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Original Paper

A Double-blind Crossover Study Comparing Prophylactic Intravenous Granisetron Alone or in Combination with Dexamethasone as Antiemetic Treatment in Controlling Nausea and Vomiting Associated with Chemotherapy

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The efficacies of granisetron plus dexamethasone and granisetron alone in controlling nausea and vomiting during two consecutive cycles of moderately emetogenic chemotherapy given for up to 5 days were compared in a two-centre, randomised, double-blind, placebo-controlled crossover study. In all, 110 evaluable patients received either dexamethasone, 20 mg i.v., or matching placebo, plus open-label granisetron, 3 mg i.v., given on each chemotherapy day. At cycle 2, patients crossed over to the alternative treatment; 72 patients completed the crossover. In these 72 patients, the complete response rates over 24 h for granisetron plus dexamethasone and granisetron plus placebo in cycle 1 were 87% and 70% (ns), respectively. In cycle 2 the complete response rates over 24 h were 73% and 62% (ns). Combining the two cycles, the complete response rates over 24 h were 80.6% (granisetron plus dexamethasone) and 65.3% (granisetron plus placebo; $P = 0.015$). Granisetron plus dexamethasone was significantly more effective in terms of times to less than complete response ($P = 0.041$), to first episode of moderate/severe nausea ($P = 0.04$), to first episode of vomiting (0.03) and to use of rescue medication ($P = 0.02$). Adverse events tended to be minor, with asthenia and insomnia the most common. Of those patients who expressed a preference, 67% prefered granisetron plus dexamethasone ($P < 0.05$). A single dose of dexamethasone added to granisetron thus enhances the efficacy of granisetron alone in preventing nausea and vomiting after moderately emetogenic chemotherapy. © **1997 Elsevier Science Ltd.**

Key words: intravenous granisetron, prophylaxis, dexamethasone, antiemesis, chemotherapy
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INTRODUCTION

NAUSEA AND vomiting are two of the most commonly reported side-effects of chemotherapy for cancer [1] and may be severe enough to deter patients from continuing therapy [2]. In recent years the increasing use of chemotherapy regimens based on cisplatin has improved clinical efficacy, although this agent is highly emetogenic. Chemotherapy often involves combinations of agents and appropriate antiemetic treatment must be used to control emesis associated with all the components of the combination [3].

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The effectiveness of corticosteroids in controlling chemotherapy-induced emesis was first noted when the MOPP regimen (mustine–vincristine–procarbazine–prednisolone) was given for treatment of Hodgkin's disease; the cycles containing prednisolone (two out of six cycles) were tolerated better with respect to emesis than those not containing prednisolone [4]. Although since then many studies have shown the effectiveness of corticosteroids in preventing chemotherapy-induced acute nausea and vomiting, relatively few have concerned moderately emetogenic chemotherapy or fractionated high doses of cisplatin. Despite this, the experience accumulated before the advent of the 5-HT_3 receptor antagonists indicated that methylprednisolone and dexamethasone, given repeatedly at high doses, were the most effective antiemetic agents against moderately emeo-

genic chemotherapy [5–10], without the side-effects associated with metoclopramide or prochlorperazine [6–9].

The 5-HT_3 receptor antagonists have also proved to be effective antiemetic agents against moderately emetogenic chemotherapy regimens, and both granisetron [11–17] and ondansetron [18–23] typically achieve complete response rates of 70–80% during the first 24 h. Moderately emetogenic chemotherapy is often given as fractionated regimens, repeated for several cycles and controlled trials have shown that not only can complete response rates fall over subsequent days [13, 24] and in subsequent cycles [25, 26], but also that a minority of patients are not optimally controlled by 5-HT_3 receptor antagonists alone and would benefit from addition of another antiemetic agent with a different mechanism of action [27].

Preliminary results in ferrets [28, 29] and humans [30, 31] suggested that addition of dexamethasone to a 5-HT_3 receptor antagonist could improve the control of acute nausea and vomiting following moderately emetogenic chemotherapy, findings that have been supported by the results of two recent randomised, double-blind, parallel-group studies [14, 15]. The aim of the present study was to assess the efficacy and tolerability of the combination of granisetron and dexamethasone compared with granisetron alone in controlling acute emesis in patients receiving two consecutive, identical doses of moderately emetogenic chemotherapy, including fractionated cisplatin.

