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ORIGINAL ARTICLE

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Single high-dose dexamethasone improves the effect of ondansetron on acute chemotherapy-induced nausea and vomiting but impairs the control of delayed symptoms

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Abstract The introduction of serotonin receptor (5-HT_3) antagonists has improved the control of acute nausea and vomiting induced by cancer chemotherapy, but they seem to have little or no effect on delayed symptoms. Corticosteroids are known to reduce both acute and delayed nausea and vomiting. The aim of the present study was to test the hypothesis that a single high dose of dexamethasone (20 mg), a long-acting corticosteroid, given after cisplatin and in addition to ondansetron (8 mg three times a day), would enhance the control of both acute and delayed nausea and vomiting. A group of 104 chemotherapy-naive ovarian cancer patients, scheduled for at least three cycles of combination chemotherapy including cisplatin (50 mg/m^2), were randomly allocated to receive either dexamethasone or placebo in addition to ondansetron. Two-thirds of the patients received doxorubin and melphalan on the day before cisplatin and 1/3 received doxorubicin immediately before cisplatin. Unexpectedly we found, in all three chemotherapy cycles, that patients receiving dexamethasone suffered from more delayed nausea and vomiting than patients receiving placebo. In patients with no acute nausea or vomiting, the boomerang effect of dexamethasone could be seen on the first day after chemotherapy. In a follow-up study on 5 patients not included in the randomized trial, dexamethasone induced a pronounced reduction in urinary cortisol excretion on the day after chemotherapy with a return to normal excretion on day 2. It is concluded that a single high dose of dexamethasone does not seem appropriate for controlling delayed nausea and vomiting.

Key words Nausea and vomiting · Cancer chemotherapy · 5-HT_3 receptor antagonists · Corticosteroids

Introduction

Serotonin receptor (5-HT_3) antagonists provide a safe and efficient way of controlling acute nausea and vomiting induced by cancer chemotherapy. Corticosteroids exert antiemetic effects as single drugs and enhance the antiemetic effects of 5-HT_3 receptor antagonists on acute nausea and vomiting [1, 12, 13, 15, 17]. With the improved possibilities of controlling acute symptoms, delayed nausea and vomiting appear as a separate entity [14].

Delayed nausea and vomiting after chemotherapy have been studied much less than the acute symptoms. One trivial reason is that the patients have been discharged from the hospital when the delayed symptoms appear. To define the conventional dividing line between acute and delayed symptoms as 24 h after chemotherapy is arbitrary. Symptoms occurring after this

time may be a mixture of persisting acute nausea and vomiting and "true" delayed symptoms, the latter probably having a different mechanism [16]. Postulated contributing factors to delayed nausea and vomiting include cerebral edema, disordered intestinal motility, and direct mucosal toxicity allowing access of endotoxins into the bloodstream [2]. Corticosteroids could be expected to affect all these mechanisms.

Repeated doses of oral dexamethasone have been shown to ameliorate delayed symptoms in several clinical trials [5, 12, 21]. A single i.v. injection of a long-acting corticosteroid in connection with the chemotherapy would be a more practical way to administer corticosteroids than to give oral medication for several days. Furthermore, concern has been expressed about the use of corticosteroids as antiemetics because of the possibility of enhanced tumor growth [9] or impaired killing of the tumor cells [18]. On the other hand, corticosteroids are important components of many antineoplastic regimens, e.g. in hematological malignanices. Furthermore, the addition of steroids did not reduce the antitumoral effect of cisplatin in experimental leukemia in mice and in studies on human cancer cell lines [1].

The aim of the present study was to find out whether a single high dose of dexamethasone, administered i.v. 6 h after cisplatin, would both add to the effect of ondansetron on acute nausea and vomiting and protect against delayed symptoms. The study was placebo-controlled and had a randomized, double-blind, parallel-group design.

Patients and methods

Patients

Chemotherapy-naive ovarian cancer patients referred to the Department of Gynecological Oncology, Radiumhemmet, for combination chemotherapy including cisplatin (50 mg/m^2) were eligible for the study. Exclusion criteria included severe concurrent disease, gastrointestinal obstruction, vomiting and/or having received antiemetics within 24 h before the start of chemotherapy. A group of 104 patients were randomized and actually received cisplatin-containing combination chemotherapy in at least one of the three cycles studied (101 in the first, 92 in the second, and 89 in the third cycle). The patients were studied during three consecutive cycles. The study was approved by the local Ethics Committee and informed consent was obtained from all patients.

