Anti-Cancer Drugs 1995, **6**, pp. 514–521

Tropisetron alone or in combination with dexamethasone for the prevention and treatment of emesis induced by non-cisplatin chemotherapy: a randomized trial

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This study compared the efficacy and tolerability of tropisetron (Navoban®, Novaban®) alone or in combination with dexamethasone for the treatment of emesis induced by moderately emetogenic non-cisplatin chemotherapy. In total, 126 patients with cancer, who had never received chemotherapy and who required at least two courses of moderately emetogenic non-cisplatin chemotherapy each lasting for a minimum of 5 days, were recruited into the study. Patients were randomized to receive tropisetron, 5 mg o.d., plus either dexamethasone, 12 mg i.v on day 1 followed by 4 mg orally b.i.d. on days 2–5, or placebo. Greater control of acute and delayed vomiting and nausea was achieved in patients given the tropisetron–dexamethasone combination than in those who received the tropisetron–placebo treatment. The majority of adverse events were mild and could be attributed to the chemotherapeutic regimen used or to the underlying disease. Patients and investigators both rated tropisetron alone or in combination with dexamethasone as a highly effective and well-tolerated antiemetic treatment. The results of this study show that tropisetron, 5 mg o.d., is an effective, well-tolerated and simple to use antiemetic treatment for patients receiving moderately emetogenic non-cisplatin chemotherapy. The addition of dexamethasone increases the efficacy of tropisetron without significantly decreasing its tolerability.

Key words: Dexamethasone, emesis, non-cisplatin chemotherapy, randomized trial, 5-HT_3 receptor antagonist, tropisetron.

Introduction

The treatment of chemotherapy-induced emesis has been improved over the last few years by the development of 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonists, which are effective, easy to administer and well tolerated[1–3]. Although these agents have significantly decreased the problem of acute nausea and vomiting (occurring within the first 24 h after chemotherapy), they do not appear to be better than conventional antiemetics when used alone for the treatment of delayed nausea and vomiting (occurring more than 24 h after chemotherapy).[4–7]

Improved control of emesis can be obtained, however, by combining 5-HT_3 receptor antagonists with corticosteroids such as dexamethasone.[6–10] Schmidt *et al.*, for example, have shown that tropisetron (Navoban®, Novoban®; Sandoz Pharma Ltd, Basle, Switzerland), a highly selective 5-HT_3 receptor antagonist,[11] is an effective, well-tolerated, once-daily treatment for emesis induced by cisplatin-based chemotherapy when used alone and in combination with dexamethasone.[9]

The present study was designed to assess whether the antiemetic efficacy of tropisetron in the treatment of emesis induced by non-cisplatin based chemotherapy could also be enhanced by the addition of dexamethasone.

Patients and methods

Study design

The study was a double-blind, randomized, controlled, parallel group study involving seven centers in the UK. Patients with histologically or cytologically

Research supported by Sandoz Pharma Ltd, CH-4002, Basle, Switzerland.

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confirmed cancer who required moderately emetogenic chemotherapy with agents other than cisplatin were eligible for inclusion. Patients were excluded if they were pregnant or breast feeding, if they had received previous chemotherapy, or if they had any medical condition that could put them at risk or interfere with the evaluation of the study drug (e.g. previous peptic ulcer, diabetes mellitus, untreated hypertension). Patients were also excluded if they had clinical evidence of malignancy of the central nervous system, if they suffered from nausea or vomiting for any reason not directly related to chemotherapy (e.g. reflux disease), if they had a previous adverse reaction to corticosteroids, or if they were taking other concomitant medication or investigational new drug.

Written informed consent was obtained from all patients.

Medication

Patients were given two consecutive courses of chemotherapy, each lasting for up to 5 days. As antiemetic treatment, all patients received tropisetron, 5 mg o.d., given i.v. on day 1 and orally on days 2—5. In addition, patients were randomized to receive either dexamethasone, 12 mg i.v. on day 1 and 4 mg orally b.i.d. on days 2–5, or placebo.

