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# Efficacy and Tolerability of Tropisetron in Comparison With a Combination of Tropisetron and Dexamethasone in the Control of Nausea and Vomiting Induced by Cisplatin-containing Chemotherapy

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**In a double-blind, randomised, multicentre study, the efficacy and tolerability of tropisetron and a combination of tropisetron and dexamethasone were compared for the control of nausea and vomiting induced by cisplatin in patients previously not entirely protected by tropisetron monotherapy. In all, 160 women with gynaecological cancers were studied during two consecutive courses of cisplatin-containing chemotherapy. During the first course (the screening course), all patients received tropisetron monotherapy [5 mg intravenous (i.v.) on day 1 and 5 mg orally on days 2–6] as antiemetic treatment. During the second course (the test course), tropisetron was compared with a combination of tropisetron and dexamethasone (20 mg i.v. on day 1 and 4.5 mg twice daily on days 2–6). This part of the study was double-blind, randomised and placebo-controlled. Candidates for randomisation were patients with partial control of nausea (< 12 h of nausea) or partial control of vomiting (1–4 episodes of vomiting) during the screening course. Patients with complete control of nausea and vomiting in the screening course continued with tropisetron monotherapy; patients with treatment failure received open rescue treatment in course 2. Total control of acute nausea was achieved in 37% of the tropisetron + placebo group and in 75% of the tropisetron + dexamethasone group ($P = 0.001$). Significantly more patients on tropisetron–dexamethasone than on tropisetron–placebo were also free of delayed nausea. Acute vomiting was prevented in 40% of the patients in the placebo group and in 75% in the dexamethasone group ($P = 0.001$). Delayed vomiting was also significantly less frequent in dexamethasone-treated patients than in placebo-treated patients. Tropisetron was well tolerated both as monotherapy and in combination with dexamethasone. The most frequent adverse events were headache (34%), constipation (12.5%) and fatigue (12.5%). Adding high doses of a corticosteroid did not induce further adverse events or disregulate concurrent diseases.**
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## INTRODUCTION

TROPISETRON (NAVOBAN®, Sandoz Pharma Ltd, Basle, Switzerland) is a highly potent and selective antagonist of serotonin type 3 (5-$HT_3$) receptors developed by systematic methyl substitutions of the serotonin molecule [1]. These types of receptors are involved both peripherally and centrally in chemotherapy-induced nausea and vomiting [2]. As early as 1986, tropisetron was found to be one of the most potent inhibitors of cisplatin-induced emesis in the ferret [3]. Clinical studies made since 1987 have confirmed the clinical value of the 5-$HT_3$ receptor antagonists in the prevention and treatment of acute cisplatin-induced nausea and vomiting [4–6]. The new group of drugs is comparable to the best antiemetic cocktails but with fewer side-effects and simpler administration schedules [7, 8]. Their success at treating acute emesis has highlighted the fact that delayed nausea and vomiting are significant problems. The optimum use of the 5-$HT_3$ receptor antagonists in the prevention of delayed emesis still has not been settled [9]. Indeed, with modern antiemetic therapy, delayed nausea and vomiting is a greater problem than acute emesis for platinum-containing chemotherapy with the worst control rates on days 2 and 3 [7]. The addition of dexamethasone improved the control of acute emesis by both metoclopramide and the new

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serotonin receptor antagonists [10–12]. In a recently published study, dexamethasone was found to be superior to ondansetron in the prevention of delayed nausea, suggesting that it may have at least partly different aetiology compared to the acute counterparts [13]. For patients completely protected from both acute and delayed emesis by 5-$HT_3$ receptor antagonist monotherapy during the first course of chemotherapy, there is no rationale for a more complex antiemetic regimen, which would eliminate the advantages of monotherapy and a simple once-a-day administration.

With this in mind, a study was designed to evaluate the benefit of adding dexamethasone to tropisetron in cisplatin-treated patients previously not fully protected by tropisetron monotherapy. This design avoided overtreatment with corticosteroids, but reserved their use for partial or complete failures on monotherapy alone.

