from our patients, that information was not included in this study. Other characteristics of the treatment groups are given in Table 2.

Antiemetic Treatments

Tropisetron. On day 1, 5 mg tropisetron in 100 ml normal saline was administered intravenously during a 15-minute period at the end of the prehydration period, i.e., immediately before the start of the cisplatin infusion. On days 2–6, each patient received a 5-mg tropisetron capsule in the morning immediately after awakening. The 5-mg dose was chosen based on dose-finding studies performed with tropisetron using a wide dose range (range, 5–100 mg/day). These studies showed no therapeutic benefit of doses greater than 5 mg/day but larger doses seemed to be associated with higher rates of side effects. The hypothesis is that 5 mg of tropisetron is enough for blockage of the 5-HT₃ receptors for at least 24 hours. Eating and drinking were not allowed during the 2 hours after drug administration to avoid provoking nausea and vomiting before the effect of tropisetron was fully established.

Antiemetic cocktail. On day 1, 3 mg/kg metoclopramide in 100 ml normal saline was administered intravenously during a 15-minute period at the end of the prehydration period, i.e., immediately before the start of the cisplatin infusion, and again 3 hours later. Twenty milligrams of dexamethasone was given intravenously with the first infusion of metoclopramide and 1 mg of lorazepam was given by mouth with the first or both infusions. On days 2–6, the patients received 10 mg metoclopramide orally or 20 mg metoclopramide as suppositories three times a day.

Efficacy Assessment

Nausea and vomiting were recorded by a research nurse on a "nursing chart" on the case report form during the patient's hospital stay and by the patient on a diary card when the patient was at home. All patients were admitted to the hospital for at least 24 hours (during the acute emetic phase), and the recordings made by the research nurse were always completed before the patient left the hospital. Records were kept for the 6 consecutive days after the cisplatin infusion in each course. Vomiting and retching were recorded as the number of separate events. Presence of nausea was recorded every hour within a 24-hour period. Every clocked hour with nausea was counted as one episode, regardless of the duration or the intensity of the nausea.

Endpoints of Efficacy

Total control of vomiting was defined as no events of vomiting or retching within a 24-hour period. Major control was defined as one to two events of vomiting or retching. Minor control was defined as three to four events of vomiting or retching. Five or more events within a 24-hour period was defined as no control of vomiting (failure). Total control of nausea was defined as no episodes of nausea, major control as one to two episodes of nausea, and minor control as three to four episodes of nausea within a 24-hour period. No control of nausea (failure) signified five or more episodes within a 24-hour period. The first 24 hours after the start of chemotherapy was defined as day 1. Day 2 was defined as the 24-hour period starting at 7.00 a.m. on the day after treatment with cisplatin. Consequently, there often was an overlap between the end of day 1 and the start of day 2. Any events of vomiting and episodes of nausea occurring during this period were counted twice; once for day 1 and once for day 2. Days 3–6 were defined as consecutive 24-hour periods starting at 7.00 a.m. Vomiting and nausea occurring within the first 24 hours after cisplatin infusion was termed

"acute." When vomiting and nausea started after that period, it was termed "delayed."

Quality of Life Assessment

Efficacy, adverse effects, and the overall quality of life were assessed in a short questionnaire that all patients completed the day before each course of treatment and on day 7 after the treatments. The questionnaire consisted of two parts. The first part had 18 questions about various symptoms. The patient stated whether the symptom had been "not at all," "a little bit," "quite a bit," or "very much" present.

The second part of the questionnaire contained five questions. The patients were asked to state whether they had been eating and drinking normally, whether they could look forward to things, enjoy books, radio, or television programs, or laugh and see the funny side of things. The ratings were "not as much as normal," "normal," or "more than normal for me." In addition, the patients also were asked to rate their overall quality of life as "poor," "acceptable," "normal," or "good."

