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An open, randomized study to compare the efficacy and tolerability of tropisetron with that of a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced emesis

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Abstract. In a prospective randomized study comprising 66 women treated for gynecologic malignancies with cisplatin-containing chemotherapy, the new 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist tropisetron (Navoban, Sandoz Pharma Ltd.) was compared with a metoclopramide cocktail for the prevention of nausea and emesis. All patients were chemotherapy-naive. Two consecutive courses (including the 1st week posttherapy) were studied. The cisplatin doses were in the range of 50–75 mg/m^2, and the regimens also contained doxorubicin, teniposide, etoposide, vincristine, and bleomycin. Complete protection against nausea during the first 24 h (course 1) was achieved in 76% of the tropisetron group and in 85% of the metoclopramide group. Emesis was prevented in 82% of the patients in both groups. During the whole 6-day period, full emetic protection was achieved in 30% and 18% of the patients in the two groups. On days 3–4 of course 1, tropisetron was superior to metoclopramide. The overall tolerability of the tropisetron was excellent or good in 94% of patients, a rate higher than that observed for the metoclopramide regimen (75%). The most common side effects for the latter regimen were sedation (82%) and extrapyramidal reactions (21%). The only significant adverse event recorded after treatment with tropisetron was headache of slight or moderate grade.

Introduction

During the past decade a growing number of antiemetic regimens to be used in conjunction with cancer chemotherapy have been presented. High-dose metoclopramide, corticosteroids, phenothiazines, and benzodiazepines alone or in various combinations are the most frequently used drugs to date [1, 7, 8, 15, 18]. For non-cisplatin-containing chemotherapy the results have been promising, but for high-dose cisplatin regimens the therapeutic efficacy of most antiemetic combinations has been far from optimal [23]. Clinically significant side effects (extrapyramidal reactions and sedation) have also been reported [14, 23]. There has been a tendency toward even more complicated regimens, containing several drugs, given according to intriguing schedules. Despite these efforts the results have not improved substantially.

The introduction of the new 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists seems to have changed the prerequisites for significant improvement of the antiemetic treatment given during chemotherapy of malignant diseases [16, 19]. This group of drugs selectively blocks 5-HT$_3$ (serotonin type 3) receptors [3]. These receptors, which are believed to mediate chemotherapy-induced nausea, have been demonstrated in sympathetic and parasympathetic neurons and fibers, in sensory neurons in the enteric nervous system, and in the central nervous system (area postrema) [4]. Both peripheral and central sites of action are possible [13].

The aim of this study was to compare the clinical efficacy of one such serotonin receptor antagonist, tropisetron (Navoban, Sandoz Pharma Ltd.) with that of a commonly used metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced nausea and vomiting. The side-effect profiles of the two antiemetic regimens were also compared. A homogeneous group of women treated for gynecologic malignancies were studied.

Patients and methods

During the period from November 1, 1988, to September 15, 1989, 66 women undergoing chemotherapy were randomized to receive a new 5-HT$_3$ receptor antagonist, tropisetron (ICS 205-930, Navoban, Sandoz Ltd., Pharmaceutical Division, Basel, Switzerland), or a cocktail consisting of high-dose metoclopramide (Primperan, H. Lundbeck A/S, Copenhagen, Denmark), dexamethasone

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Table 1. Characteristics of the study patients

Variable	Patients (*n*)	
Patients undergoing randomization	66	
Median age (range)	64.5	(27 – 80) years
Median weight (range)	62	(43 – 103) kg
Median height (range)	161	(143 – 180) cm
Type of primary tumor:		
Ovarian carcinoma	44	(67%)
Endometrial carcinoma	6	(9%)
Cervical carcinoma	8	(12%)
Other gynecologic malignancy	8	(12%)
Type of chemotherapy:		
Cisplatin-doxorubicin	45	(68%)
Cisplatin-teniposide-vincristine	10	(15%)
Cisplatin-etoposide-bleomycin	9	(14%)
Cisplatin alone	2	(3%)

(Decadron, Merck Sharp & Dohme International, Rahway, N. J., USA), and lorazepam (Temesta, KabiVitrum AB, Stockholm, Sweden) as antiemetic therapy. Tropisetron (5 mg) was given as a 15-min i.v. infusion in 100 ml *N* saline at 30 min before the start of chemotherapy on day 1 and as a single p.o. dose (capsule) of 5 mg on days 2–6. The metoclopramide regimen consisted of a 3.0-mg/kg dose of metoclopramide given at 30 min before the start of chemotherapy and a second dose given 3 h later. On days 2–6, metoclopramide was given at 10 mg t.d.s. orally. Dexamethasone (20 mg) was given as an i.v. dose with the first dose of metoclopramide. Lorazepam was given as a 1-mg tablet with both doses of metoclopramide. Dexamethasone and lorazepam were not given during the follow-up period on days 2–6.