## MATERIAL AND METHODS

During the period 1 February 1991 to 29 February 1992, a double-blind, randomised, placebo-controlled, multicentre study was conducted at four Swedish gynaecological oncology centres (Örebro, Linköping, Lund and Uppsala) and one Finnish gynaeoclogical centre (Helsinki). Only women with gynaecological cancers were included (Table 1). The inclusion criteria are presented in Table 2. Tropisetron plus placebo was compared with tropisetron plus dexamethasone (Decadron®, MSD, Rahway, New Jersey, U.S.A; Dexacortal®, N.V. Organon, Oss, Holland) for the prevention of acute and delayed nausea and vomiting during cisplatin-containing chemotherapy in patients previously not fully controlled by tropisetron monotherapy. The various chemotherapy regimens used are presented in Table 3. The cisplatin infusion time was 2 h after a 1 h period of prehydration. The cisplatin dose varied between 50 and 100 mg/m$^2$. The chemotherapy was administered on inpatient basis. Background factors regarding motion sickness, nausea during pregnancy, and alcohol intake were not recorded in this study.

Two consecutive courses were studied in patients without prior experience of chemotherapy. All patients received a unique study number at entry, which corresponded to the prepackaged treatment to be given during the randomised, double-blind, placebo-controlled test course. Patients randomised in course 2 (tropisetron + placebo or tropisetron + dexamethasone) were well-balanced with regard to age, weight, height, diagnoses, chemotherapy regimen and cisplatin doses (mean 60 mg/m$^2$) (Table 4).

The first course was a screening course in which all patients

*Table 1. Characteristics of the intention-to-treat population at entry*

| | | |
|---|---|---|
| Numbers of patients entered | 160 | |
| Mean age (years) | 58 | |
| Age range (years) | 21–81 | |
| Mean weight (kg) | 65 | |
| Mean height (cm) | 163 | |
| Coexistent diseases (at entry)* | 63 | (39%) |
| Prior medication (at entry)* | 100 | (63%) |
| Concomitant medication* | 96 | (60%) |
| Primary diagnosis* | | |
| Ovarian cancer | 111 | (69%) |
| Endometrial/cervical cancer | 43 | (27%) |
| Other gynecological tumors | 6 | (4%) |
| Previous cancer treatment* | | |
| Abdominal surgery | 146 | (91%) |
| Radiotherapy | 39 | (24%) |

*No. of patients (%).

*Table 2. Inclusion criteria for the study*

1. Histologically or cytologically confirmed gynaecological malignant tumour
2. Patients scheduled to be treated with any cisplatin-containing chemotherapeutic regimen with the following characteristics:
   (a) Cisplatin given on day 1 only
   (b) Cisplatin dose ≥ 50 mg/m$^2$ body surface area, given over a maximum of 2 h
   (c) Other agents allowed on days 1–6
   (d) At least two identical courses foreseen with 3–4 weeks between the courses
3. Over 16 years of age at entry in the study
4. Informed consent obtained

*Table 3. Characteristics of the various chemotherapy regimens used*

| Regimen no. | Agents | Days of treatment | No. of patients |
|---|---|---|---|
| 1 | Doxorubicin | 1 | |
| | Cisplatin | 1 | 59 |
| 2 | Epirubicin | 1 | |
| | Cisplatin | 1 | 69 |
| 3 | Epirubicin | 1 | |
| | Cisplatin | 1 | |
| | Cyclophosphamide | 1 | 6 |
| 4 | Cisplatin | 1 | |
| | VM-26 | 1 | |
| | Vincristine | 1 | 10 |
| 5 | Cisplatin | 1 | |
| | 5-Fluorouracil | 5 | 5 |
| 6 | Cisplatin | 1 | |
| | VP-16 | 3 | |
| | Bleomycin | 1 | 1 |
| 7 | Other | 1 | 10 |
| Total | | | 160 |