Efficacy evaluation

Primary efficacy variables. Control of acute (day 1) and delayed (days 2–5) vomiting, and acute and delayed nausea, was assessed for each of the two consecutive chemotherapy courses and was graded according to the degree of control (Table 1). Patients recorded the total number of vomits and hours of nausea experienced on daily diary cards. Vomiting was defined as either 'the forceful expulsion of stomach content to the outside, via the mouth' or 'a violent retching without vomitus, when the stomach was empty'. One vomiting event was classed as one vomit or retch and only when one such event was separated from another by at least 15 min without vomiting could it be counted as two events. Nausea was denoted as the feeling of an imminent need to vomit and its duration was used to grade the control of nausea. Efficacy endpoints were defined as control of vomiting and nausea, and were divided into complete (total control), partial (sum of major and minor control) and treatment failure (no control). Patients receiving 'rescue' antiemetic treatment were classified as treatment failures.

Secondary efficacy variables. Control of acute vomiting was analyzed by center and by chemotherapeutic regimen. Patients and investigators also gave an overall assessment of the effectiveness and tolerability of the two antiemetic treatments using a five-point scale at the last study visit before the study was unblinded.

Adverse events

Adverse events were recorded directly onto the adverse events section of the case report form by the investigators. In addition, adverse events identified from patients' diary cards were transcribed onto this form and collated with information provided by the investigators. Serious adverse events were reported separately according to good clinical practice guidelines.

Table 1. Efficacy criteria on days 1–5

	Control of vomiting	Control of nausea	Control of vomiting and nausea combined
Total	no events of vomiting	no nausea	no vomiting and no nausea
Major	one or two events of vomiting	1–2 h of nausea	one or two events of vomiting and/or 1–2 h of nausea
Minor	three or four events of vomiting	2–4 h of nausea	three or four events of vomiting and/or 2–4 h of nausea
No control	five or more events of vomiting	more than 4 h of nausea	five or more events of vomiting and/or more than 4 h of nausea

Evaluations before, during and after treatment

Baseline examinations were carried out in the week preceding the start of the first course of chemotherapy and included an electrocardiogram, a physical examination, and measurement of blood pressure and pulse rate after 3 min of rest. Blood samples were taken for standard hematological and laboratory determinations. These measurements were repeated prior to the start of the second chemotherapy course and 1–5 days after the end of the study (after course 2).

Statistical analysis

Differences in response between treatment groups were assessed by the Mantel–Haenszel test[12] for categorical data and by analysis of variance or the van Elteren test[13] for discrete numerical data. The statistical procedures were adjusted for center differences and the two-sided *p* values presented were based on an average response across centers. The Breslow–Day test[14] was used to determine significant differences in treatment outcomes between centers and to assess the interaction between chemotherapy regimen and antiemetic treatment outcome.

Results

Patient characteristics

The 126 patients (17 men, 109 women) who were entered into the study were well-balanced for baseline characteristics and co-existing disease (Table 2).

Most patients received chemotherapy based on single-agent carboplatin (median dose, 750 mg; interquartile range, 725–900 mg) and cyclophosphamide (median dose, 1000 mg; interquartile range, 750–1190 mg). Carboplatin was used almost exclusively as monotherapy and always given on day 1 only. Cyclophosphamide was combined with other cytostatic agents, predominantly 5-fluorouracil plus either methotrexate or doxorubicin, in 72% of patients, and was given on day 1 in 70% of cases. The other chemotherapy regimens consisted almost entirely of high-dose epirubicin, either alone or in combination with 5-fluorouracil. The chemotherapeutic regimens used in course 2 were identical in composition and similar in dosage to those in course 1, but in some cases doses were decreased by up to 25% in order to avoid repeat bone marrow toxicity.

