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On-demand antiemetic treatment with the serotonine antagonist tropisetron in cisplatin-treated cancer patients

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Fourteen cancer patients treated with cisplatin received repeated infusions of tropisetron on-demand in conjunction with emesis. In subsequent chemotherapy courses, prophylactic tropisetron was given in a dose identical to the cumulated dose in study course 1. Tropisetron in study course 1 abolished emesis after 7.5 min (5 mg). Duration of effect was more than 7 h in 50% of the patients. No relationship between dose and duration of effect was seen. After study course 2, eight of 10 patients preferred prophylactic tropisetron. Two patients with hypertension had a severe increase in blood pressure probably related to tropisetron. It is concluded that tropisetron has an instant and lasting effect on nausea and vomiting when given on-demand. The majority of patients, however, prefer prophylactic treatment. Hypertension may be a side effect from tropisetron and caution should be displayed in hypertensive patients.

Key words: Antiemetics, 5-HT_3 antagonists, tropisetron.

Introduction

Nausea and vomiting are the most distressing side effects from chemotherapy seen from the patients' point of view.[1] In particular, cisplatin causes nausea and vomiting in the majority of patients, the severity of side effects getting worse with increasing doses.[2]

The mechanism of emesis induced by chemotherapy is only partly understood. The older hypothesis that dopamine receptors in the area postrema are triggered by cytotoxic drugs has been replaced by the understanding that enterochromaffine cells in the upper gastrointestinal tract release serotonine under the influence of cytotoxic drugs. Serotonine stimulates vagal afferents in the gut. The afferent fibers of the vagus terminate in the area postrema and in the caudal region of the nucleus tractus solitarius,[3] generating the emetic reflex.

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The first serotonine antagonists appeared in the late 1980s. Animal studies proved their ability to prevent emesis after cisplatin and to eliminate already established emesis.[4]

Clinical studies with the serotonine antagonists, primarily granisetron, ondansetron and tropisetron, soon showed a substantial antiemetic effect in cisplatin treated patients.[5] In non-cisplatin containing chemotherapy, approximately 70% of the patients have obtained major/complete control,[6] but further clarification in this setting is needed. Comparative studies with a serotonine antagonist versus a combination of high dose metoclopramide and steroids have shown equal or better effects from the serotonine antagonist in acute nausea and vomiting with complete protection in 60–70% of patients who received cisplatin for the first time,[7] but without the CNS toxicity seen with metoclopramide.

Concerning tropisetron, a phase 1 trial showed that it could safely be given in doses up to 48 mg/m^2 without severe side effects.[8]

Later phase 2 studies with prophylactic use of tropisetron revealed an effect similar to other serotonine antagonists.[9] In clinical trials and in daily use, antiemetics are administered prophylactically, which is considered to be optimal compared with rescue treatment. It may be rational to block the receptors before the administration of chemotherapy but controlled clinical trials proving the correctness of this approach have not been performed. Moreover, many patients do not experience nausea and vomiting until several hours after the administration of chemotherapy, and some patients, especially elderly men with a history of alcohol abuse, may even be free from nausea and vomiting after cisplatin treatment.

The prophylactic treatment also makes it difficult to study characteristics like time to antiemetic effect, optimal dose and duration of effect. Taking into

account the ability of the serotonine antagonists to abolish nausea and vomiting, we found it ethically acceptable to perform a study with tropisetron on-demand in cisplatin treated patients.

The aim of the present study was to evaluate time to effect, duration of effect and optimal dosage of tropisetron. Moreover, we wanted to investigate the ability of tropisetron to abolish already established nausea and vomiting and, finally, to investigate whether prophylactic treatment with tropisetron in subsequent chemotherapy series would give a better antiemetic protection than treatment on-demand.

Materials and methods

Protocol design

The trial was an open dose finding study with tropisetron in 16 patients. The study design is presented in Table 1.