The patient series consisted of 66 consecutive women with gynecological malignancies (Table 1) treated at the Department of Gynecologic Oncology, Örebro Medical Center Hospital. This series was also part of a multicenter study involving 7 other centers and a total of 260 patients, the results of which will be presented elsewhere.

The chemotherapy regimens were of three types, all of which contained cisplatin (50–75 mg/m^2) and were given on a 1-day schedule (Table 2). The chemotherapy infusions were preceded by prehydration with 1000 ml *N* saline and 500 ml mannitol (150 mg/ml) for 1 h. Cisplatin (Platinol, Bristol-Myers Int., Group, N. Y., USA) was given as a 2-h infusion (1000 ml *N* saline). The other antineoplastic drugs included in the regimens were: doxorubicin (Adriamycin, Farmitalia Carlo Erba S.p.A., Milan, Italy), teniposide (Vumon, Bristol-Myers Int., Group, N. Y., USA), vincristine (Oncovin, Eli Lilly and Company, Indianapolis, Ind., USA), bleomycin (Bleomycin, H. Lundbeck A/S, Copenhagen, Denmark), and etoposide (Vepesid, Bristol-Myers Int., Group, N. Y., USA).

The patients were observed at the hospital for the first 24 h and at home during days 2–6. The efficacy, tolerability, and safety parameters were recorded by the investigator in collaboration with the patients on specially designed case-record forms. Pre- and posttreatment quality of life assessments were performed as a complement to the registration of the effect and side-effect parameters. Routine hematology and blood-chemistry profiles as well as ECGs before and after therapy were taken.

Table 2. Chemotherapy regimens used

Drugs	Doses	Interval
Cisplatin (Platinol)	75 mg/m^2	4 weeks
Cisplatin (Platinol)	50 mg/m^2	4 weeks
Doxorubicin (Adriamycin)	50 mg/m^2	4 weeks
Cisplatin (Platinol)	60 mg/m^2	3 weeks
Teniposide (Vumon)	100 mg/m^2	3 weeks
Vincristine (Oncovin)	1.5 mg	3 weeks
Cisplatin (Platinol)	60 mg/m^2	3 weeks
Etoposide (Vepesid)	100 mg/m^2	3 weeks
Bleomycin (Bleomycin)	25 mg	3 weeks

Table 3. Efficacy of the antiemetic regimens during the first 24 h of course 1

Effect	Antiemetic regimen	
	Tropisetron	Metoclopramide cocktail
Nausea:		
None	25 (76%)	28 (85%)
Slight	6 (18%)	3 (9%)
Moderate	1 (3%)	2 (6%)
Severe	1 (3%)	0
Vomiting:		
None	27 (82%)	27 (82%)
1–2 episodes	3 (9%)	5 (15%)
3–4 episodes	1 (3%)	1 (3%)
>4 episodes	2 (6%)	0

The study design was of an open, randomized type with parallel groups. All patients were chemotherapy-naive. The first two consecutive courses of chemotherapy (3–4 weeks apart) were studied. All patients included were available for analysis. In the statistical analysis the X^2 test and the Mann-Whitney *U*-test were used.

Results

In the complete series of patients, full nausea protection was achieved in 76% of the tropisetron group and in 85% of the metoclopramide group ($X^2 = 0.383$; $P = 0.536$) during the first 24 h of course 1. Vomiting was prevented in 82% of the patients in both groups. Major emetic protection (slight or moderate nausea and/or one or two episodes of vomiting) was achieved in 15% of the tropisetron group and in 12% of the metoclopramide group. Two treatment failures (severe nausea and/or more than four episodes of vomiting) were noted in the tropisetron group but none was observed in the metoclopramide group (Table 3). For patients who experienced any degree of nausea during the first 24 h the median number of vomiting episodes was 1.5 (range, 0–17) in the tropisetron group and 1.0 (range, 0–2) in the metoclopramide group (Mann-Whitney *U*-test, $P = 0.19$).