Thirteen patients in the tropisetron–placebo group stopped treatment during or after course 1, and three patients during course 2; eight patients in the tropisetron–dexamethasone group terminated treatment during or after course 1 and none

Table 2. Patient characteristics

	Tropisetron + placebo	Tropisetron + dexamethasone	*p* value[a]
No. of patients entered	63	63	
Starting treatment			
course 1	63	63	
course 2	50	55	
Completing treatment			
course 1	59	60	
course 2	47	55	
Males	8 (13%)	9 (14%)	0.8
Females	55 (87%)	54 (86%)	
Mean age (years)	52	51	0.9
Mean weight (kg)	66.2	66.4	0.9
Mean height (cm)	162	163	0.6
No. of patients with			
co-existent diseases	33 (52%)	30 (48%)	0.6
prior medication	45 (71%)	50 (79%)	0.2
concomitant medication	46 (73%)	53 (84%)	0.1

[a]The *p* values result from statistical tests to investigate the differences between treatment groups adjusting for center. The van Elteren test was used for age, height and weight, otherwise the Mantel–Haenszel test was used.

during course 2. Most discontinuations were related to the underlying cancer or to complications of chemotherapy and only three patients in the tropisetron–placebo group stopped treatment because of inefficacy.

Control of vomiting

Total control of acute and delayed vomiting over the two courses of chemotherapy is shown in Figure 1. Total control of acute vomiting (occurring in the first 24 h after chemotherapy, i.e. on day 1) was achieved in 75% of patients in the tropisetron–placebo group and in 89% of patients in the tropisetron–dexamethasone group during the first course of chemotherapy ($p = 0.032$) and in 76 and 96%, respectively, during the second course of chemotherapy ($p = 0.001$). Total plus partial control was above 89% in both treatment groups and did not differ significantly between the two courses of chemotherapy.

There was greater total control of delayed vomiting (occurring more than 24 h after chemotherapy, i.e. on days 2–5) in the tropisetron–dexamethasone group than in the tropisetron–placebo group. In course 1, total control was achieved in 81 and 59% of patients respectively ($p = 0.002$), while in course 2 the corresponding values were 85 and 66% ($p = 0.006$). These percentages were based on a worst-day analysis, where the day with the worst antiemetic outcome for each patient was chosen for statistical evaluation.

More patients in the tropisetron–placebo group had major control of delayed vomiting. In course 1, major control of vomiting was achieved in 21% of patients in the tropisetron–placebo group compared with 8% in the tropisetron–dexamethasone group. The corresponding figures in course 2 were 20 and 7%, respectively.

The proportion of patients with minor control of delayed vomiting and in whom treatment failed did not differ significantly between the two antiemetic groups.

Control of nausea

Figure 2 shows the number of patients with total control of acute and delayed nausea in the two treatment groups, based on a worst-day analysis. During course 1, total control of acute nausea was achieved in 43% of patients in the tropisetron–pla-

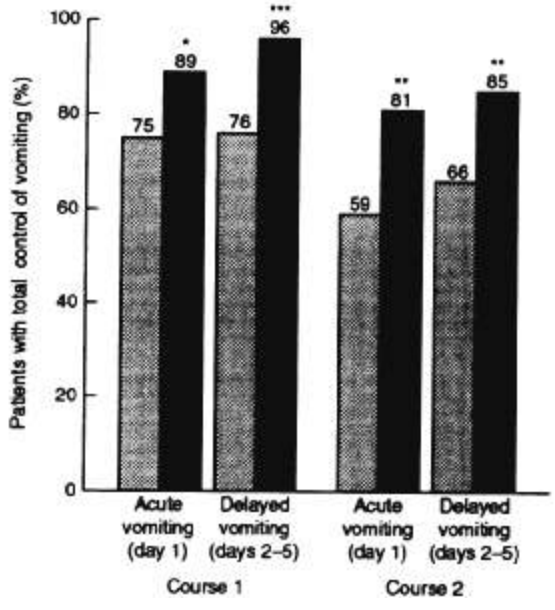

Figure 1. Total control of vomiting over two courses of chemotherapy based on a worst-day analysis. ▨, Tropisetron plus placebo; ■, tropisetron plus dexamethasone. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with tropistron plus placebo.