Chemotherapy

Cisplatin (50 mg/m^2), was given as an i.v. infusion during 1–2 h. The day of cisplatin administration is defined as day 0 of the chemotherapy cycle. Two-thirds of the patients received doxorubicin (40 mg/m^2, i.v. bolus) and melphalan (0.4 mg/kg, 90-min i.v. infusion) on the day before cisplatin administration and one-third received doxorubicin (50 mg/m^2) as an i.v. bolus injection immediately before the administration of cisplatin. Most patients were discharged from the hospital on the first day after chemotherapy.

Antiemetic therapy

Ondansetron (8 mg three times a day) was given to all patients i.v. on the day of cisplatin administration (as a 15-min infusion in 100 ml 0.9% saline immediately before and 2 h and 6 h after the start of the cisplatin infusion) and p.o. for 5 days thereafter. The patients were randomized to receive a single i.v. dose of 20 mg dexamethasone or placebo given immediately after the last i.v. dose of ondansetron. No oral corticosteroid was given. Patients on 2-day chemotherapy received 8 mg ondansetron p.o. three times a day on the non-cisplatin day (day –1).

Evaluation of nausea and emesis

Nausea and emesis were recorded by the patients themselves daily for 2 weeks. Nausea was recorded on a four-grade scale: none, mild (did not interfere with daily life), moderate (interfered with daily life), or severe (bedridden due to nausea), and emesis as the number of emetic episodes. An emetic episode was defined as a single vomit or retch or any number of continuous vomits and/or retches. Two episodes were defined as being separated by the absence of vomiting and retching for at least 1 min. A failure was defined as more than five emetic episodes per day. The patients were instructed to fill out the record form every morning as an average estimation of the symptoms on the previous day.

For the evaluation of the comparability of the study groups, some individual characteristics that could modify the severity of nausea and emesis [11] were assessed before treatment.The patients were asked about their previous susceptibility to nausea and emesis and they completed the State Trait Anxiety Inventory [22], the Eysenck Personality Questionnaire [6], and the Autonomic Perception Questionnaire [3].

Urinary cortisol excretion

After the paradoxical effect of dexamethasone on delayed nausea was revealed (see Results), we studied urinary cortisol excretion in 5 non-naive ovarian cancer patients on platinum-based combination chemotherapy outside the study population proper. They received, in two consecutive cycles, single doses of 20 mg or 8 mg dexamethasone on the cisplatinum day, in addition to ondansetron. Twenty-four-hour urine collections were carried out the day before treatment and for 5 days thereafter. Cortisol was analyzed by radioimmunoassay using kits from Farmos (Turku, Finland).

Statistics

To describe the effect of dexamethasone, we calculated a ratio between the proportions of patients with no nausea or emesis in the dexamethasone group compared to the placebo group. Thus a protective effect of dexamethasone gives a figure above unity and an impairment gives a figure below unity. A variance proposed by Greenland and Robins [8] was used for the calculation of the 95% confidence interval.

Results

Daily self-reports of nausea during the three chemotherapy cycles are presented in Fig. 1A–C. The proportions of patients with no or severe nausea in the two