In the first study course, the patients received repeated doses of tropisetron on-demand. During the second and following courses, they received one single prophylactic infusion of tropisetron in a dose identical to the cumulated dose given in study course 1. The patients were hospitalized for 24 h in each study course and, on admittance, regular hourly observations of nausea and vomiting were started. In course 1, the mean value of one to three recordings obtained before chemotherapy was regarded as the baseline value. Thereafter, the patients received chemotherapy and hourly recordings continued. Tropisetron was delivered in 10 and 40 ml ampoules containing 20 and 80 mg, respectively. The drug was diluted with 200 ml normal saline and was administered via an infusion pump with an infusion rate of 40 mg/h. The maximal allowed dose per 24 h was 80 mg. The pump was switched on and off as nausea or vomiting appeared and disappeared. Appearance was defined as a patient's spontaneous complaint of nausea or vomiting or routine recordings showing nausea worse than baseline values. Disappearance was defined as the cessation of vomiting or recordings of nausea below the baseline level for the actual patient. During infusion of tropisetron, recordings of nausea and vomiting were done at least every 15 min. The exact time for appearance and disappearance of nausea and vomiting was recorded and the dose necessary to abolish the symptoms could then be calculated from the duration of the infusion. Likewise, the duration of effect, i.e. the time from the end of one infusion to the start of the next one, could be measured. The cumulated dose of tropisetron for 24 h was calculated for each patient.

Table 1. Design of the study

Course no.	1	2	3 and onwards
Tropisetron	on-demand	prophylactically	same
Dose	max 80 mg	cumulated dose in course 1	same
Evaluation	VAS + Em am global assessment	VAS + Em am global assessment preference	global assessment

VAS, visual analog scale; Em am, emetic amount.

In the case of lack of effect from tropisetron or unacceptable side effects, the patients went off the study before the total dose of 80 mg was reached. Intravenous metoclopramide (50–100 mg) and methylprednisolone (250 mg, i.v.) were used as salvage therapy.

In study course 2 and the following courses, a single 15 min infusion of tropisetron was given before chemotherapy in a dose identical to the cumulated dose given during study course 1. In case of bothering nausea and vomiting, time for occurrence and severity was recorded, the patient went off the study and salvage antiemetic treatment was given.

The patients continued in the study with tropisetron in this fixed dose as long as they felt satisfied and did not require other antiemetics.

The study was conducted in accordance with Helsinki Declaration II. All patients gave written informed consent to participate in the study. The study protocol was approved by The Danish Health Authorities and the Local Ethical Committee before activation.

Patients

Sixteen patients, 15 with recurrent head and neck cancer and one with ovarian cancer (stage 2), were included. Patient characteristics are shown in Table 2.

All patients were treated with cisplatin at ≥ 50 mg/m^2 or greater and were planned to receive at least three chemotherapy courses. The patients were either chemotherapy naive or had received one or two chemotherapy courses with emesis prior to entrance in the study. All patients were considered able to cooperate. Bilirubin was below twice the upper normal limit and alanine aminotransferase below three times the upper normal limit. Renal function was normal or slightly impaired. No patient suffered from bronchial asthma

Table 2. Patient characteristics

Patient	Age\sex	Tumor	Chemotherapy	Prior chemotherapy	Known alchoholism
1	67/m	h&n	cis + 5-FU[b]	+	–
2	54/m	h&n	cis + 5-FU[b]	+	+
3	36/m	h&n	cis + 5-FU[b]	–	–
4	58/f	h&n	cis + 5-FU[b]	–	+
5	54/m	h&n	cis + 5-FU[b]	–	+
6[a]	50/f	h&n	cis + 5-FU[b]	–	+
7	45/m	h&n	cis + 5-FU[b]	–	+
8	48/m	h&n	cis + 5-FU[b]	–	+
9	48/f	h&n	cis[b]	–	–
10	48/m	h&n	cis[b]	–	–
11	51/m	h&n	cis + 5-FU[b]	–	+
12	68/m	h&n	cis + 5-FU[b]	–	–
13	58/f	h&n	cis + 5-FU[b]	–	?
14[a]	65/f	h&n	cis[b]	+	?
15	58/m	h&n	cis[b]	+	–
16	58/f	ovary	cis + adm + cyclo[c]	+	–

[a]Exclusion from the study.
[b]Cisplatin 100 mg/m^2, with or without 5-FU 1000 mg/m^2.
[c]Cisplatin 50 mg/m^2, adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2.
h&n, head and neck.

or severe cardiac insufficiency including branch or AV block.