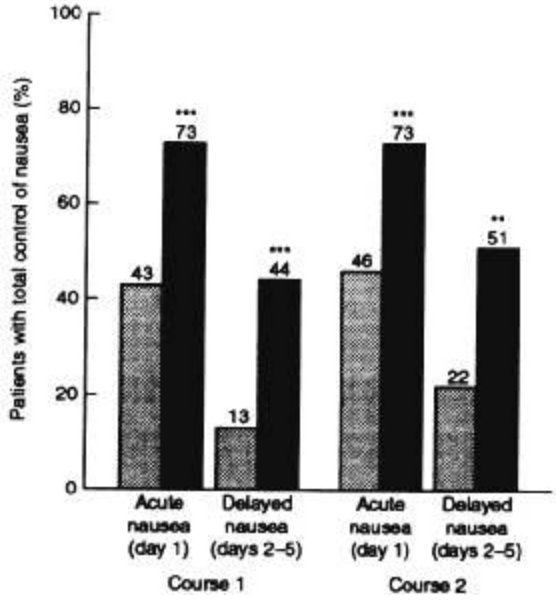

Figure 2. Total control of nausea over two courses of chemotherapy based on a worst-day anlaysis. ▨, Tropisetron plus placebo, ■; tropisetron plus dexamethasone. $^{**}p < 0.01$, $^{***}p < 0.001$ compared with tropisetron plus placebo.

cebo group and in 73% of patients in the tropisetron–dexamethasone group ($p = 0.001$). Partial control of acute nausea was achieved in 28 and 18% of patients in each group, respectively. Similar results were achieved during course 2. Total plus partial control of acute nausea was greater in the tropisetron–dexamethasone group than in the tropisetron–placebo group in course 1 (91 versus 71%, $p = 0.008$) but not in course 2 (93 versus 84%, p 0.187).

Based on a worst-day analysis, total control of delayed nausea was significantly higher in the tropisetron–dexamethasone group than in the tropisetron–placebo group. In course 1, total control of delayed nausea was achieved in 44% of patients in the tropisetron–dexamethasone group and in 13% in the tropisetron–placebo group ($p = 0.001$). In course 2, the corresponding figures were 51 and 22% ($p = 0.002$). There was partial control of delayed nausea in 24 and 35% of patients in the tropisetron–placebo and the tropisetron–dexamethasone groups, respectively, during course 1, and in 38% and 20%, respectively, during course 2. The proportion of patients with delayed nausea in whom treatment failed was higher in the tropisetron–placebo group than in the tropisetron–dexamethasone group. During course 1, 57% of patients in the tropisetron–placebo group failed treatment compared with 16% in the tropisetron–dexamethasone group ($p < 0.001$). The corresponding values during course 2 were 48 and 24%, respectively. In courses 1 and 2 appropriate assessment of the relevant efficacy data, as per the study protocol, was not achieved in 6% of patients in the tropisetron–placebo group and 5% of patients in the tropisetron–dexamethasone group. Consequently, these patients were not assessed.

Overall control of vomiting and/or nausea

Overall total plus partial control of vomiting and nausea combined on days 1–5 is shown in Figure 3. The tropisetron–dexamethasone combination yielded higher total control rates of nausea and vomiting combined than the tropisetron–placebo combination over the two courses of chemotherapy ($p < 0.001$). Total plus partial control of vomiting and nausea combined was achieved in 34% of patients in the tropisetron–placebo group and 75% of patients in the tropisetron–dexamethasone group during course 1, and 44 and 70% of patients, respectively, during course 2.