*Table 4. Characteristics of the two randomised groups (schedules $B_1$ and $B_2$) in course 2*

| | Tropisetron + placebo | Tropisetron + dexamethasone |
|---|---|---|
| Mean age (years) | 59 | 58 |
| Mean weight (kg) | 67 | 64 |
| Mean height (cm) | 163 | 164 |
| Primary diagnosis* | | |
| Ovarian cancer | 21 | 20 |
| Endometrial/cervical cancer | 11 | 8 |
| Other gynaecological tumours | 3 | 0 |
| Cisplatin* | | |
| Mean dose (mg/m$^2$) | 60 | 60 |
| Range (mg/m$^2$) | 50–100 | 50–100 |
| Infusion time (h) | 2.0 | 2.0 |

*No. of patients.

received tropisetron monotherapy. Tropisetron (5 mg) was given as a short i.v. infusion (15 min) at the end of the prehydration period and immediately before the start of the cisplatin infusion. On days 2–6, tropisetron was taken as an oral capsule (5 mg) with a sip of water once in the morning on awaking.

The antiemetic treatment of the test course ($n$ = 144) was determined by the outcome of the antiemetic therapy of the screening course ($n$ = 160). 16 patients did not receive the antiemetic study medication in course 2 (wrong treatment allocation, 6; non-adherence to selection criteria, 2; additional antiemetic agents, 1; study medication ineffective, 3; adverse events, 1; uncooperative, 3). Four different schedules were used. Schedule A (tropisetron monotherapy) was used for patients with complete protection against nausea and vomiting during course 1 (days 1–6). Schedules $B_1$ (tropisetron + placebo) and $B_2$ (tropisetron + dexamethasone) were used in the randomised part of the study, for patients showing partial control of nausea and/or vomiting during the screening course (course 1). Dexamethasone (Decadron®, 20 mg) was given as a short i.v. infusion at the end of the prehydration period on day 1. During days 2–6, dexamethasone (Dexacortal®, 9 mg) was given in the form of three tablets of 1.5 mg each in the morning and in the evening, or a matching placebo. Schedule C (tropisetron + open rescue treatment) was used for patients showing treatment failure in the screening course. The rescue treatment mainly consisted of a corticosteroid (dexamethasone or betamethasone, 20 mg) and a benzodiazepine (lorazepam, 1–2 mg), and was usually only given on day 1 of the test course.

The primary aim of the study was to compare the antiemetic outcome of the randomised subgroups (schedules $B_1$ and $B_2$) in course 2, and the secondary aim was to study other subgroups in course 2 (schedules A and C).

On day 1, nausea and vomiting were recorded on a nursing chart, starting at the beginning of the infusion of cisplatin, at 4-h intervals until the next morning. On days 2–6, the patients themselves recorded the observations twice a day (morning and evening) on the patient diary card. The following definitions were used for the efficacy analyses: vomiting was calculated as events, and nausea as the number of hours with nausea per 24-h period. The intensity of nausea was not analysed in this report. Vomiting: total control = no vomiting during a 24-h period; partial control = 1–4 events of vomiting; no control (failure) = 5 or more events of vomiting. Nausea: total control = no nausea during a 24-h period; partial control = 1–12 hours of nausea; no control (failure) = more than 12 h of nausea. Control of vomiting and nausea combined on days 1–6: complete response = no vomiting and no nausea on any of days 1 to 6 of the chemotherapy course; partial response = 1–4 events of vomiting and/or 1–12 h of nausea on any of days 1–6 of the chemotherapy course; no response = 5 or more events of vomiting and/or more than 12 h of nausea on any of days 1–6.

An adverse event was defined as a noxious clinical occurrence or an abnormal laboratory result observed in a patient receiving the test drug (tropisetron), which was related in time but not necessarily caused by its administration. Adverse events were divided into serious (life-threatening, requiring prolonged hospitalisation, or causing permanent disablement or incapacity) and non-serious (all other). Adverse events were recorded from all available sources, i.e. serious adverse event report forms, case report forms (CRF), comments made by the investigator in the CRF, and comments made by the patients on the diary cards.