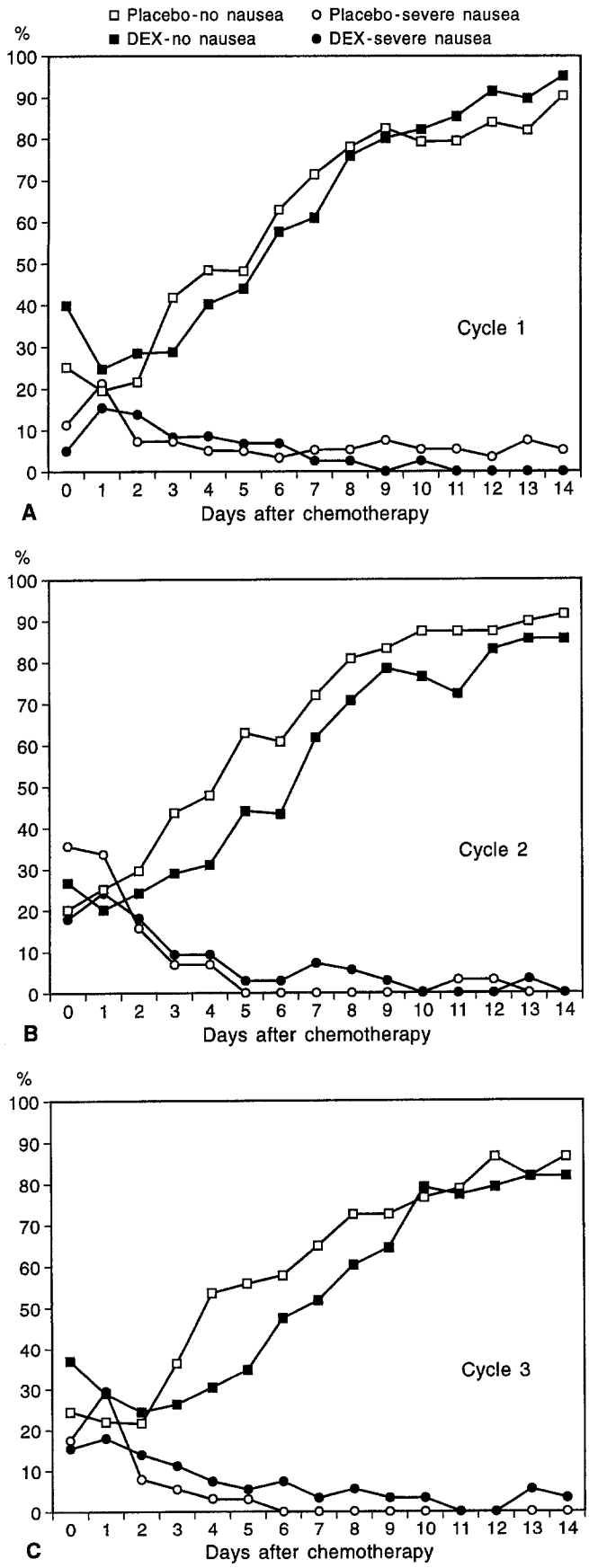

Fig. 1A–C Proportions of patients experiencing no or severe nausea, as defined in Patients and methods, in the ondansetron + dexamethasone and ondansetron + placebo groups during the first (**A**), second (**B**), and third (**C**) chemotherapy cycles

treatment groups (ondansetron + dexamethasone and ondansetron + placebo) are shown day by day for 14 days.

The addition of dexamethasone increased the proportion of patients protected from acute nausea (day 0) in all three cycles. In contrast, from day 3 after chemotherapy, a consistent pattern of more nausea was found in the dexamethasone group. This was most pronounced on days 4 and 5 in cycles 2 and 3. The relative risk of nausea in the dexamethasone group, as compared to the placebo group during the first week after chemotherapy, is shown in Table 1.

The differences in the treatment groups between the proportions of patients with severe nausea were small but consistent in all three cycles: a reduced proportion of patients with severe acute nausea but an increased proportion with severe delayed nausea in the dexamethasone group (Fig. 1A–C).

Figure 2A–C shows the proportions of patients with no or severe emesis during the three chemotherapy cycles. On the cisplatinum day and the first post-chemotherapy day, and in all cycles, dexamethasone increased the proportion of patients with no emesis and reduced the proportion with severe emesis. In cycles 2 and 3 from day 3 onward, the proportion of patients without emesis was lower in the dexamethasone group than in the placebo group. The relative risk of emesis in the placebo group as compared to the dexamethasone group during the first week after chemotherapy is shown in Table 2.

As described in Patients and methods, about two-thirds of the patients had received doxorubicin and melphalan on the day before cisplatin chemotherapy together with oral ondansetron (8 mg three times a

Table 1 Ratios and 95% confidence intervals for the proportions of patients with no nausea in the dexamethasone group compared to the placebo group. A ratio greater than 1 means a protective effect of dexamethasone whereas a ratio less than 1 means an impairment. The numbers of patients in the dexamethasone and placebo groups were 48 and 53 respectively in the first cycle, 46 and 46 in the second, and 42 and 47 in the third