Safety Assessment

Against the background of the symptoms of the underlying cancer disease and the side effects originating from the cisplatin-containing chemotherapy, it was difficult to identify the adverse events associated with the antiemetics. Thus, and to be able to compare the two antiemetic regimens, safety information from all available sources was considered, i.e., conventionally reported adverse events, unusual symptoms reported by the patient on the diary cards, quality of life assessments, electrocardiogram results, data on vital signs, and laboratory values.

All adverse events were classified as severe or non-severe (a combination of adverse events graded as mild or moderate). A 12-lead electrocardiogram was recorded before and after each course. Electrocardiogram changes between baseline and the end of the chemotherapy courses were assessed and, when necessary, comments were made regarding the changes. Vital signs data were recorded at screening before the start of treatment and at 8-hour intervals while the patient was in the hospital. A systolic blood pressure greater than 170 mm Hg, a diastolic blood pressure greater than 100 mm Hg, a body temperature greater than 38.0°C, or a radial pulse greater than 120 beats per minute was classified as abnormal. For each patient the most abnormal value (if any) was selected from all of the readings taken during a course. Laboratory data were recorded at screening and at the end of each chemotherapy course to identify clinically relevant influences of the anti-

emetic treatments on hematologic and biochemical parameters. Values outside clinically relevant ranges were classified as abnormal (hemoglobin, less than 6.2 mmol/l; leukocyte count, less than 2.8×10^9 /l; thrombocytes, less than 75×10^9 /l; sodium, less than 125 mmol/l; potassium, less than 3.0 mmol/l; creatinine, greater than 176.8 μ mol/l; aspartate transaminase, alanine transaminase, and alkaline phosphatase greater than two times the upper normal limit, and α -amylase greater than three times the upper normal limit). For vital signs and laboratory values, an abnormality was classified as newly occurring if all previous values were normal.

Statistical Methods

All statistical tests for the comparison of treatment groups are presented with two-sided *P* values.

Between-treatment group comparisons were made using the Mantel-Haenszel test¹⁸ for sex and the van Elteren test¹⁹ for age, height, and weight, adjusting for trial center.

Comparisons between treatments for control of nausea and vomiting were made using the Mantel-Haenszel test¹⁸ and Fisher's exact test,²⁰ when necessary. Ninety-five percent confidence intervals (95% CI) for the average responses were derived for each treatment group using a normal approximation to the binomial distribution.²¹ Because patients who vomited five or more times or who had 12 hours of continuous nausea within 24 hours of the start of chemotherapy (treatment failures) were withdrawn from the study, there was a positive selection bias on the following days in course 1 and possibly in course 2. Thus, statistical analyses were performed for course 1 on day 1 data only, and data for the following days and for course 2 were only summarized. The total control of vomiting on days 1-6 of both chemotherapy courses also was summarized. For the quality of life assessments, the van Elteren test was used to detect a difference between treatments, adjusting for trial center.

Results

Control of Vomiting and Nausea on Day 1, Both Courses

Total control of vomiting was achieved in 63% of the patients in the tropisetron group and in 64% of the patients in the antiemetic cocktail group during the first 24 hours after the start of the cisplatin infusion in course 1. The percentages of major and minor control rates and treatment failure also were similar for the two regimens. During the same period of time in course 2, the

Table 3. Frequency of Patients With Total, Major, Minor, or No Control of Vomiting (Treatment Failure) in the First 24 Hours of Courses 1 and 2 of Chemotherapy

	Tropisetron (%)	Antiemetic cocktail (%)
Course 1		
No. of patients	131	128
Control of vomiting		
Total	83 (63)	82 (64)
Major	24 (18)	18 (14)
Minor	7 (6)	11 (9)
Treatment failure	17 (13)	17 (13)
95% CI*		
Total	(54, 71)	(55, 72)
Total or major	(74, 88)	(70, 85)
Course 2		
No. of patients	120	112
Control of vomiting		
Total	56 (47)	53 (47)
Major	32 (27)	26 (23)
Minor	7 (6)	15 (13)
Treatment failure	25 (21)	18 (16)
95% CI*		
Total	(38, 56)	(38, 57)
Total or major	(64, 81)	(61, 79)

CI: confidence interval.