The study was approved by the local ethical committee of each participating centre and adhered to the guidelines of the Helsinki Declaration and its amendments.

The stastistical analyses were made by Quintiles Ireland Ltd. All patients who received (part of) the study medication were included in all of the analyses according to the intension-to-treat principle. The database was created in Clintrial (Oracle on Micro VAX 3900). After rigorous quality control procedures, the data were downloaded into data sets for the Statistical Analysis System (SAS). The Mantel–Haenszel test [14] was used to test for differences in response between treatment groups when data were categorical. Fisher's exact test [15] was used when the expected cell frequencies were too small for Mantel–Haenszel statistics. In the case of discrete numeric data, analysis of variance was used to test for differences in response between treatments. The statistical procedures were adjusted for the centres and the two-sided $P$-values were presented. In the case of binary responses, 95% confidence intervals were presented for proportions of responsive patients. The confidence intervals were based on a normal approximation to the binomial distribution [16]. The Breslow–Day test [17] was used to determine whether the treatment differences were uniform across centres.

## RESULTS

Acute vomiting was completely prevented in 53% and acute nausea in 47% in the first course (the screening course). Vomiting and nausea combined were prevented completely in 38% during the first 24 h. Delayed vomiting and nausea were entirely absent in 23 to 61% during days 2 to 6. The worst control rate of vomiting (43%) occurred on day 2 and of nausea (27–43%) on days 2, 3, and 4. Frequencies of partial and no control (failure) are presented in Table 5. Overall, 19 patients (12%) experienced no vomiting and no nausea at all during course 1 (days 1–6) and continued to take tropisetron monotherapy (schedule A) in course 2. Partial responses were recorded in 63 patients (39%) and they continued with the randomised part of the study (schedule $B_1$ versus $B_2$) in course 2. Finally, 62 patients did not respond in course 1 and, therefore, continued with open rescue treatment (schedule C) in the test course. There were no

*Table 5. Efficacy analysis of course 1. Proportion of patients showing control of vomiting, nausea, and vomiting and nausea combined. Results are presented for each of days 1–6 and for the entire course, based on a worst-day analysis*

| Day | 1 | 2 | 3 | 4 | 5 | 6 | Overall |
|---|---|---|---|---|---|---|---|
| Vomiting | | | | | | | |
| Total control (%) | 53 | 43 | 58 | 79 | 81 | 83 | 28 |
| Partial control (%) | 31 | 30 | 33 | 13 | 14 | 13 | 34 |
| No control (%) | 15 | 26 | 6 | 4 | 1 | 0 | 34 |
| Not assessed (%) | 1 | 1 | 3 | 4 | 4 | 4 | 3 |
| Nausea | | | | | | | |
| Total control (%) | 47 | 27 | 37 | 43 | 54 | 62 | 15 |
| Partial control (%) | 48 | 54 | 46 | 45 | 38 | 34 | 59 |
| No control (%) | 4 | 18 | 15 | 8 | 4 | 0 | 23 |
| Not assessed (%) | 1 | 1 | 3 | 4 | 4 | 4 | 3 |
| Vomiting and nausea combined | | | | | | | |
| Complete response (%) | 38 | 23 | 32 | 41 | 53 | 61 | 12 |
| Partial response (%) | 43 | 44 | 48 | 44 | 38 | 36 | 39 |
| No response (%) | 19 | 31 | 17 | 11 | 6 | 0 | 39 |
| Not assessed (%) | 1 | 1 | 3 | 4 | 4 | 4 | 10 |

Not assessed refers to patients who prematurely discontinued the treatment.