No patient had received prior treatment with a serotonine antagonist, and there was no other reason for nausea and vomiting than cytostatic treatment.

Cisplatin was administered as a 1 h infusion with pre- and post-hydration, and 5-fluorouracil was administered as 24 h infusion. Chemotherapy was repeated in the same dosage every 3 weeks until progression of the disease or unacceptable side effects. Doses are listed in Table 2.

Parameters

Efficacy parameters:

(i) A visual analog scale (VAS) for nausea, recorded by the patient, 100 mm long and horizontal, end-barred but otherwise unmarked, the extremes being marked 'no nausea' and 'unbearable nausea', respectively. The patients were not allowed to see their previous recordings.
(ii) Measurements of emetic amount in grams.
(iii) Patient recorded global assessments after the 24 h study period; nausea intensity and severity of vomiting were graded as none, slight, moderate or severe.
(iv) Preference for course 1 or 2 after course 2.

Parameters for toxicity:

(i) Body temperature, heart rate and blood pressure every 6 h and at least once during infusion of tropisetron.
(ii) Before each study course and after the third: physical examination, ECG, hemoglobin, WBC, platelets, alanine aminotransferase, lactate dehydrogenase, bilirubin, prothrombine time, creatinine, carbamide, potassium, sodium and α-amylase.

In study course 1 and 2, VAS and emetic amount were recorded hourly and every 15 min during infusion of tropisetron. Recordings were left out during sleep. Global assessment and preference were obtained the next morning. In study course 3 and the following courses only a statement of the patients' satisfaction with the antiemetic treatment was recorded.

Statistics

Non-parametric statistical tests were used as VAS and emetic volumes do not fulfill the requirements for parametric statistics.[10] Doses, infusion time and duration of effect are described by median value and range.

Results

Study course 1

Two patients were ineligible, one had no nausea and vomiting (patient 6) and one was unable to

cooperate (patient 14). Thus 14 patients were left for evaluation. Ten patients received chemotherapy for the first time.

During study course 1, the observation time ranged from 12 h 30 min to 24 h 12 min per patient.

Baseline values for nausea and vomiting were low, indicating that anticipatory nausea and vomiting was not a problem (Table 4).

The median time from start of infusion of cisplatin until the first infusion of tropisetron was 2 h 25 min (50 min–4 h 28 min). The first infusion of tropisetron relieved nausea and vomiting instantly after a median dose of 5 mg (Table 4). With an infusion rate of 40 mg/h this means that the patients were free from symptoms 7.5 min after the infusion began.

Five patients were without symptoms during the rest of study course 1, nine patients required further tropisetron. Two patients received two infusions, seven patients required three or more infusions. The median doses of infusions number 2 and 3 increased to 10 and 20 mg, respectively, but for the seven patients who received all three infusions there is no significant difference.

The median cumulative dose per patient was 34.5 mg (2–80) (Table 2). It also appears from Table 2 that nine patients graded their nausea intensity as none or slight and seven patients graded vomiting as none or slight. Two patients were unable to use the grading system but indicated the efficacy of tropisetron as 'good' for both nausea and vomiting.

A log dose–effect curve for the first infusion of tropisetron in all 14 patients showed an ED_{50} of 5 mg with a slope of approximately 62%. The slope for the five patients who received only one infusion was identical, indicating that these patients did not belong to a different population. Parallel curves, shifted to the right, were drawn for the second (nine patients) and third infusion (seven patients) showing ED_{50} values of 7.5 and 15 mg. Wilcoxons two-tailed signed rank test showed no significant difference between the first, second and third dose of tropisetron. The log dose–effect curve for the seven patients who received both first, second and third infusion of tropisetron is shown in Figure 1. In this subgroup, no significant difference between ED_{50} was found either. The VAS score before tropisetron gave no indication of the dose necessary to relieve symptoms (Figure 2).