* Confidence intervals for the proportion of patients with total or major control are based on a normal approximation to the binomial distribution.

percentage of total control of vomiting was slightly lower (47%), but the percentages were similar in both treatment groups (Table 3). The total control of vomiting varied between 33% and 100% in the tropisetron group and between 29% and 100% in the cocktail group when analyzed by trial center. However, except for one center, the results of the two treatment groups were similar at all centers, thus excluding a selection bias in favor of one of the two antiemetic treatments.

Nausea was prevented completely in 40% in the tropisetron group and in 61% in the metoclopramide-cocktail group during the first 24 hours of course 1. This difference was statistically significant ($P < 0.001$). The combined rate of total and major control also was greater in the antiemetic cocktail group: 77% compared with 68% in the tropisetron treatment group ($P = 0.097$) (Table 4). The rate of total or partial control (major plus minor) of nausea varied from 50% to 100% for the tropisetron group and from 56% to 100% for the metoclopramide cocktail group between the trial centers.

Control of Vomiting and Nausea on Days 1–6, Both Courses

The total rate of control of vomiting increased from 63% on day 1 to 93% on day 6 in the tropisetron group

Table 4. Frequency of Patients with Total, Major, Minor, or No Control (Treatment Failure) of Nausea in the First 24 Hours of Courses 1 and 2 of Chemotherapy

	Tropisetron (%)	Antiemetic cocktail (%)	P value
Course 1			
No. of patients	131	128	
Control of nausea			
Total	53 (40)	78 (61)	
Major	37 (28)	21 (16)	
Minor	10 (8)	17 (13)	
Treatment failure	31 (24)	12 (9)	
95% CI*			
Total	(32, 49)	(52, 69)	0.001
Total or major	(60, 76)	(69, 84)	0.097
Course 2			
No. of patients	120	112	
Control of nausea			
Total	41 (34)	53 (47)	
Major	19 (16)	19 (17)	
Minor	20 (17)	14 (13)	
Treatment failure	40 (33)	26 (23)	
95% CI*			
Total	(26, 43)	(38, 57)	
Total or partial	(41, 59)	(55, 73)	

CI: confidence interval.

* Confidence intervals for the proportion of patients with total or major control are based on a normal approximation to the binomial distribution.

and from 64% to 89% in the antiemetic cocktail group (Fig. 1). Forty-nine of the 131 (37%) patients in the tropisetron treatment group had total control of vomiting during all 6 days of course 1, compared with 56 of the 128 (44%) patients in the cocktail treatment group. The proportion of patients with either total or partial control (major plus minor control) was similar in both treatment groups on all days. During course 2, the rate of

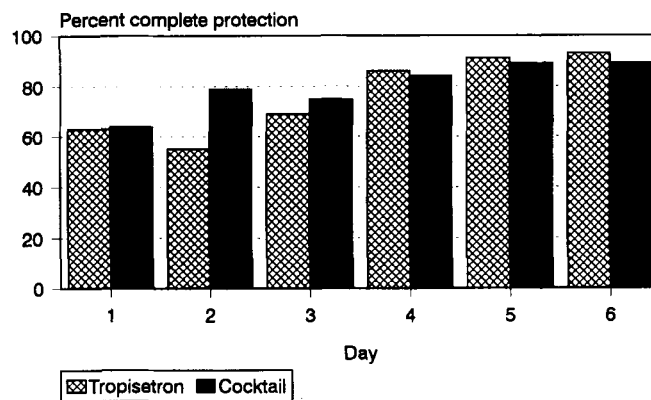


Figure 1. The frequency of complete control of vomiting during course 1, days 1–6. There was no statistically significant difference in the efficacy of the two antiemetic treatments.