Vomiting was completely prevented during

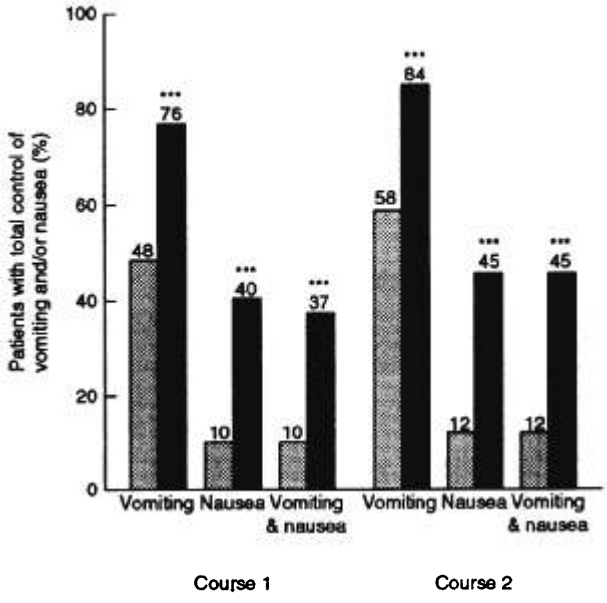

Figure 3. Overall control of vomiting and nausea combined on days 1–5. ▨, Tropisetron plus placebo; ■, tropisetron plus dexamethasone. ***$p < 0.001$ compared with tropisetron plus placebo.

course 1 in 48% of patients in the tropisetron–placebo group and in 58% of patients during course 2, with major protection in a further 24 and 26% of patients in course 1 and 2, respectively. Patients in the tropisetron–dexamethasone group had a significantly higher rate of overall control of vomiting, 76% in course 1 ($p < 0.001$) and 84% in course 2 ($p < 0.001$). In addition, the rates of total plus partial control of vomiting were superior in this group compared with the tropisetron–placebo group during course 1 (92 versus 82%, $p = 0.032$), but not during course 2 (93 versus 90%, $p = 0.348$).

Patients in the tropisetron–dexamethasone group had higher rates of total control of nausea than patients in the tropisetron–placebo group during both courses of chemotherapy (40 versus 10%, $p < 0.001$ in course 1; 45 versus 12%, $p < 0.001$ in course 2).

Secondary efficacy criteria

No difference was found between centers in total or total plus partial control of acute vomiting in either of the two treatment groups ($p > 0.05$, Breslow Day test). Additionally, no differences were found in the control of total or total plus partial control of acute vomiting between the two principal chemotherapy groups used in this study.

In the overall assessment made at the end of the study, both investigators and patients rated the efficacy of the tropisetron–dexamethasone treatment higher than that of the tropisetron–placebo combination. The tolerabilities of the two treatments, however, were given similar ratings by both investigators and patients (Table 3).

Safety evaluation

The majority of adverse events were identified from the patients' diaries (75% in course 1 and 81% in course 2) and were generally mild. Most adverse events were ascribed to the underlying cancer and to the sequelae of the chemotherapy, and many of the adverse events in course 2 were recurrences of adverse events already recorded in the same patients in course 1.

The most frequent side-effects in the tropisetron–placebo group over the two courses of chemotherapy were headaches ($n=52$) and constipation ($n=26$), both of which are known side-effects of 5-HT_3 receptor antagonists. These side-effects also occurred with a similar frequency in the tropisetron dexamethasone group. Overall, patients in the tropisetron–dexamethasone group experienced more episodes of dyspepsia ($n=25$), dizziness (n = 13), insomnia ($n=16$) and flushing ($n=16$) than those in the tropisetron–placebo group ($n=8$, 7, 2 and 4, respectively) over the two courses of chemotherapy, but experienced fewer headaches during the second course of chemotherapy. These differences may be attributable to dexamethasone.

Six patients in the tropisetron–dexamethasone group discontinued chemotherapy and antiemetic treatment prematurely as a result of adverse events, compared with four in the tropisetron–placebo group. In seven of these patients, discontinuation was attributable to the sequelae of the underlying cancer or to the chemotherapy. In the tropisetron–dexamethasone group, one patient developed hematemesis and two developed heartburn, which were attributed to dexamethasone.