significant differences regarding age, weight, height, coexistent diseases, primary diagnosis or previous cancer treatment between patients allocated to treatment schedules A, B or C. 35 patients were randomized to schedule $B_1$ (tropisetron + placebo) and 28 patients to schedule $B_2$ (tropisetron + dexamethasone). Acute vomiting was completely prevented in 40% after treatment with schedule $B_1$ and in 75% after treatment with schedule $B_2$ ($P = 0.001$, Figure 1). Acute nausea was entirely controlled in 37% by tropisetron + placebo and in 75% by tropisetron + dexamethasone ($P = 0.001$, Figure 2). Significantly more patients on the tropisetron–dexamethasone combination than on the tropisetron–placebo combination were free of delayed vomiting on days 2 to 6 ($P = 0.007$). Delayed nausea was prevented entirely in 71–89% of the patients in the dexamethasone group compared with 9–63% in the placebo group ($P < 0.001$). The significant reduction in the rate of control of nausea on days 2 to 4 seen in course 1 (Table 5) and in the placebo group in course 2 was not noted in the tropisetron–dexamethasone group (Figure 2).

In schedule A (tropisetron monotherapy), 74% of the patients were free of acute vomiting and 63% were free of acute nausea. Partial control was achieved in 26 and 37%, respectively. No treatment failures occurred in this group. Delayed vomiting and nausea were relatively well controlled in this group (Figure 3). In schedule C (tropisetron + open-label rescue), acute vomiting and nausea were controlled in 68% and 63%, comparable to patients on schedules A and $B_2$. However, delayed vomiting (44% on day 3) and nausea (16% on day 3) were less well controlled (Figure 4). The overall (days 1–6) treatment failure, vomiting and nausea combined, in this group was 42%. In 50% of the patients receiving schedule C, a partial response (overall) was recorded and only 3% achieved complete control of both vomiting and nausea during all 6 days of course 2.

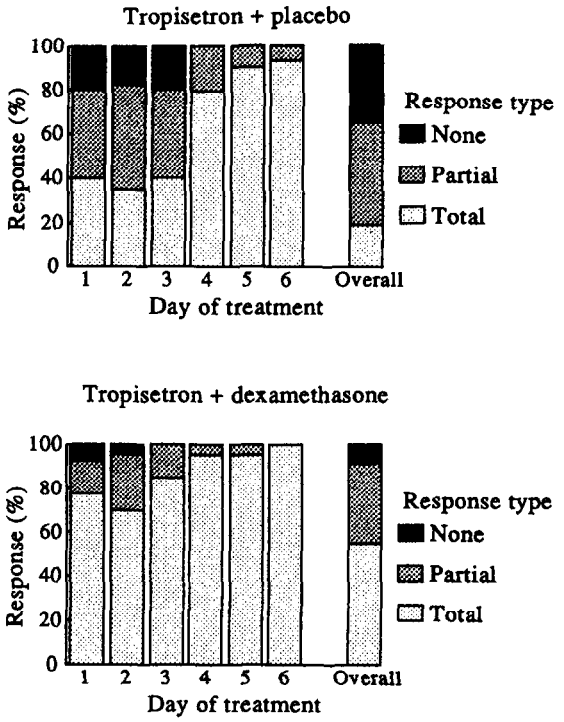


**Figure 1. Prevention of vomiting during the test course (course 2). Patients randomised to tropisetron plus placebo (schedule $B_1$) did significantly ($P = 0.007$) worse than those randomised to tropisetron plus dexamethasone (schedule $B_2$).**