Day	Cycle 1	Cycle 2	Cycle 3
0	1.6 (0.9–2.9)	1.3 (0.6–2.9)	1.5 (0.8–2.9)
1	1.3 (0.6–2.8)	0.8 (0.4–1.7)	1.3 (0.6–2.7)
2	1.4 (0.7–2.7)	0.8 (0.4–1.7)	1.1 (0.5–2.4)
3	0.7 (0.4–1.2)	0.7 (0.4–1.2)	0.7 (0.4–1.4)
4	0.8 (0.5–1.3)	0.7 (0.4–1.1)	0.6 (0.3–1.0)
5	0.9 (0.6–1.4)	0.7 (0.5–1.0)	0.6 (0.4–1.0)
6	0.9 (0.7–1.3)	0.7 (0.5–1.1)	0.8 (0.6–1.2)
7	0.9 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.6–1.1)

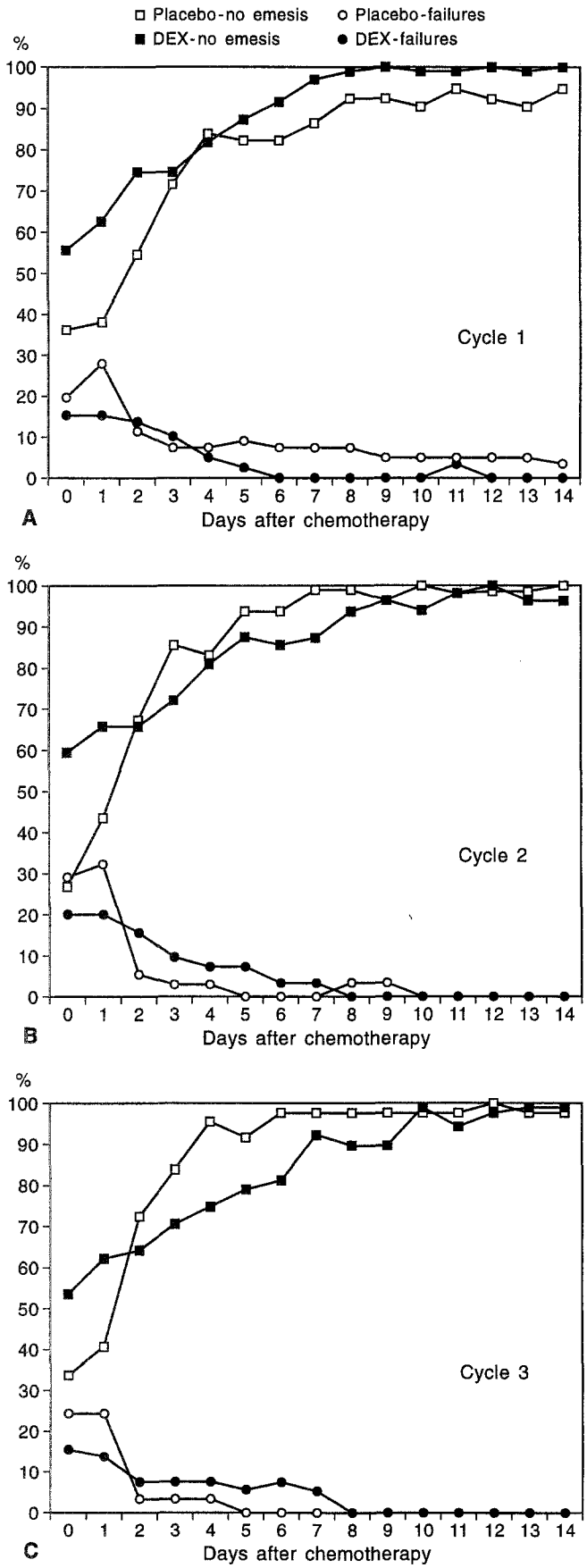

Fig. 2A–C Proportions of patients experiencing no or severe emesis, as defined in Patients and methods, in the ondansetron + dexamethasone and ondansetron + placebo groups during the first (**A**), second (**B**), and third (**C**) chemotherapy cycles

day) whereas one-third received doxorubicin on the cisplatin day. There was no difference in the occurrence of nausea and vomiting on the days studied and there was no difference in the proportion of patients receiving dexamethasone and placebo between the two patient groups (not shown).