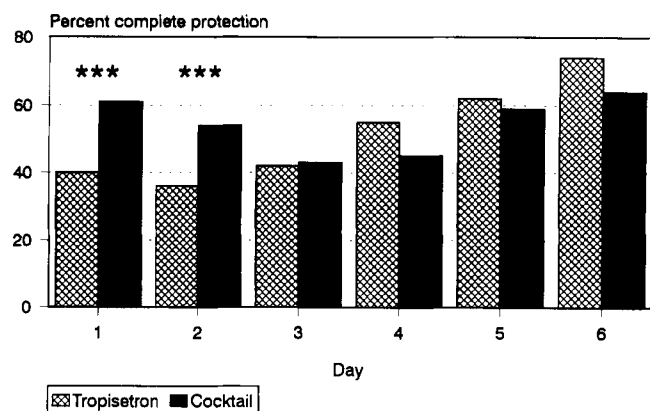


Figure 2. The frequency of complete control of nausea during course 1, days 1–6. The metoclopramide antiemetic cocktail was significantly (***) ($P < 0.001$) more efficacious during days 1 and 2. During days 3–6 the efficacy of the two regimens was similar.

complete protection from vomiting varied from 47% on day 1 to 94% on day 6 in the tropisetron group and from 47% to 92% in the metoclopramide cocktail group.

The proportion of patients with total control of nausea was larger in the antiemetic cocktail treatment group on days 1 and 2, but the results of the two treatments were similar on days 3–6 (Fig. 2). With the exception of day 1, the proportion of patients with total or partial control (major plus minor control) of nausea was similar in both treatment groups. Twenty-eight of the 131 (21%) patients in the tropisetron group had total control of nausea for the entire period (days 1–6), compared with 31 of the 128 (24%) patients in the antiemetic cocktail treatment group. There was no statistically significant difference between treatment groups with respect to total control of nausea for days 1–6. A similar pattern, with respect to control of nausea, was recorded in course 2 with no significant differences between the two antiemetic regimens.

If days 1–6 of both chemotherapy courses are combined, complete control of vomiting was achieved in 23% of patients by tropisetron and in 22% by the metoclopramide cocktail.

The influence of different types of cancer on the efficacy of the antiemetic treatments was not analyzed because the gynecologic cancer types were so predominant in this study.

Adverse Effects

In general, the two antiemetic regimens were well tolerated. Most of the reported adverse events were related to the malignant disease or to the chemotherapy. Ad-

verse events occurring with a frequency of more than 5% or recorded as severe are given in Table 5.

Serious Adverse Events

In the tropisetron group, two serious adverse reactions with uncertain causation were reported in two patients. One had a transient paresis of the right arm and the other a transient weakness of the left arm. Both patients had gynecologic cancer and were receiving treatment at the same center. The investigator considered a relationship with tropisetron unlikely, and treatment was continued in both patients. The symptoms did not recur. No serious adverse events were reported in the antiemetic cocktail group. Seven patients in each treatment arm died during the study period, but none of the deaths were associated with the antiemetic treatments.

Severe, Nonserious Adverse Events

Tropisetron. The following adverse events were reported for more than one patient: constipation (5 patients), asthenia (5), fever (3), sepsis (2), dysphagia (2), and dyspnea (2). The following events were reported in only one patient: urticaria, dizziness, paresis, headache, confusion, diarrhea, abdominal pain, hiccup, dehydration, thirst, cardiac failure, chest pain, hemoptysis, pleural effusion, pulmonary edema, pulmonary embolism, thrombocytopenia, pyelonephritis, renal failure, ascitic fluid, and fungal infection.