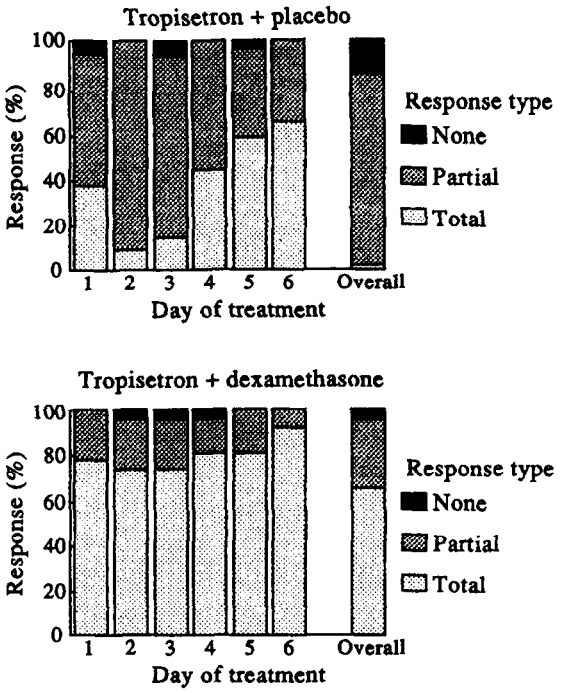


**Figure 2. Prevention of nausea during the test course (course 2). Patients randomised to tropisetron plus placebo (schedule $B_1$) did significantly ($P < 0.001$) worse than those randomised to tropisetron plus dexamethasone (schedule $B_2$).**

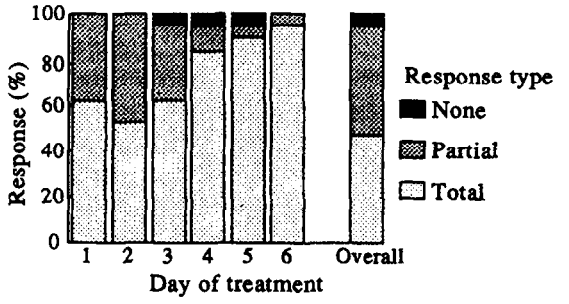


**Figure 3. Prevention of nausea during the test course (course 2) among patients treated with tropisetron monotherapy. All these patients showed complete protection against both nausea and vomiting in the screening course (course 1).**

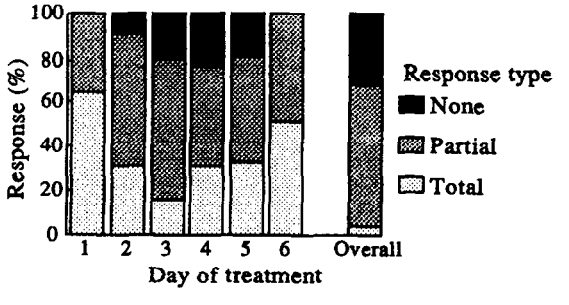


**Figure 4. Prevention of nausea during the test course (course 2) among patients treated with tropisetron plus open-label rescue treatment. The rescue treatment mainly consisted of a corticosteroid and lorazepam. All these patients were treatment failures in the screening course (course 1).**

*Table 6. Adverse events recorded during course 1 (the screening course). Days 1–6 were evaluated*

| Course 1 | Tropisetron monotherapy $n = 160$ | |
|---|---|---|
| | *n* | % |
| Headache | 55 | 34.4 |
| Constipation | 20 | 12.5 |
| Fatigue | 20 | 12.5 |
| Diarrhoea | 15 | 9.4 |
| Dizziness | 13 | 8.1 |
| Abdominal pain | 6 | 3.8 |

The most common adverse events recorded during the first course of chemotherapy were headache (34.4%), constipation (12.5%), fatigue (12.5%), diarrhoea (9.4%), dizziness (8.1%) and abdominal pain (3.8%). Other types of adverse events occurred in only a few patients. No serious adverse reactions probably related to tropisetron were recorded. During course 2, the number of adverse events was lower in the tropisetron monotherapy and the tropisetron + dexamethasone groups than in the tropisetron + placebo and the tropisetron + open rescue treatment groups (Tables 6, 7). No serious adverse events possibly related to the tropisetron–dexamethasone combination were noted.