PATIENTS AND METHODS

The study was a randomised, double-blind, placebo-controlled, crossover trial conducted in two centres in the French-speaking region of Switzerland. It was performed in accordance with the Declaration of Helsinki and was approved by the ethical review committee of the Hôpital Cantonal Universitaire de Genève. All patients gave written informed consent.

Patients over 18 years of age were eligible for inclusion if they were scheduled to receive two identical consecutive courses of chemotherapy lasting up to 5 days each, and if they had a WHO performance status score of 2 or less. Patients were excluded if they had marked hepatic dysfunction, congestive heart failure (NYHA grades III or IV), pre-existing acute or chronic nausea and/or vomiting, active peptic ulceration, primary or secondary brain tumours, gastric compression or gastro-intestinal tumours likely to lead to subacute obstruction, or previous gastrectomy. Other exclusion criteria were a change in dose of central nervous system (CNS)-active medication (except short-acting benzodiazepines) within 1 week of the study, scheduled treatment with corticosteroids (other than dexamethasone or those given as part of the chemotherapy regimen), other antiemetic drugs, concomitant upper abdominal radiotherapy, use of any investigational new drug in the 1 month before or during the study, or know sensitivity or reaction to steroids.

Patients were screened for inclusion a maximum of 14 days before the start of the study.

Chemotherapy

Patients received one of the chemotherapeutic drugs listed in Table 1, either as monotherapy or combined with other cytotoxic agents. Any other non-emetogenic chemotherapy was administered as normal. Cisplatin was usually given at a rate of 1 mg/min, administered first in any combination regimen. Chemotherapy was given either on day 0 only or as a fractionated regimen for up to 5 days (days 0–4). Those patients who completed the first course of chemotherapy returned (typically after 3 weeks) for a second identical course.

Table 1. Chemotherapeutic agents administered. Other cytotoxic agents were allowed with these agents, and other non-emetogenic chemotherapy was administered as usual

Chemotherapeutic agent	Dose (mg/m^2)	Percentage of patients ($n = 72$)*
Carboplatin	>300	7 (5/72)
Cisplatin	>20 daily up to day 4	36 (26/72)
Cyclophosphamide	>600	3 (2/72)
Darcarbazine	>350	1 (1/72)
Doxorubicin	>25	15 (11/72)
Other chemotherapy		38 (27/72)

*Only patients who completed both arms of the crossover

Antiemetic therapy

At 30 min before the start of chemotherapy on day 0, patients were randomised to receive either a standard intravenous dose of dexamethasone, 20 mg, or matching placebo, infused over 25 min. All patients then received intravenous granisetron, 3 mg, infused over 5 min. For fractionated chemotherapy regimens, the above antiemetic regimen was followed on each day, for a maximum of 5 days of chemotherapy (days 0–4). If nausea and vomiting occurred after the initial dose of granisetron, patients could receive up to two additional doses of granisetron by slow intravenous infusion. Patients whose nausea and vomiting was not adequately controlled by the additional doses of granisetron were withdrawn from the study and given another antiemetic of their physician's choice.

At the second treatment cycle, patients crossed over to receive the alternative antiemetic treatment (granisetron plus dexamethasone or placebo), administered as before.

Granisetron (SmithKline Beecham, Thörishaus, Switzerland) was supplied as open-label ampoules containing a minimum of 3 mg. Dexamethasone, 20 mg, and its matching placebo were supplied by E. Merck (Darmstadt, Germany). Active dexamethasone and placebo were indistinguishable on shaking, thus ensuring that the study blinding was maintained.

Evaluation of efficacy

The same procedures were followed in both chemotherapy courses. Patients were either monitored as in-patients for the duration of their chemotherapy (up to 5 days) or could be discharged 2 h after receiving chemotherapy. The patients' subjective assessments of nausea and vomiting were recorded retrospectively for each 24 h period to the end of chemotherapy. After discharge, patients recorded their assessments for 5 days on diary cards which were returned at the start of the second course and at the follow-up visit 6–14 days after the start of the second chemotherapy course. Nausea was recorded as none, mild, moderate or severe; the number of vomiting (including retching) episodes was recorded as none, one, two, three, four or more than four.