Table 5. Number of Patients Suffering Adverse Events. When an Adverse Event Recurred in the Same Patient in More Than One Treatment Course, Only One Entry Was Made

Side effect	Tropisetron (N = 131)		Antiemetic cocktail (N = 128)	
	All N (%)	Severe N (%)	All N (%)	Severe N (%)
Urticaria	1 (0.8)	1 (0.8)	—	—
Dizziness	16 (12.1)	1 (0.8)	8 (6.3)	—
Dystonia	—	—	2 (1.6)	2 (1.6)
Headache	55 (41.7)	1 (0.8)	28 (21.9)	—
Oculogyric crisis	—	—	1 (0.8)	1 (0.8)
Paresis	2 (1.6)	2 (1.6)	—	—
Tremor	—	—	11 (8.6)	—
Agitation	—	—	5 (3.9)	2 (1.6)
Anxiety	3 (2.8)	—	5 (3.9)	1 (0.8)
Somnolence	1 (0.8)	—	6 (4.7)	1 (0.8)
Asthenia	32 (24.2)	5 (3.8)	48 (37.5)	10 (7.8)
Constipation	32 (24.2)	5 (3.8)	8 (6.3)	1 (0.8)
Diarrhea	19 (14.4)	1 (0.8)	32 (25.0)	1 (0.8)
Abdominal pain	11 (8.3)	1 (0.8)	9 (7.0)	2 (1.6)

Antiemetic cocktail. Asthenia was reported in 10 patients. Dystonia, agitation, abdominal pain, stomatitis, acute renal failure, and fever were reported in two patients each. The following events were reported in only one patient: oculogyric crisis, anxiety, somnolence, constipation, diarrhea, ileus, chest pain, dyspnea, pneumonia, respiratory insufficiency, arterial thrombosis in the leg, pain, sepsis, fungal infection, and abscess.

Comparisons Between the Two Treatment Arms

The frequency distribution of the adverse events confirmed that headache, dizziness, and constipation were side effects of tropisetron. For the antiemetic cocktail, diarrhea and fatigue were noted most often. Side effects related to the extrapyramidal system or to akathisia were reported for the antiemetic cocktail as follows: dystonia (severe in 2 patients), dysphonia (1 patient), hyperkinesia (3), muscular stiffness (3), trembling (11), leg cramps (1), agitation (5 patients, severe in two), anxiety (5 patients, severe in 1), nervousness (5). The cumulative frequency was 31%, although several of these symptoms occurred in the same patient. Five percent of these symptoms were reported as severe. Three patients in the antiemetic cocktail treatment arm discontinued the medication because of the extrapyramidal side effects. Extrapyramidal symptoms were reported with a cumulated frequency of 7% for tropisetron, with none of these symptoms being reported as severe. No evidence emerged that any of the regimens aggravated the risk of bone marrow toxicity or nephrotoxicity attributable to the chemotherapy.

Quality of Life

Before treatment, the two groups did not differ in the responses of the patients to any of the 23 questions asked, and there were no differences between the assessments made before the two treatment courses. In posttreatment evaluations in both treatment groups, the patients reported more nausea, vomiting, being ill, being tired or sleepy, and having more problems with eating than was reported in the pretreatment evaluation (Table 6). Patients assigned randomly to the tropisetron regimen experienced more constipation and headache than did those assigned to the metoclopramide cocktail regimen.

Discussion

Tropisetron, used as a single drug and administered once a day (5 mg), was as effective as a combination of high-dose metoclopramide, dexamethasone, and lorazepam in preventing acute and delayed emesis induced by cisplatin chemotherapy. With both regimens, complete control of vomiting on the first day of chemotherapy was achieved in slightly more than 60% of the pa-

tients. Failure of each of the treatments was recorded in 13% of the patients. In a double-blind, randomized study, Marty et al.²² achieved complete control of cisplatin-induced vomiting in 46% of patients receiving ondansetron, another 5-HT₃ receptor antagonist. Regarding the prevention of nausea, there was a difference in favor of the metoclopramide cocktail on days 1 and 2, but not on the following days of the follow-up period. This might be an effect of the steroid given in the antiemetic cocktail on day 1. Tropisetron prevented nausea completely in 40% of patients during the first 24 hours of course 1, and this can be compared with the 38% for ondansetron reported by Marty et al.²² When the entire treatment period (days 1–6 for courses 1 and 2) was analyzed, no significant differences were noted between the two regimens.