## DISCUSSION

Tropisetron is an effective first-line antiemetic agent for the prevention of acute cisplatin-induced nausea and vomiting. Tropisetron monotherapy completely prevented both acute vomiting and nausea in approximately 50% of the cases and partial control was achieved in a further 30–40%. Delayed nausea and vomiting were less well controlled. Days 2, 3 and 4 showed the worst control rates, whereas the chemotherapy was given only on day 1 in most of the treatment courses. This has also been demonstrated in other studies, both with 5-$HT_3$ receptor antagonists and other antiemetic treatments, such as various cocktails [7, 18]. Twenty-seven per cent of the patients without nausea and vomiting on day 1 suffered some delayed nausea or vomiting on days 2 to 6. Half of the patients who suffered an incomplete response were treatment failures. Without a placebo comparison, the present study does not allow a direct conclusion as to how effective tropisetron was for the prevention of delayed nausea and vomiting. When nausea and vomiting were combined and the whole treatment period (days 1–6) was analysed, only 12% of the patients were completely free of symptoms after the first course of chemotherapy. Another 39% showed partial responses and 39% no response or treatment failure. However, very strict efficacy criteria were used. In this study, the impact of both acute and delayed emesis (i.e. vomiting and nausea) was taken into account as a cumulative incidence, and classified as overall antiemetic control during a 6-day period after chemotherapy.

*Table 7. Adverse events recorded during course 2 (the test course). Days 1–6 were evaluated*

| Course 2 | Antiemetic schedule | | | |
|---|---|---|---|---|
| | A $n = 19$ *n* (%) | $B_1$ $n = 35$ *n* (%) | $B_2$ $n = 28$ *n* (%) | C $n = 62$ *n* (%) |
| Headache | 3 (15.8) | 12 (34.3) | 3 (10.7) | 20 (32.3) |
| Constipation | 0 (0.0) | 7 (20.0) | 4 (14.3) | 6 (9.7) |
| Fatigue | 2 (10.5) | 2 (5.7) | 1 (3.6) | 5 (8.1) |
| Diarrhoea | 1 (5.3) | 1 (2.9) | 1 (3.6) | 5 (8.1) |
| Dizziness | 0 (0.0) | 2 (5.7) | 2 (7.1) | 7 (11.3) |
| Abdominal pain | 0 (0.0) | 1 (2.9) | 0 (0.0) | 5 (8.1) |

The selection of the antiemetic treatment of course 2 was based on the antiemetic outcome of course 1. This strategy took into account that patients with incomplete control of emesis would suffer more nausea and vomiting during subsequent highly emetogenic chemotherapy than those with complete control during course 1. Thus, the randomised treatment in course 2 was given only to patients with a partial response in course 1. The purpose was to determine whether the randomised treatment of course 2 could produce similar, better or worse control of emesis compared to course 1. If just patients with treatment failure had been randomised, subsequent antiemetic treatments could only produce similar or better, but not worse results. Furthermore, this strategy enabled us to give the patients with a treatment failure in course 1 open-label rescue treatment in course 2, thus avoiding randomisation to the placebo group.

Corticosteroids have documented antiemetic properties when given as monotherapy and in combination with other antiemetic agents, e.g. metoclopramide [10] and the new 5-$HT_3$ receptor antagonists [11]. In two recent studies, ondansetron plus dexamethasone were superior to ondansetron monotherapy for the prevention of acute emesis induced by cisplatin-containing chemotherapy [11], but dexamethasone alone was as effective as ondansetron monotherapy in preventing acute and delayed emesis after treatment with moderately emetogenic non-cisplatin-containing chemotherapy, and significantly more patients on dexamethasone (87%) than on ondansetron (72%) reported control of delayed nausea (days 2–5) [13]. Levitt and colleagues [19] found, in a randomised study of breast cancer patients receiving the CMF regimen, that dexamethasone and metoclopramide prevented acute nausea significantly better than did ondansetron alone. Patients receiving combination therapy had food intakes that equalled or exceeded those of the patients given ondansetron. For emesis prevention, the two regimens were equally effective. Since corticosteroids are potent drugs with known side-effects, they should only be used when single drug regimens of other antiemetic agents are inadequate.