The most common hematological abnormalities at the end of the study were newly occurring thrombocytopenia ($n=7$), leucocytopenia ($n=18$) and anemia ($n=23$). Two patients with pre-existing anemia experienced a worsening of their condition. These abnormalities were attributed to the aggressive chemotherapy regimens used.

One patient entered the study with an elevated level of aspartate aminotransferase (AST) and another with an elevated level of alanine amino transferase (ALT). Neither of these two patients experienced any further increase in the levels of AST or ALT. A transient rise in the level of AST, but not of ALT, occurred in two patients, which was attributed to high-dose methotrexate and carboplatin treatment. The most common biochemical abnormalities at the start of the study were elevated levels of γ-glutamyltransferase (γ-GT) ($n=20$) and alkaline phosphatase (ALP) ($n=5$). Many of the patients with these abnormalities, however, suffered from bone and/or liver metastases, which may account for these findings. Two patients experienced a transient rise in the level of ALP and five in the level of γ-GT. The most likely explanations for these findings were tumour progression and treatment with high-dose methotrexate.

Discussion

The results of this study show that tropisetron, alone or in combination with dexamethasone, is an effective antiemetic treatment during moderately emeto-

Table 3. Percentage of investigators and patients rating the efficacy and tolerability of the two antiemitic treatments as good or very good

Treatment group	Efficacy rated as good or very good		Tolerability rated as good or very good	
	Investigators (%)	Patients (%)	Investigators (%)	Patients (%)
Course 1				
tropisetron + placebo	68	68	82	81
tropisetron + dexamethasone	83	84	84	81
Course 2				
tropisetron + placebo	59	62	78	82
tropisetron + dexamethasone	89	86	74	81

monotherapy and tropisetron in combination with dexamethasone provided good control of acute nausea and vomiting and delayed vomiting over two courses of chemotherapy. During course 1, for example, total control of acute vomiting was achieved in 75% of patients receiving tropisetron monotherapy and in 89% of patients receiving the tropisetron–dexamethasone combination. The corresponding figures for delayed vomiting were 59 and 81%, and for acute nausea were 43 and 73%. Based on a worst-day analysis, however, tropisetron alone or in combination was less effective in controlling delayed nausea than acute vomiting and nausea and delayed vomiting, with only 13% of patients in the tropisetron–placebo group and 44% of patients in the tropisetron–dexamethasone group achieving total control of delayed nausea during course 1. In all cases the antiemetic efficacy of tropisetron was enhanced by the addition of dexamethasone. This finding supports the results of previous studies, which show that the addition of dexamethasone enhances the antiemetic efficacy of tropisetron during cisplatin chemotherapy.[9,15]

The present study also provides further evidence that delayed nausea is the most difficult form of emesis to treat. The addition of dexamethasone to tropisetron significantly improved the control of delayed nausea and therefore had a large impact on the overall outcome of vomiting and nausea combined. As the ultimate goal of antiemetic treatment is to alleviate all nausea and vomiting during the entire chemotherapy course, the results of the present study confirm the value of combination antiemetic therapy consisting of a 5-HT_3 receptor antagonist and a high-dose corticosteroid.[15]

The difference between the results for acute and delayed emesis may stem from a different pathophysiology of these two entities and could suggest that 5-HT_3 receptors do not play a major role in delayed emesis. This may explain why adding dexamethasone, which acts on receptors other than those for 5-HT_3, enhances the efficacy of tropisetron in the treatment of delayed nausea. As delayed nausea remains difficult to treat, it is also possible that factors other than chemotherapy play a role. For example, nausea could be an expression of general malaise or anxiety which manifests itself on the days after chemotherapy when the patient has returned home.