Table 2. Patient characteristics at randomisation

Variable	Treatment group at first cycle	
	Granisetron plus dexamethasone ($n = 56$)	Granisetron plus placebo ($n = 54$)
Males/females (number of patients)	34/22	33/21
Mean age (years)	55.5	53.8
Range	(18–82)	(22–74)
Mean height (cm)	168.3	168.0
Mean weight (kg)	65.6	66.0
Range	(47–87.7)	(44–103)
Alcohol consumption (number of patients)		
<10 units/week	34	38
10–20 units/weeks	15	7
>20 units/week	7	9
WHO performance status score (number of patients)		
0	9	5
1	39	38
2	8	11
Chemotherapy naive (number of patients)	37	39
Primary tumour site (percentage of patients)		
Lung	32.1	27.8
Lymphoma	12.5	16.7
Breast	8.9	13.0
Stomach	8.9	9.3

Complete response (no moderate or severe nausea, no vomiting, no rescue antiemetics and no withdrawal from treatment) was assessed over the first 24 h of each chemotherapy course. Patients who were not complete responders were defined as non-responders. In addition, analyses of time to less than complete response, to first episode of vomiting, to first episode of moderate/severe nausea and to use of rescue antiemetics during chemotherapy were performed over the whole chemotherapy period.

Both intention-to-treat and efficacy-evaluable analyses were performed and gave similar results.

Patient and physician preference

Both patients and physicians were asked after the end of the second chemotherapy course to express their preference for antiemetic treatment as session 1, session 2 or no preference.

Tolerability

Blood pressure, heart rate and temperature were measured before the administration of antiemetic drugs on day 0 of each chemotherapy course and on each following day of chemotherapy up to a maximum of 5 days. Routine haematological and biochemical tests were performed at the same times.

Adverse events reported by the patients or observed by clinicians were recorded for each 24 h period of each chemotherapy course, during the diary card period, at the start of the second course of chemotherapy and at the final follow-up visit. For each adverse event, the duration, frequency, severity and outcome were noted, together with details of any treatment given. Clinicians also assessed the relationship of the adverse event to study treatment.

Statistical analysis

Statistical analysis was carried out using the data presented as a crossover trial. Where appropriate, statistical analysis of the parallel trial data was used to confirm the crossover results.

In the crossover analysis, categorical data and cycle effects were compared with the Mainland–Gart test. Treatment by cycle interactions for complete responders were assessed with the Hills and Armitage test, confirmed by Prescott's test. Crossover survival data were analysed using the method proposed by France and associates [32]. Confidence intervals for the odds ratio were calculated by the case–control Mantel–Haenzel test.

RESULTS

Unless otherwise stated, the results given below relate to the crossover analysis.

Patients' characteristics

A total of 111 patients of Caucasian origin entered the study, of whom one did not receive study medication or chemotherapy due to disease progression. Approximately 40% of the patients had local or distant/widespread metastases. Of the 110 intention-to-treat patients, 76 were receiving chemotherapy for the first time.

During cycle 1, 56 patients received granisetron plus dexamethasone and 54 received granisetron plus placebo. The two groups were well matched for demographic variables (Table 2). Thirty-nine patients in the granisetron plus dexamethasone group and 33 patients in the granisetron plus placebo group crossed over. Thus, during cycle 2, 33 patients received granisetron plus dexamethason and 39 received granisetron plus placebo. In total, 38 patients failed to complete both cycles: for 32 of these only cycle 1 data were available, and for another 6 patients only baseline cycle 2 data were recorded. In total, 72 patients crossed over as intended. In cycle 1, additional granisetron was required by 18/33 patients (55%) in the granisetron plus placebo group and by 13/39 patients (33%) in the granisetron plus dexamethasone group. This trend was also evident