There was no significant difference in VAS scores before the first, second and third infusion of tropisetron.

Duration of effect was more than 7 h in 50% of the patients. There was no connection between dose

Table 3. Study course 1: results

Patient	Tropisetron		Global assessment		Continued in study	Off study due to
	no. of infusions	cumulative dose (mg)	nausea	vomit		
1	2	18	sl	n	yes	
2	3	27	sl	sl	no	hypertension
3	2	70	'good'	'good'	yes	
4	8	73	mo	se	no	died
5	1	2	'good'	'good'	no	refused
6	0	0				uncooperative (ineligible)
7	5	80	mo	sl	yes	
8	1	7	sl	sl	yes	
9	3	20	sl	mo	yes	
10	1	2	sl	sl	yes	
11	1	11	n	sl	yes	
12	5	62	sl	mo	yes	
13	1	44	sl	mo	yes	
14	0	0				did not request tropisetron (ineligible)
15	8	42	sl	sl	yes	
16	5	80	se	mo	no	lack of effect

Two patients were unable to specify the intensity of nausea and vomiting, but stated that the effect was 'good'. Two patients were ineligible, one was unable to cooperate and one did not request tropisetron.
n, none; sl, slight; mo, moderate; se, severe.

Table 3. Main results from study course 1, infusion number one, two and three

	Median	Range
Baseline values (14 patients):		
VAS	0 mm	0–10
Em am	0 g	0–0
First infusion of tropisetron (14 patients)		
VAS	22.5 mm	0–100
Em am	64 g	0–495
dose	5 mg	0.66–44
duration of effect	845 min	10–1215
Second infusion of tropisetron (nine patients)		
VAS	23 mm	0–80
Em am	0 g	0–120
dose	10 mg	1.33–36.66
duration of effect	96 min	7–925
Third infusion of tropisetron (seven patients)		
VAS	23 mm	10–57
Em am	0 g	0–110
dose	20 mg	6.66–30.66
duration of effect	225 min	4–540

Duration of effect is measured until the next infusion of tropisetron or until the end of the study period.
VAS, visual analog score; Em am, emetic amount.

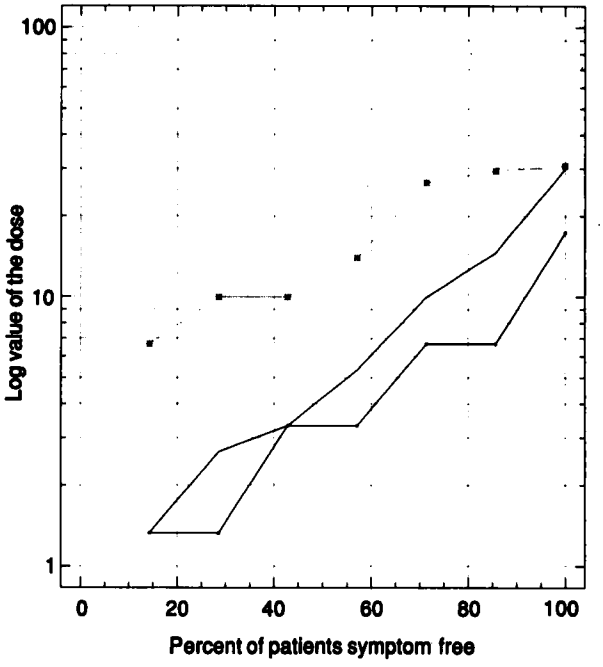

Figure 1. Percent of patients symptom free after first, second and third dose of tropisetron (mg). Study course 1, seven patients. —•—, first dose; —, second dose; ··✱··, third dose.

and duration of effect (Figure 3). There was no difference in duration of effect between the three first doses.

Four patients left the study after study course 1 because of lack of effect (1), hypertension (1), death from septicemia (1) and conviction that tropisetron made him vomit (1).