The comparative treatment, a metoclopramide-containing antiemetic cocktail, showed surprisingly good efficacy compared with that of similar antiemetic cocktails reported earlier,^{4,5} although Kris et al.^{16,17} report similarly high control rates. It cannot be ruled out that the anxiolytic component (lorazepam) of the cocktail was beneficial in the control of the rather subjective experience of nausea, whereas the more objective signs of vomiting and retching were not influenced to the same extent. The amnesia effect induced by lorazepam also may influence the recording of nausea. In this study, nausea was less well controlled than was vomiting in both antiemetic treatment arms. One reason for this difference might be the strict criteria (clock-hour episodes) used for measuring nausea. Intensity and duration did not matter. Five minutes of nausea sufficed to rule out classification as total control. This aspect of the study makes a direct comparison of the current results with those of other studies difficult.

A large variation between the nine centers in this study was seen regarding the prevention of vomiting and nausea, with a range of 30–100% for complete control. Differences between the treatment populations regarding sex, age, cancer diagnoses, stage distributions, chemotherapy regimens, and types of treatment (curative, palliative, adjuvant, neoadjuvant) may explain this variation. The number of patients recruited by some of the centers also was small (range, 14–66 patients).

Both antiemetic regimens were well tolerated. For tropisetron, headache, dizziness, and constipation were statistically confirmed side effects. None of these were recorded as severe. None of the patients receiving tropisetron discontinued the treatment because of side effects. As expected, extrapyramidal reactions and symptoms related to akathisia dominated in the antiemetic cocktail group. Three patients in the antiemetic cocktail treatment arm discontinued treatment because of extra-

Table 6. Quality of Life Assessments Before and After Course 1 of Chemotherapy

Question	Tropisetron			Antiemetic cocktail			P value
	Pretreat	Posttreat	Mean diff *	Pretreat	Posttreat	Mean diff *	
Nauseated	0.12	0.99	-0.88	0.22	1.06	-0.84	0.589
Vomited	0.06	0.85	-0.79	0.11	0.91	-0.80	0.803
Constipated	0.41	0.94	-0.52	0.45	0.45	0.00	< 0.001
Headache	0.23	0.62	-0.39	0.35	0.41	-0.07	0.002
Feeling ill	0.31	0.80	-0.50	0.31	0.89	-0.57	0.346
Tired/sleepy	0.70	1.48	-0.78	0.73	1.31	-0.59	0.178
Trembling	0.19	0.17	0.02	0.10	0.23	-0.12	0.081
Normal eating	1.14	1.64	-0.50	1.24	1.59	-0.35	0.098
Overall rate	1.59	1.35	0.24	1.48	1.33	0.15	0.484

diff: difference.

Mean value of a score, range 0-3, 3 denoting the worst of these categories. For the overall rating, 3 denotes the best quality of life (good).

* The difference was calculated as the pretreatment score minus the posttreatment score, hence a positive difference denotes an improvement in the quality of life. The mean values of these differences were then calculated.

pyramidal side effects. No evidence emerged that any of the antiemetic regimens aggravated the risk of bone marrow toxicity or nephrotoxicity resulting from aggressive cisplatin chemotherapy. Thus, it seems that the spectrum of side effects favors tropisetron.

The various 5-HT₃ receptor antagonists on the market differ in chemical structure, potency, receptor specificity, and the pharmacokinetic profile (dose response, duration of action, half-life).²³ Ondansetron shows more differences than do tropisetron and granisetron. The clinical relevance of these differences remains to be defined. The dosing schedules vary, and tropisetron appears to be the simplest drug to use, with a once-daily regimen of 5 mg IV on day 1 and orally on days 2 to 6.