During days 2–6 the rate of full nausea protection decreased for both treatment arms, but significantly more

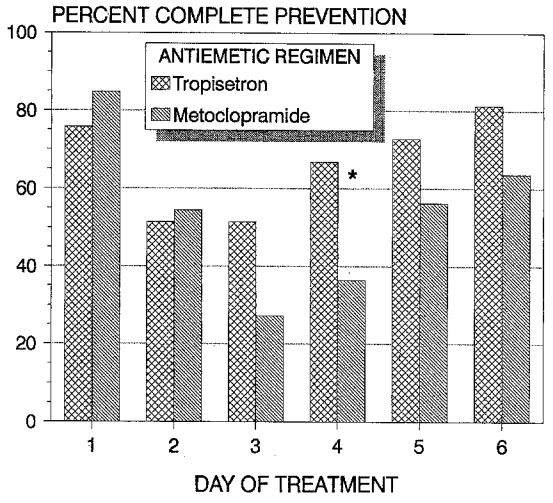

Fig. 1. Rate of complete protection from cisplatin-induced nausea during days 1–6 of the first course of chemotherapy. On day 4, tropisetron was significantly more effective than metoclopramide ($X^2 = 4.91$; * $P = 0.027$)

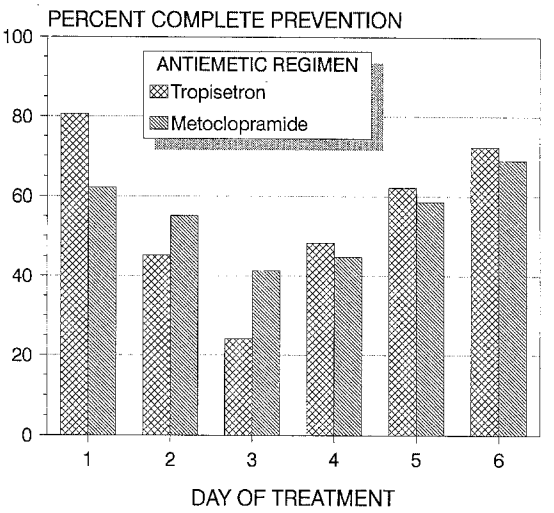

Fig. 2. The rate of complete protection from cisplatin-induced nausea during days 1–6 of the second course of chemotherapy. There was no significant difference between the two antiemetic regimens

Table 4. Efficacy of the antiemetic regimens during the first 24 h of course 2

Effect	Antiemetic regimen	
	Tropisetron	Metoclopramide cocktail
Nausea:		
None	25 (81%)	18 (62%)
Slight	1 (3%)	2 (7%)
Moderate	3 (10%)	8 (28%)
Severe	2 (6%)	1 (3%)
Vomiting:		
None	27 (87%)	16 (55%)
1–2 episodes	0	8 (28%)
3–4 episodes	1 (3%)	3 (10%)
>4 episodes	3 (10%)	2 (7%)

so in the metoclopramide group on days 3–4 ($X^2 = 4.914$; $P = 0.027$; Fig. 1). The number of vomiting episodes did not differ between the two groups during the first course.

During the whole 6-day period, full emetic protection was achieved in 30% of the tropisetron group and in 18% of the metoclopramide group ($X^2 = 0.743$; $P = 0.389$). Major emetic protection was achieved in 52% and 67% of the patients in the two groups. Treatment failures occurring at any time during the study period, were recorded in six patients (18%) on tropisetron medication and in five (15%) receiving treatment with the metoclopramide cocktail.

During the first 24 h of the second course of chemotherapy, tropisetron gave complete nausea protection in 81% of cases as compared with 62% for the metoclopramide cocktail ($X^2 = 1.714$; $P = 0.191$). The corresponding figures for major protection were 13% and 34% for the two groups. Two treatment failures (6%) were noted in the tropisetron group and one treatment failure (3%) was recorded in the metoclopramide group. Vomiting was recorded in 4 patients (13%) during tropisetron treatment and in 13 patients (45%) during treatment with the metoclopramide cocktail ($X^2 = 6.03$; $P = 0.014$; Table 4).