Side effects

Two male patients (patients 2 and 7), with arterial hypertension but at the time of the investigation without antihypertensive treatment, had an increase in blood pressure after tropisetron (Figures 4 and 5). Both patients had a slightly increased but not alarming blood pressure before chemotherapy. After start of tropisetron, patient 2 had progressive hypertension as infusions were reported. Tropisetron was stopped after a cumulated dose of 27 mg and his blood pressure slowly returned to normal.

Patient 7 had an increase in blood pressure not clearly related to tropisetron, and the blood pressure returned to normal after treatment with diuretics, sedatives and chlorpromazine. This patient did

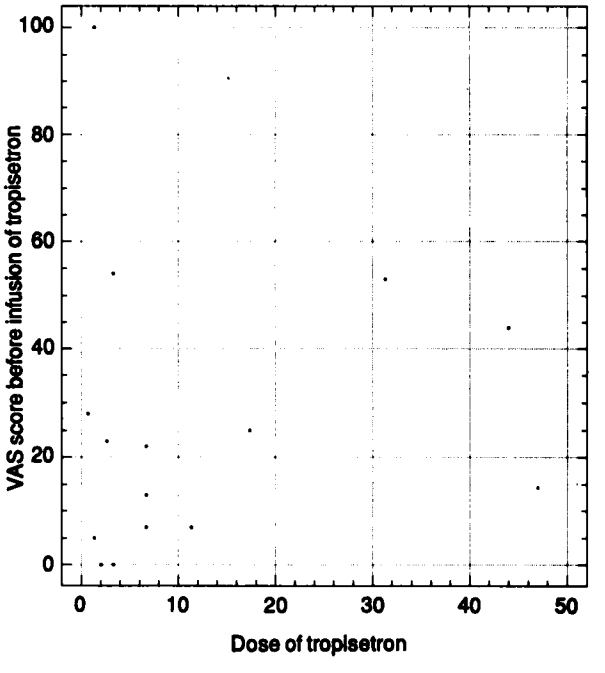

Figure 2. Dose of first infusion of tropisetron (mg) versus VAS score before start of infusion.

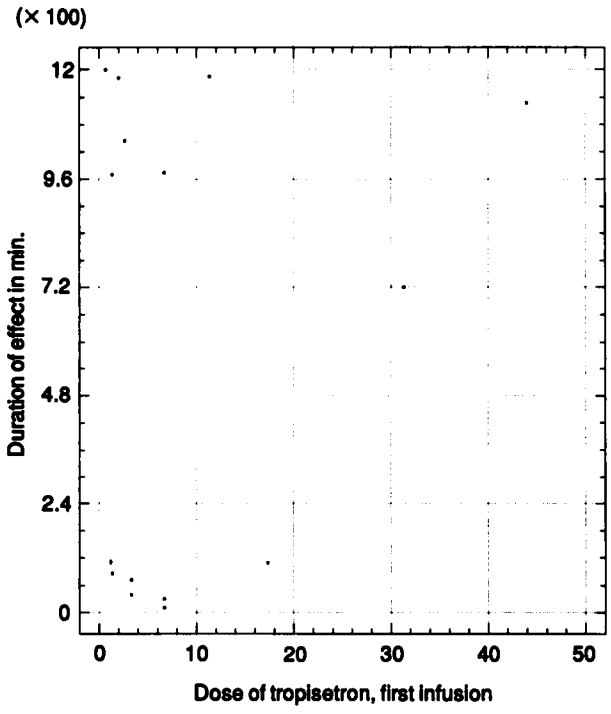

Figure 3. Duration of antiemetic effect (min) versus the first dose of tropisetron (mg).

not receive tropisetron during his next chemotherapy treatment. No hypertension occurred and as the hypertension during study course 1 was not clearly related to tropisetron, he received one more course with tropisetron, this time administered prophylactically. The systolic blood pressure again rose to 180 mmHg, the diastolic pressure to 145 mmHg and he went off study.