On questioning, patients and investigators both thought that tropisetron alone or in combination with dexamethasone was a highly effective and well tolerated antiemetic treatment. The main side-effects reported were headache and constipation for tropisetron monotherapy, both of which are known side-effects of 5-HT_3 receptor antagonists. The addition of dexamethasone to tropisetron increased the frequency of dyspepsia, flushing and insomnia compared with the tropisetron–placebo combination. Moreover, only three out of 126 (2%) of patients in the tropisetron–dexamethasone group experienced severe heartburn and dyspepsia, which were attributed to the dexamethasone and were reasons for patients withdrawing prematurely from the study. Other adverse events were often attributed to the underlying cancer, the chemotherapy or co-existent disease. Of particular note was that no diabetic complications were reported in patients treated with tropisetron and dexamethasone.

In conclusion, tropisetron, 5 mg o.d, is an effective, well-tolerated and simple to use antiemetic monotherapy for patients receiving moderately emetogenic non-cisplatin chemotherapy. The addition of relatively high doses of dexamethasone during five consecutive days of chemotherapy enhances the effectiveness of tropisetron and is generally well tolerated, although some side-effects emerged that warrant caution when using this combination routinely.

References

1. Bruntsch U, Rüfenacht E, Parker I, *et al.* Tropisetron in the prevention of chemotherapy-induced nausea and vomiting in patients responding poorly to previous conventional antiemetic therapy. *Ann Oncol* 1993; **4** (Suppl 3): S25–9.
2. Gralla RJ, Current issues in the management of nausea and vomiting. *Ann Oncol* 1993; **4** (Suppl 3): S3–7.
3. Sorbe BG, Hogberg T, Glimelius B, *et al.* A randomized, multicentre study comparing the efficacy and tolerability of tropisetron, a new 5-HT_3 receptor antagonist, with a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin induced emesis. *Cancer* 1994; **73**: 445–54.
4. Marty M. Ondansetron in the prophylaxis of acute cisplatin-induced nausea and vomiting. *Eur J Cancer* 1989; **25** (Suppl 1): S41–5.
5. Tabona MV. An overview on the use of granisetron in the treatment of emesis associated with cytostatic therapy. *Eur J Cancer* 1990; **26** (Suppl 1): S37–41.
6. De Bruijn K. Topisetron: a review of the clinical experience. *Drugs* 1992; **43** (Suppl 3): 11–22.
7. Aapro MS. Review of experience with ondansetron and granisetron. *Ann Oncol* 1993; **4** (Suppl 3): S9–14.
8. Cunningham D, Turner A, Hawthorn J, *et al.* Ondansetron with and without dexamethasone to treat chemotherapy-induced emesis. *Lancet* 1989; **337**: 1323.
9. Schmidt M, Sorbe B, Högberg T, *et al.* Efficacy and tolerability of tropisetron and dexamethasone in the

control of nausea and vomiting induced by cisplatin. *Ann Oncol* 1993; **4** (Suppl 3): S31–4.
10. Jantunen IT, Kataja VV, Johansson RT. Ondansetron and tropisetron with dexamethasone in the prophylaxis of acute vomiting induced by non-cisplatin-containing chemotherapy. *Acta Oncol* 1992; **31**: 573–5.
11. Kutz, K. Pharmacology, toxicology and human pharmacokinetics of tropisetron. *Ann Oncol* 1993; **4** (Suppl 3): S15–8.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719–48.
13. Van Elteren PH. On the combination of independent two sample tests of Wilcoxon. *Bull Int Statistical Inst* 1958; **37** (part 3): 351–61.
14. Breslow NE, Day NE. The analysis of case-controlled studies. In: Davis W, ed. *Statistical methods in cancer research* Lyon: International Agency for Research on Cancer 1980: 1.
15. Kris MG, Baltzer L, Pisters KMW, *et al.* Enhancing the effectiveness of the specific serotonin antagonists. *Cancer* 1993; **72**: 3436–42.

(Received 25 April 1995; accepted 18 May 1995)