In cycle 1, only 8 patients in each group were completely free from nausea and emesis during the whole study period. In cycle 2, 6 patients in the dexamethasone group and 7 in the placebo group had no nausea or emesis at all and in cycle 3 the corresponding figures were 7 and 5.

To be able to study "pure" delayed symptoms without the influence of persisting acute symptoms, we performed a restricted analysis on patients with no nausea on the cisplatinum day (Fig. 3A–C). In all three cycles, delayed nausea was more frequent in those patients who had received ondansetron + dexamethasone. However, since dexamethasone increased the proportion of patients without acute nausea, there were fewer patients in the placebo group: 12 as compared to 21, 9 to 12, and 10 to 17 in cycles 1, 2, and 3 respectively. This entails a risk of selecting more nausea-resistant patients in the placebo group and biasing the results. Therefore demographics for candidate risk factors for nausea and vomiting [11] in the whole study groups and in the subsets of patients with no acute nausea in the three cycles are shown in Table 3.

Figure 4 shows the urinary cortisol excretion data in the 5 non-naive patients after a single dose of 20 mg dexamethasone in addition to ondansetron. A pronounced inhibition was evident on the first day after chemotherapy, but the recovery was rapid. The data were similar after a single dose of 8 mg (not shown).

Table 2 Ratios and 95% confidence intervals for the proportions of patients with no emesis in the dexamethasone group compared to the placebo group. A ratio greater than 1 means a protective effect of dexamethasone whereas a ratio less than 1 means an impairment. The numbers of patients in the dexamethasone and placebo groups were 48 and 53 respectively in the first cycle, 46 and 46 in the second, and 42 and 47 in the third

Day	Cycle 1	Cycle 2	Cycle 3
0	1.5 (1.0–2.4)	2.3 (1.3–3.9)	1.6 (1.0–2.6)
1	1.7 (1.1–2.5)	1.5 (1.0–2.3)	1.5 (1.0–2.3)
2	1.4 (1.0–1.8)	1.0 (0.7–1.3)	0.9 (0.7–1.2)
3	1.0 (0.8–1.3)	0.9 (0.7–1.1)	0.8 (0.7–1.1)
4	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.8 (0.7–0.9)
5	1.1 (0.9–1.3)	0.9 (0.8–1.1)	0.9 (0.7–1.0)
6	1.1 (0.9–1.3)	0.9 (0.8–1.1)	0.8 (0.7–1.0)
7	1.1 (1.0–1.3)	0.9 (0.8–1.0)	0.9 (0.9–1.1)