Table 5. Efficacy of the antiemetic regimens during the combined first 2 courses of chemotherapy[a]

Emetic protection	Antiemetic regimen	
	Tropisetron	Metoclopramide cocktail
Complete	4 (12%)	3 (9%)
Major	19 (58%)	23 (70%)
Failure	10 (30%)	7 (21%)

[a] Days 1–6 of each course

During days 2–6 the rate of complete nausea protection decreased, as in course 1, and reached nadir values on day 3. No significant difference between the two treatment regimens was recorded (Fig. 2).

During the whole 6-day period of course 2, complete emetic prevention (nausea and/or vomiting) was achieved in 15% of the tropisetron group and in 12% of the metoclopramide group. Major emetic prevention was achieved in 64% and 76% of the patients in the two groups. Treatment failures, occurring at any time during the study period, were recorded in seven patients (21%) on tropisetron medication and in four patients (12%) receiving treatment with the metoclopramide cocktail.

The relative antiemetic efficacy of the two regimens as determined by combining the data on the first two courses of chemotherapy is presented in Table 5. The overall evaluation of the efficacy made by the investigators showed an excellent or a good effect in 65% of the patients receiving the tropisetron regimen and in 56% of those given the metoclopramide regimen. The effect was regarded as poor in 16% and 19% of the patients, respectively.

The most frequent side effect of the antiemetic therapy recorded in this series was sedation (Table 6). Sedation was significantly more common ($X^2 = 11.074$; $P = 0.001$) after treatment with the metoclopramide cocktail (82%) than after treatment with tropisetron (36%). The median intensity of the drowsiness was 55 mm and 26 mm for the

Table 6. Side effects associated with the antiemetic therapy

Side effect	Antiemetic regimen		X^2	*P* value
	Tropisetron	Metoclopramide cocktail		
Sedation	12 (36%)	27 (82%)	11.074	0.001
Headache	15 (45%)	7 (21%)	3.341	0.068
Extrapyramidal reactions	0	7 (21%)	5.753	0.016
Diarrhea	2 (6%)	6 (18%)	1.280	0.258

two regimens as measured on a visual analog scale (VAS; 100 mm). On direct query, only 11% of the patients claimed to have experienced the sedation induced by the antiemetic drugs as an unpleasant side effect. Extrapyramidal reactions (dystonic reactions and akathisia) were recorded only after treatment with metoclopramide (21%). Headache was slightly more common in the tropisetron group (45%) during the first course of chemotherapy, but it was seldom of severe clinical relevance. During the second course of chemotherapy the frequency of headache was similar for the two antiemetic regimens (24%). Diarrhea was a minor problem in both groups.

The overall tolerability was rated as excellent or good in 94% of the treatment sessions for tropisetron and in 75% of the sessions for the metoclopramide cocktail. In five cases (16%) the tolerability was regarded as poor for the metoclopramide combination, but in no case was treatment with tropisetron considered to be poorly tolerated. This evaluation was made by the investigators after the second course of chemotherapy.

Discussion

The ideal agent for treatment of chemotherapy-induced nausea and emesis should be highly efficacious (more than 90% complete protection), devoid of disturbing side effects (extrapyramidal reactions and sedation), and easy to give (preferably by oral medication). No such agent or regimen existed in the past. The introduction of the 5-HT_3 receptor anatagonists during the last few years has changed our scenario, and these agents seem to fulfill most of the criteria for the ideal antiemetic drug [4, 19, 22, 25]. A prerequisite for this improvement was the identification of the serotonin type 3 receptor as well as its main importance in the mediation of chemotherapy-induced nausea and emesis [10] and the synthesis of specific antagonists to this group of receptors [20]. Extrapyramidal reactions are not seen, since the dopamine receptors are unaffected and significant sedation is not reported [4]. Headache and constipation may occur but are seldom of clinical significance when the agents are used for antiemetic purposes.

The prophylactic efficacy during the first 24 h was promising, with a 91% rate of complete or major protection against nausea and an 82% rate of complete prevention of emesis being noted after the administration of a single 5-mg i.v. dose of tropisetron before the cisplatin infusion. The metoclopramide cocktail, containing three drugs, reached the same level of efficacy but induced significantly more sedation and a 20% frequency of extrapyramidal reactions. The administration of the cocktail was more complicated.