The quality of life assessments confirmed that the patients experienced nausea and vomiting during treatment to a greater extent than before, that there were no differences between the two treatment groups, and that the patients receiving tropisetron reported headache and constipation more often. The quality of life instrument was rather crude, and it gave only an overall evaluation of the efficacy parameters.

The methodology of this study was characterized by the patients' participation in the recording of the efficacy and safety data. Both vomiting and nausea were used as endpoints for efficacy. A crossover study design was not chosen because the progression of disease, the experience of previous treatment failure, and other factors would have made the results difficult to interpret. A placebo-controlled design was considered unethical for such a debilitating side effect as cisplatin-induced emesis. Clinical trials involving antiemetic agents ideally should be double-blind, but this approach was not chosen for this study for the following reasons: (1) a cocktail containing high-dose metoclo-

pramide was used as the comparative treatment, a regimen that has well recognized side effects that easily could have identified this treatment arm; and (2) the comparative treatment schedule was considerably more complicated than that for tropisetron, and this would have presented significant logistical problems to match.

The number of adverse events reported by the patients in their diaries nearly equaled those reported by the investigators in both treatment arms. Thus, the incidence of adverse events in this study may be higher than that reported in other studies. As a corollary, the patients' self-reporting of efficacy has made possible a more realistic reflection of the patients' perspective than has been the case previously.²⁴ This was especially true of nausea, a condition for which the most reliable information comes from the patients. In contrast, events of vomiting can be observed and can be recorded without the patient's involvement.

High-dose metoclopramide, dexamethasone, and lorazepam have been shown to be moderately effective antiemetics when given as monotherapy.²⁵ A synergistic or at least additive action between these three components given together as an antiemetic cocktail has been demonstrated in numerous clinical trials.^{4-6,16,17} In this study the antiemetic cocktail and tropisetron were similarly effective in the control of vomiting. In the antiemetic cocktail treatment arm, peroral low-dose metoclopramide (10 mg three times a day) was used to prevent delayed vomiting and nausea (days 2-6). A remaining effect of the corticosteroid and perhaps of lorazepam (given on day 1) may influence the recorded treatment efficacy on day 2. Nausea also was less well controlled on days 1 and 2 in the tropisetron group than in the antiemetic cocktail group. It has been suggested that the antiemetic efficacy of high-dose metoclopra-

side stems from weak antagonism of 5-HT₃ receptors and that the antidopaminergic actions play a minor role.^{9,10} The efficacies of the tropisetron and the antiemetic cocktail treatments against vomiting were similar, which suggests that the dexamethasone or lorazepam (anxiolytic) component of the antiemetic cocktail also might enhance the antinausea activity of tropisetron. Thus, a combination of tropisetron and dexamethasone could be evaluated in future studies to determine if it improves overall (acute and delayed) antiemetic activity. The role of the 5-HT₃ receptor antagonists in prevention of delayed nausea and vomiting is under debate, and additional studies are needed to elucidate this topic. Dexamethasone seems to be an important agent in this context.^{26,27}

Documentation of the entire chemotherapy courses allowed the reflection of day-to-day clinical practice and did not overemphasize the hospital period while neglecting what happened to the patient at home. In our opinion, recordings of nausea, even though more subjective, are as important as the recording of vomiting, and both of these parameters should be considered to enhance the clinical relevance of the results.

The restriction of the study to only two consecutive courses could be interpreted as a disadvantage because clinical practice shows that patients usually are treated for more than two courses. The prospective investigation of at least two, but preferably more, consecutive courses could be recommended for future studies.

In conclusion, tropisetron is an effective antiemetic agent that can be used as monotherapy in the dose schedule used in this trial, a combination of intravenous and oral therapy. Tropisetron can be used without special precautions in all patients who are treated with aggressive chemotherapeutic agents such as medium- and high-dose cisplatin. The efficacy and safety data of this study show that tropisetron represents a single agent and a once-daily alternative to current antiemetic cocktail treatments for emesis induced by anti-cancer chemotherapy.

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