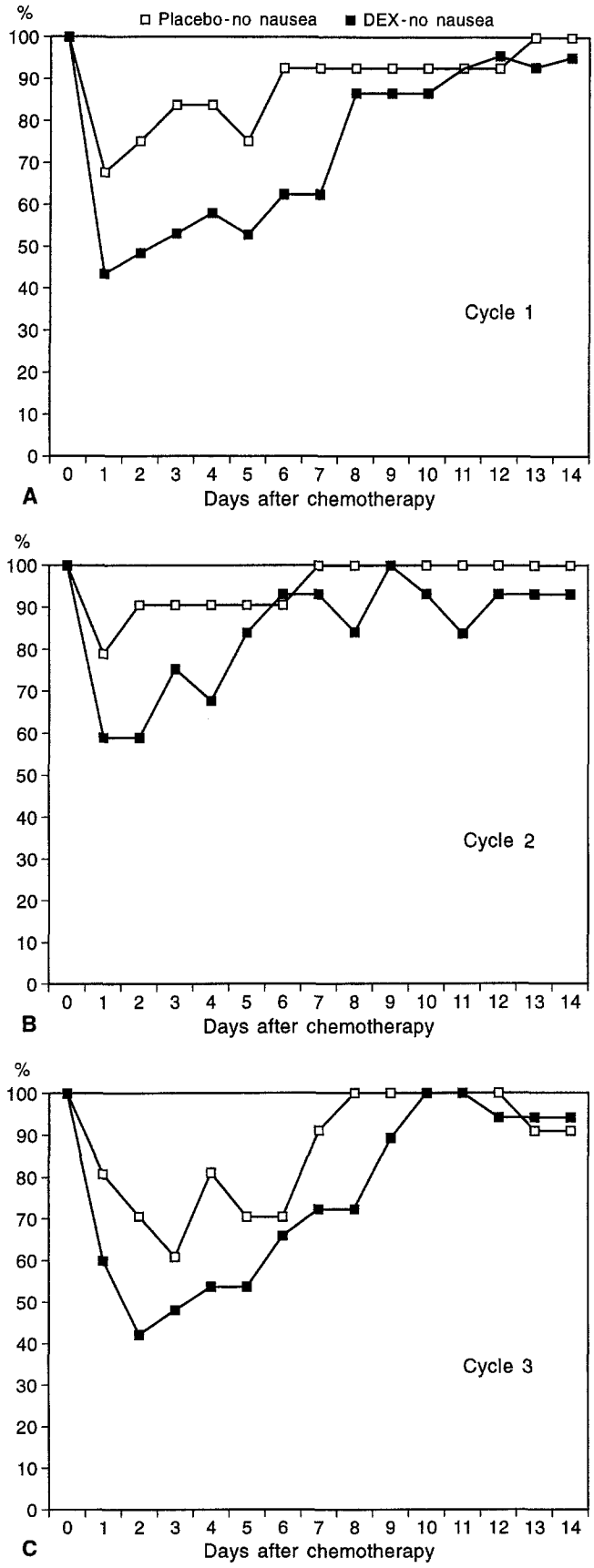

Fig. 3A–C Results of subgroup analyses concerning delayed nausea among patients with no acute nausea. The proportions of patients experiencing no nausea in the ondansetron + dexamethasone group and ondansetron + placebo group during the first (**A**), second (**B**), and third (**C**) chemotherapy cycles

Eleven patients (4 in the dexamethasone group) were withdrawn from the study during cycles 2 or 3. Four of these patients developed a rash during the first infusion of ondansetron, but it is difficult to evaluate the cause/effect relationship since ondansetron was administered concomitantly with mannitol. No provocation test was performed. Seven patients decided to withdraw from the study for various reasons. Headache and constipation were the most frequent adverse effects reported.

Discussion

Prior studies have shown that dexamethasone administered before chemotherapy improves the effect of ondansetron on acute nausea and vomiting [19, 21]. This study shows that, also when administered 6 h after cisplatin, dexamethasone improves the effect of ondansetron (8 mg three times a day) on acute nausea and vomiting. However, contrary to the hypothesis, a single high dose of dexamethasone impaired the control of delayed nausea and emesis.

The finding of a "cross-over" of the curves representing the proportions of patients with no or severe symptoms in the dexamethasone and placebo groups on days 2–3 after chemotherapy was consistent for all three cycles studied. A model for a formal statistical test to determine whether the differences between the groups are significant would have to incorporate the condition that repeated measurements are made on the same individuals during three cycles and during different days of the same cycle. Also, arbitrary assumptions would have to be made as to when "true" acute symptoms end and delayed symptoms begin, as well as how long the effect of dexamethasone could be expected to last. The assumptions that would have to be made would compromise the possibility of interpreting such summary statistics, so we chose to present the data graphically and with a day-by-day comparison for each cycle. Of course, causality cannot be inferred from the borderline significant confidence intervals seen on some single days, especially since multiple comparisons have been made.

In the subgroups experiencing delayed nausea only, the adverse effect of dexamethasone could be seen on the first day after chemotherapy whereas in the whole study population the initial beneficial effect of dexamethasone turned into an adverse effect around day 3 after chemotherapy. This indicates that nausea occurring

Table 3 Demographics of candidate risk factors of nausea and vomiting in the whole study group and the subgroups with no acute nausea

Characteristic	Ondansetron + dexamethasone				Ondansetron + placebo			
	All	No acute nausea			All	No acute nausea		
		1	2	3		1	2	3
Number of patients	53	21	12	17	51	12	9	10
Age, mean (years)	52	52	49	50	57	58	60	60
Previous susceptibility to (%)								
Nausea in general	70	71	75	71	71	33	56	50
Vomiting in general	55	57	58	58	58	33	22	50
Motion sickness	43	23	33	29	44	8	22	0
Nausea during pregnancy	59	53	33	42	50	36	22	50
Personality (mean values on the inventories)								
State anxiety	44	46	43	45	46	45	43	47
Trait anxiety	35	35	37	36	36	35	39	36
Neuroticism	6.3	6.0	6.3	5.8	5.1	3.5	5.3	4.8
Autonomic perception	68	68	63	67	64	60	57	67