No other changes in blood pressure or vital signs were recorded. In one patient alanine aminotransferase increased from 20 U/l before tropisetron to 140 U/l 3 weeks later. She died from septicemia the day after alanine aminotransferase was measured. The increase was considered due to cardiac failure and stasis of the liver. One patient complained of slight dizziness for 4 days after tropisetron. One complained of diarrhoea. Headache and constipation were not observed.

Study course 2

Ten patients (Table 5) received tropisetron prophylactically in doses from 7 to 80 mg, representing their cumulated total dose of tropisetron in study course 1. Six patients were totally free from nausea and VAS scores in the remaining four patients were

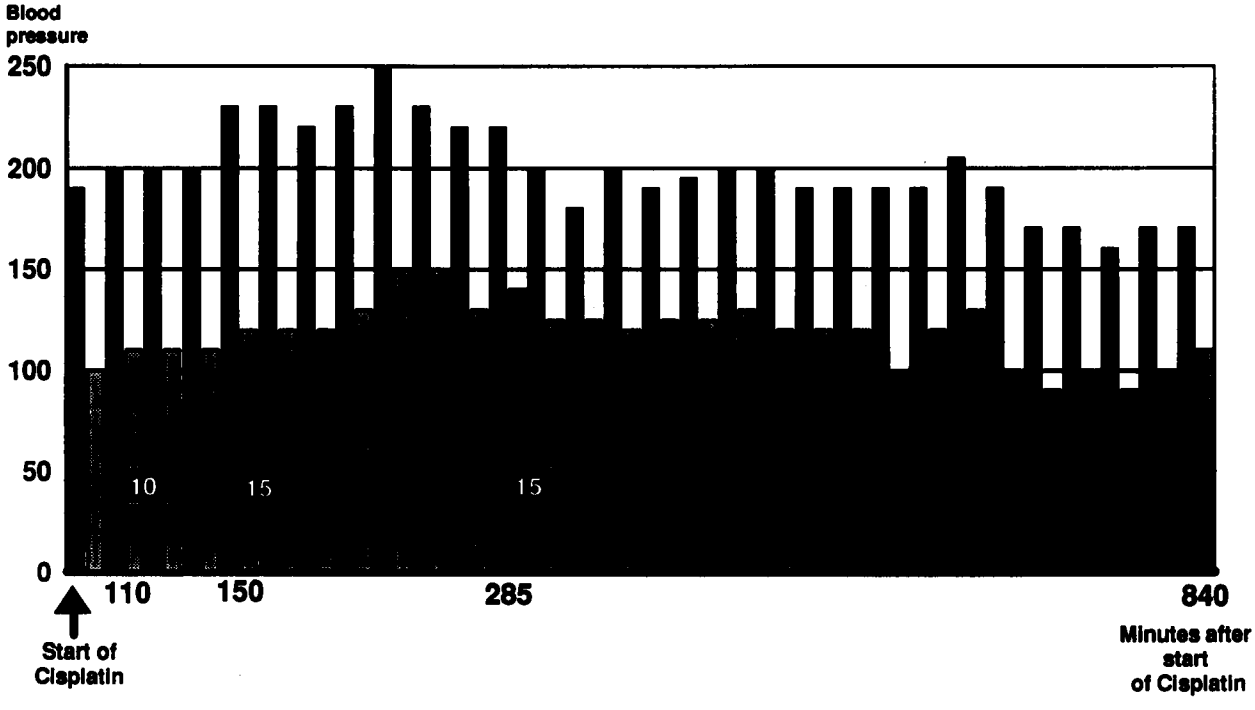

Figure 4. Systolic (■) and diastolic (▒) blood pressure in relation to time and infusion of tropisetron (N). Patient 2.