A number of 5-HT_3 receptor antagonists have been studied in clinical trials. Besides tropisetron, the most commonly used agents are ondansetron (Glaxo) and granisetron (SmithKline Beecham). Granisetron and tropisetron are more potent and have longer half-lives (8–10 h) than ondansetron (3 h). These differences may affect the ease of administration (single-injection versus multiple-dosing schedules) and the frequency of side effects. However, the clinical importance of these pharmacokinetic data must be further evaluated.

Ondansetron given as a continuous infusion was superior to high-dose metoclopramide against acute emesis when given with cisplatin (50–100 mg/m^2), with 70% of the patients achieving complete or major control with ondansetron as compared with 40% of those on metoclopramide [6, 9, 19]. Granisetron was found to be as effective as a combination of metoclopramide and dexamethasone, with 70% of patients achieving complete or major control of emesis induced by high-dose cisplatin (>50 mg/m^2) [2]. Both ondansetron and granisetron remain effective during repeated courses of chemotherapy.

In the present study the prophylactic antiemetic effect decreased for both regimens during the follow-up period and reached nadir values on day 3 posttherapy. During this period, tropisetron was superior to metoclopramide. This was also true with regard to emesis protection during the first 24 h of course 2. The complexity of the metoclopramide cocktail and the potential risk of the occurrence of alarming adverse events due to metoclopramide itself [14] prevented an adequate extension of this medication during the critical follow-up period. The peroral formulation of tropisetron as 5-mg capsules, on the other hand, is well suited for long-term medication outside the clinic. Since the capsules were taken only once a day, every morning before the first meal, the patients' compliance was high. The administration of divided doses three or four times a day to nauseated and vomiting patients is not a good practice. The antiemetic therapy should be simplified as far as possible both during the first 24 h and during the follow-up period. This goal was achieved with tropisetron in the present study. The metoclopramide cocktail was also relatively simple to give, but the extension of treatment with tablets of metoclopramide (10 mg t.i.d) on days 2–6 was obviously insufficient.

The role of the serotonin receptor antagonists in the control of delayed emesis remains controversial, and any superiority over conventional antiemetics is not yet apparent. When ondansetron was compared with metoclopramide there was no difference in the control of delayed emesis as measured by vomiting, although the control of delayed nausea was superior with metoclopramide. Despite this finding, the patients preferred ondansetron, probably due to the lower frequency of adverse events [6, 9, 19]. It has been shown that single i.v. doses of granisetron can control emesis in 40%–44% of patients for up to 7 days after cisplatin administration, but a significant num-

ber of patients nonetheless fail to achieve control of delayed nausea and vomiting. The efficacy of granisetron against delayed emesis warrants further studies when the oral preparation becomes more widely available [11]. In comparative trials, dexamethasone has contributed significantly to the antiemetic effect of ondansetron in both acute and delayed phases of emesis during cisplatin chemotherapy [21, 24]. For moderately emetogenic chemotherapy, dexamethasone has been found to be as effective as, if not superior to, ondansetron with regard to delayed emesis [12]. A combination of metoclopramide and dexamethasone has been found to be superior to ondansetron in the prevention of both acute and delayed emesis during cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy for breast cancer [17].

In the future, more attention must be paid to the 1st week following the infusion of chemotherapeutic agents and to the problems with delayed nausea and emesis that occur after the patients have left the hospital. This period should be carefully evaluated in further clinical trials on antiemetic therapy.

In terms of its lack of disturbing side effects and the simplicity of its administration, tropisetron fulfills the criteria for an ideal antiemetic agent. However, prophylactic efficacy of more than 90% full protection against nausea and emesis was not met, particularly during the follow-up period. Nonetheless, the overall treatment results (efficacy and tolerability) achieved in this series using tropisetron as prophylaxis of cisplatin-induced nausea and emesis are the best thus far recorded at our clinic for women with gynecologic malignancies. The dose levels of cisplatin used in this study were in the 50- to 75-mg/m^2 range, and we know that higher doses might impose further challenges with regard to the therapeutic efficacy of this type of serotonin receptor antagonist [19]. Further studies are therefore needed to evaluate the optimal dose levels, modes of administration, and combination therapy with other antiemetic drugs [5].

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