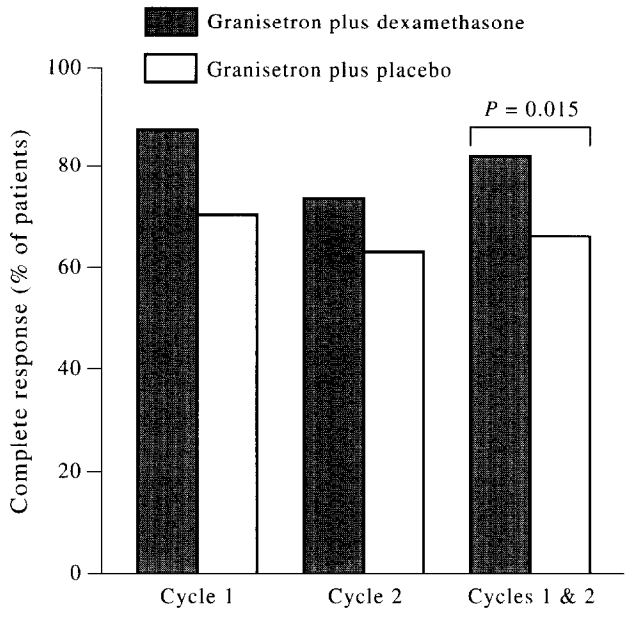

Figure 1. Complete response rates over the first 24 h of chemotherapy in patients who completed the crossover.

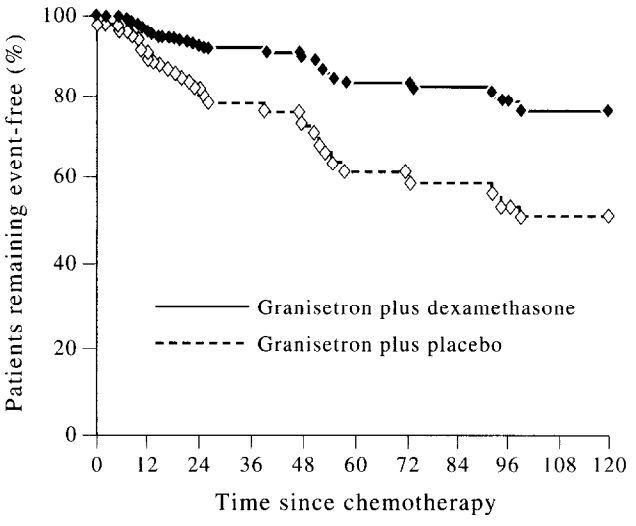

Figure 2. Time to first episode of vomiting over cycles 1 and 2 of chemotherapy (crossover analysis), based on average survivor function and Cox model regression coefficient.

in cycle 2, when 9 patients (27%) receiving granisetron plus dexamethasone needed rescue medication compared with 17 (44%) in the granisetron plus placebo group.

Cisplatin plus doxorubicin or 5-fluorouracil were the cytostatic treatments most commonly administered (Table 1). Most of the patients received their chemotherapy over 1 day only.

Complete responses

The complete response rates over the first 24 h of each treatment cycle for patients who crossed over are shown in Figure 1. Combining cycles 1 and 2 , the complete response rate over 24 h for those patients who crossed over was 80.6% (58/72) for the granisetron plus dexamethasone group and 65.3% (47/72) for the granisetron plus placebo group ($P = 0.015$). There was no evidence of a carry-over effect. A cycle effect was identified, however, with a higher proportion of complete responders over 24 h in cycle 1 than in cycle 2 ($P = 0.051$). The superiority of the combination of granisetron plus dexamethasone was confirmed by the parallel-group analysis, which in cycle 1 showed a significant difference in complete response rates (granisetron plus dexamethasone, 84% (47/56); granisetron plus placebo, 63% (34/54); $P = 0.013$). In cycle 2, 73% (24/33) on granisetron and dexamethasone and 62% (24/39) on granisetron plus placebo had a complete response.

Patient preference

Of the 43 patients who crossed over and expressed a preference, 67% (29/43) preferred the combination of granisetron plus dexamethasone ($P = < 0.05$), although 29 patients expressed no preference. No cycle effect was observed.

Subgroup analyses

The proportion of complete responders over the first 24 h was also analysed by age, sex, alcohol consumption and naivety to chemotherapy. The proportions of complete responders were higher in elderly patients (over 65 years) and in patients who consumed 10–20 units/week of alcohol. Neither sex nor naivety to chemotherapy influenced the complete response rate.

Other efficacy variables

Granisetron plus dexamethasone was significantly more effective than granisetron plus placebo over the whole chemotherapy period in terms of time to less than complete responses ($P = 0.041$), time to first episode of moderate/severe nausea ($P = 0.04$), time to first episode of vomiting ($P = 0.03$) (Figure 2) and time to use of rescue antiemetic medication ($P = 0.02$). No cycle effects were detected. In addition, more physicians preferred the combination treatment ($P < 0.05$).