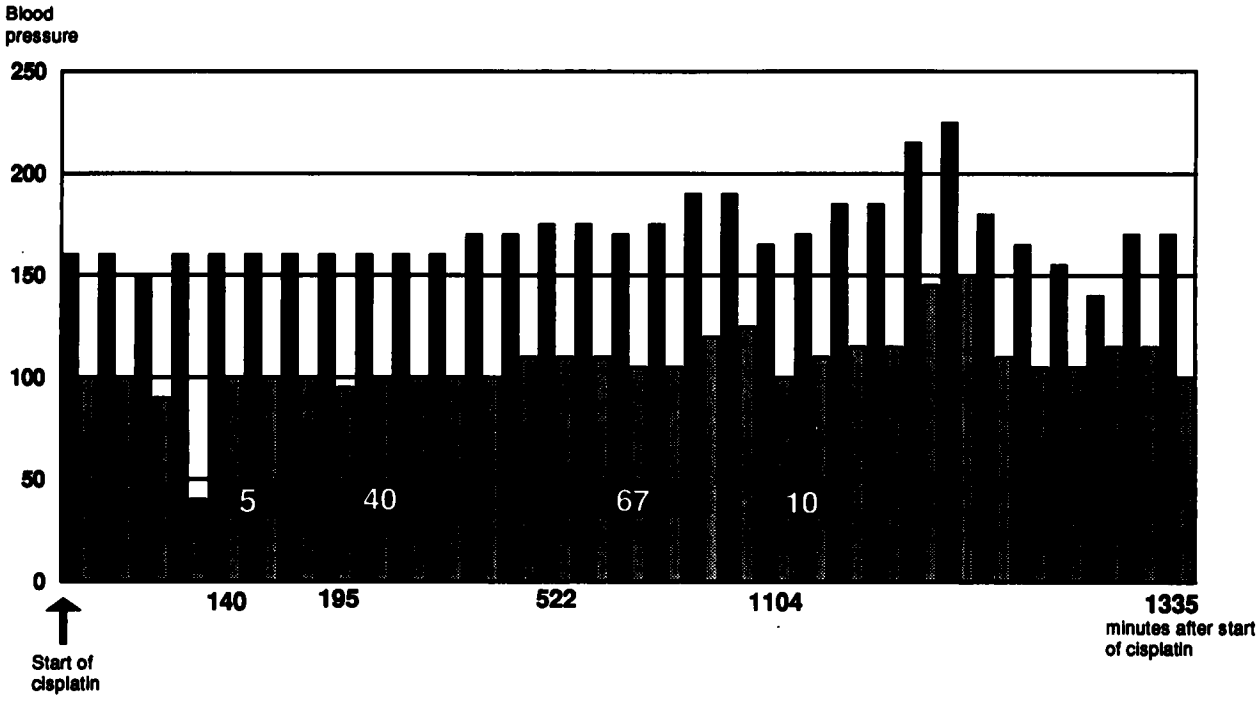

Figure 5. Systolic (■) and diastolic (▒) blood pressure in relation to time and infusion of tropisetron (N). Patient 7. One 2 min infusion of tropisetron omitted for clarification.

low. Six patients did not vomit. Maximal emetic volume was 350 g.

After the second study course, eight of 10 patients preferred the prophylactic treatment to the treatment on demand.

Four patients left the study after course 2 for the following reasons: lack of effect (1), progressive disease (1), death from tumor bleeding (1) and hypertension (1).

Study course 3 and the following courses

Six patients went on to study course 3 without any need for other antiemetics and with a sufficient antiemetic effect from tropisetron. No side effects were observed. Three patients left the study after course 3 because of progressive malignant disease (1), termination of chemotherapy (1) and lack of effect (1).

Table 5. Study course 2

Patient	Tropisetron (mg)	VAS		Emetic volume	Overall assessment		Preferred course no.	Side effects
		average	median		nausea	emesis		
1	18	3	3	0	sl	n	2	
3	70	6	0	350	sl	sl	2	dizzy
7	80	28	28	313	se	sl	1	hypertension
8	7	0	0	0	n	n	2	
9	20	20	21	48	mo	sl	1	
10	2	0	0	0	sl	n	2	
11	11	0	0	0	n	n	2	
12	62	0	0	350	n	sl	2	dizzy
13	42	0	0	0	n	n	2	
15	44	1	0	0	sl	n	2	

n, none; sl, slight; mo, moderate; se, severe.