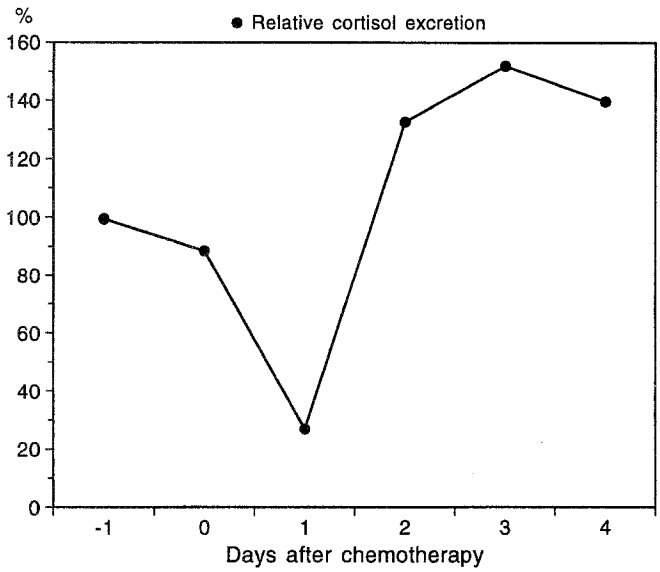

Fig. 4 Daily urinary excretion of cortisol relative to baseline assessed on the day before chemotherapy (day -1). A single dose of 20 mg dexamethasone was administered on the chemotherapy day (day 0). Relative mean values for 5 patients are shown

up to about 3 days after chemotherapy can be a mixture of persisting acute and delayed nausea possibly originating by different mechanisms. Fewer patients in the placebo group than in the dexamethasone group had no acute nausea with a possible selection of patients less prone to experiencing nausea and vomiting. Previous studies have shown that susceptibility to nausea in other situations and also a high level of neuroticism are risk factors for nausea in cancer chemotherapy [11]. The patients without acute nausea in the placebo group had less previous susceptibility to nausea than the patients without acute nausea in the dexamethasone group, especially during the first cycle ($P=0.07$, Fisher's exact test). However, the entire dexamethasone and placebo groups were well balanced with regard to these risk factors.

Joss et al. [13] recently reported data on nausea and vomiting during a period of 5 days after chemotherapy including cisplatin above 50 mg/m^2. As antiemetics, single doses of dexamethasone (20 mg) or placebo were given i.v. before cisplatin in combination with ondansetron 8 mg three times daily. In patients with nausea and vomiting in previous chemotherapy cycles, an impaired effect of dexamethasone could be seen on day 5 after chemotherapy. However, no such effect was seen when 8 mg dexamethasone as a single i.v. dose was combined with granisetron [4], which indicates that the steroid dose might be of importance for the boomerang effect. Recently, an Italian study on moderately emetogenic chemotherapy for chemotherapy-naive patients reported that a total dose of 24 mg dexamethasone, given in repeated doses on the chemotherapy day (8 mg i.v. before chemotherapy and four oral doses of 4 mg every 6 h), was effective against delayed nausea when given alone or in addition to granisetron [20].

The reason for the paradoxical effect of dexamethasone on delayed nausea is not clear. One contributing factor could be the inhibition of endogenous cortisol production. In previous studies, we found that a high urinary cortisol excretion was associated with a low level of chemotherapy-induced nausea and vomiting [7].

However, the disadvantage of delayed nausea in the dexamethasone group persisted much longer than the reduction in cortisol excretion. There are no data to support the suggestion that the molecular mechanisms underlying delayed nausea brought about a long-term effect also during the period when endogenous cortisol production was restored. Another consequence of this hypothesis would be that exogenous dexamethasone cannot replace endogenous cortisol in counteracting the mechanism leading to delayed nausea. However, previous studies have indicated an interchangeability between endogenous and exogenous steroids since dexamethasone administered together with ondansetron reduced acute emesis only in patients with low urinary cortisol excretion [10].

In conclusion, this study shows that single high-dose dexamethasone, which enhances the effects of 5-HT_3 receptor antagonists on acute chemotherapy-induced nausea and emesis, impairs the control of delayed nausea. Lower single doses or repeated doses of corticosteroids over consecutive days should preferably be used.

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