In this study, the combination of tropisetron and dexamethasone was evaluated for patients not fully protected by tropisetron monotherapy. The study was made in a double-blind, placebo-controlled and randomised manner to avoid unwanted bias and placebo effects. The dexamethasone or the placebo was given during all 6 days of the study. This design made it possible to draw conclusions about both acute and delayed nausea and vomiting. Vomiting and nausea were evaluated separately and also combined as acute, delayed and overall results. Nausea was more difficult to prevent than vomiting during both the first 24 h and later on, regardless of the type of antiemetic schedule. Day 2 was the worst day with regard to control of vomiting, and days 2–4 were the worst days regarding prevention of nausea. Patients showing complete control of emesis on tropisetron monotherapy also did well in the second course of chemotherapy. This means that, in a proportion of patients, tropisetron was clearly efficacious for both acute and delayed type of emesis (schedule A). Patients not fully protected by tropisetron monotherapy benefited (improved to complete response or maintained

a partial response) significantly from an addition of dexamethasone, regarding both acute and delayed as well as overall nausea and vomiting. In the tropisetron–dexamethasone group, delayed nausea and vomiting were as well controlled as the acute counterparts. Patients randomised to tropisetron + placebo either maintained a partial response or deteriorated to no response. The difference between the dexamethasone and placebo groups was highly significant for delayed nausea. This is a significant and important conclusion from this study. When rescue treatment (corticosteroid + lorazepam) was given in an open-label manner, as was carried out in this study, the patients with no response in course 1 either improved to partial response or remained no responders in course 2. The addition of open-label rescue treatment was beneficial, but short-lasting (days 1–2) when the corticosteroid and the benzodiazepine were given only on day 1, in contrast to the 6-day dexamethasone administration, which prevented all nausea and vomiting in half of the patients with a previously incomplete control of emesis. Delayed nausea and vomiting were not adequately prevented either in the tropisetron–placebo group or in the group who received open-label rescue treatment. These antiemetic schedules were inferior to the schedule in which dexamethasone was given during all 6 days in relatively high doses (20 mg on day 1 and 9 mg on days 2–6).

The tropisetron treatment was well tolerated. The most frequent adverse events were headache, constipation and fatigue. Diarrhoea and abdominal cramps were also recorded by some patients. Headache and constipation are well-known side-effects of the 5-$HT_3$ receptor antagonists. In this study, the majority of the cases of headache were reported by the patients themselves in diaries and, therefore, comparisons with other studies of 5-$HT_3$ receptor antagonists may be difficult if the source and method of data collection are different. In course 2, there were differences in the frequency of headache in the four groups. The reason for this is not clear, but it merits further exploration. Patients with a good antiemetic response suffered from fewer adverse events than those with a poorer antiemetic response. A certain percentage of the recorded adverse events was probably associated with the toxicity of the chemotherapy and not related to the antiemetic treatment. The addition of high-dose dexamethasone did not produce additional adverse events that would preclude recommendation of its use in combination with tropisetron. No evidence emerged regarding loss of diabetic control or induction of hyperglycaemia, hypertension, or an increased risk of infection. In a few patients, life-threatening pneumocystis carinii pneumonia (PCP)-like infections associated with high dose dexamethasone have been reported by other authors [20].

The patient population studied was at particualr risk for antiemetic treatment failure. Only women with gynaecological cancers were included. Of these, 90% had undergone previous abdominal surgery, and 25% of these had also had previous radiotherapy. Furthermore, all patients received cisplatin chemotherapy, often in combination with other emetogenic agents, particularly anthracyclines. The results of this study justify the recommendation that patients showing incomplete antiemetic control by tropisetron monotherapy should receive additional corticosteroid treatment for all 6 days of an antiemetic treatment course. This regimen is simple, well tolerated and does not produce undue risks associated with either tropisetron alone or tropisetron in combination with high-dose corticosteroids. The optimum dose of the corticosteroid is not known and further dose-finding studies are warranted. Placebo-controlled studies to evaluate the value of tropisetron in prevention of delayed nausea and vomiting should also be performed in the future.


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