Table 6. Reasons for patients to go off study

Patient	Off study after course no.	Reasons to go off study	ICS (mg) in each course
1	3	progressive disease	18
2	1	hypertension	27
3	3	lack of effect	70
4	1	progressive disease	73
5	1	thought that ICS made him vomit	2
6	excluded		0
7	2	hypertension	80
8	7	progressive disease	7
9	2	lack of effect	20
10	5	chemotherapy stopped	2
11	6	chemotherapy stopped	11
12	3	chemotherapy stopped	62
13	2	progressive disease	44
14	excluded		0
15	2	died in tumor bleeding	42
16	1	lack of effect	80

Three patients continued in the study and received five, six and seven courses with sufficient antiemetic efficacy (Table 6).

Discussion

Serotonine antagonists adhere to 5-HT_3 receptors in the CNS and the alimentary tract,[11] and are without influence on dopamine receptors.[12] They are devoid of extrapyramidal side effects and are at least as effective as high dose metoclopramide and steroids in cisplatin induced nausea and vomiting.

In the present study we found an impressive antiemetic effect from tropisetron when given on demand. This is in agreement with one animal[4] and two human studies[13,14] in which the serotonine antagonist granisetron was effective as rescue treatment after chemotherapy induced nausea and vomiting without prophylactic antiemetic treatment. However, it is generally preferred to administer antiemetic treatment prophylactically and eight of 10 patients in the present study preferred the prophylactic treatment after course 2. This may be due to the fact that patients treated prophylactically are free from the outbursts of nausea and vomiting that trigger the on-demand treatment. Moreover, it was unavoidable that patients were more often reminded of the possibility of nausea and vomiting in study course 1 as they were never left alone but attended cautiously by an observer for 24 h. Finally, the possibility remains that 5-HT_3 receptors have already been affected by the chemotherapy and therefore the effect of tropisetron is impaired. However, the prompt effect in study course 1 makes this explanation less probable.

It has been claimed that the serotonine antagonists have no proven sustained effect as the patients receive an increasing number of chemotherapy series.[15] The present study comprised 39 courses and only three patients left the study due to treatment failure, three patients received as many as seven courses with satisfactory effect. This seems to substantiate a sustained effect.

The present study showed an ED_{50} of 5–15 mg in study course 1, with a non-significant tendency to higher doses as the number of infusions progressed. Patients who needed only one infusion did not have a dose–response curve different from other patients.

No relationship between dose and duration of effect was found; approximately 50% of the patients were free from symptoms in more than 7 h whether they received doses of 3, 6, 9 mg or more (Figure 4). Moreover, a higher VAS score did not seem to require a higher dose of tropisetron.

Other studies with serotonine antagonists published after the initiation of the present have shown no correlation between effect and dose levels of tropisetron[16] and granisetron.[17] In conjunction with this, two studies with ondansetron concluded that there was no correlation between plasma concentration and clinical effect.[18,19] The findings in the present study of a log dose–effect but no correlation between dose and duration of effect may support these observations.

Concerning side effects, only hypertension turned out to be a problem. Two patients with mild

hypertension became severely hypertensive during treatment with tropisetron. This side effect has not been described before: three of 54 patients treated with cisplatin-based chemotherapy and tropisetron 10 mg b.i.d. developed mild hypotension which did not necessitate discontinuation of the treatment.[9] A phase 1 study showed that tropisetron 48 mg/m^2 could safely be given with no side effect on blood pressure.[8]

The other side effects (dizziness, diarrhea and elevation of alanine aminotransferase) are not clearly related to tropisetron and have not been described as side effects from serotonine antagonists.

It can be concluded from the present study that tropisetron gives an instant relief from nausea and vomiting when administered on-demand. Prophylactic treatment, however, is preferred by the majority of the patients. No coherence between dose and effect and dose and duration of effect was found. A non-significant trend towards a need for higher doses in patients receiving repeated infusions was noted. We think there is a reason to suspect that hypertension could be a side effect from tropisetron although the literature until now has not confirmed this suspicion and we advise caution in hypertensive patients.

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