Tolerability and safety

There were no significant differences in the safety profiles of the two antiemetic regimens. The most common adverse effects, which included abdominal pain, asthenia, constipation, fever, headache and insomnia, tended to be minor and were reported by 92/110 patients in cycle 1 and by 51/72 in cycle 2. Adverse events were evenly distributed between the two groups: in cycle 1, 44 patients (78.6%) receiving granisetron plus dexamethasone and 48 (88.9%) receiving granisetron plus placebo reported adverse events, compared with 23 (69.7%) and 28 (71.8%), respectively, in cycle 2 (non-significant). Mean changes in heart rate, blood pressure and temperature were small and similar in the two groups.

Overall, a total of 24 patients reported serious adverse events (13 in patients receiving granisetron plus dexamethasone and 11 in patients receiving granisetron plus placebo). None of the serious adverse events was related to study medication; all were due to the underlying disease or its treatment.

At cycle 1, adverse events or deaths leading to withdrawal were reported in 13 patients (including 5 who died) who received granisetron plus placebo and 8 (including 4 who died) who received granisetron plus dexamethasone; 3 patients withdrew at cycle 2. None of the adverse events leading to death or withdrawal was considered to be drug related.

DISCUSSION

Although single cisplatin doses below 50–60 mg/m^2 are less emetogenic than single high doses [33], and non-cisplatin chemotherapy is usually considered as only moderately emetogenic, the emetogenic potential of these regimens should not be underestimated. For example, cyclophosphamide–methotrexate–5-fluorouracil produces nausea and vomiting in 70–90% of patients, which may be severe in 50–60% [34, 35].

The question of whether 5-HT$_3$ receptor antagonists have any advantage over corticosteroids or whether a combination of the two types of agent would further improve the control of acute and/or delayed emesis following moderately emetogenic chemotherapy has been examined in several studies, with somewhat conflicting results. In the study of Jones and associates [22], ondansetron was equally effective compared with dexamethasone in controlling acute nausea and vomiting, although dexamethasone was more effective against delayed nausea. In three other studies, however, granisetron was more effective and less toxic than dexamethasone plus a phenothiazine [11, 12, 16], but the efficacy of phenothiazines is doubtful and dexamethasone was given only as a single dose. Two randomised, double-blind, parallel-group studies have recently shown the benefit of using a combination of antiemetic agents for acute emesis in patients receiving moderately emetogenic chemotherapy [14, 15]. Thus, granisetron, 3 mg i.v., plus dexamethasone, 8 mg i.v., produced a complete response in 85% of patients compared with 75.9% receiving granisetron alone ($P = 0.053$) [14]. Similarly, complete protection from vomiting and from nausea were achieved in 70.6% and 55.1% of patients given dexamethasone, in 72.3% and 48.2% of those receiving granisetron alone and in 92.6% and 71.9% of those receiving granisetron plus dexamethasone ($P < 0.001$) [15].

In the study reported here, a number of patients withdrew after the first cycle of antiemetic treatment. Withdrawal was not random and for example, patients who did not respond in the first cycle tended to withdraw. Despite this, the crossover data are statistically valid and are supported by the results of parallel-group analysis. The reasons for a selective withdrawal warrant further investigation, particularly as they reflect clinical experience and highlight the problems of such studies in patients with cancer.

In cycle 1, the complete response rate over the first 24 h achieved with granisetron plus dexamethasone (87%) was higher than with granisetron plus placebo (70%). These findings are similar to those of other studies comparing granisetron plus dexamethasone with granisetron plus placebo [14, 15], and clearly show the benefit of adding dexamethasone to granisetron to control acute emesis following moderately emetogenic chemotherapy. It is also interesting to note that 65% (72/110) of the study population were low alcohol consumers, a group in whom control of acute emesis is more difficult to achieve [36]; however, only 39% (43/110) of the study population were women, who as a group are usually poorly responsive to antiemetic treatment.

The complete response rates over 24 h in cycle 2 were lower than in cycle 1, and this reflects the reported experience with ondansetron plus dexamethasone over repeated cycles [25, 37]. In the study of Campora and associates [26], however, the efficacy of ondansetron plus dexamethasone in achieving complete control of acute emesis was maintained over six courses of cyclophosphamide–doxorubicin chemotherapy, although acute nausea was much less well controlled. Despite the observed decrease in efficacy, it has been reported that complete response rates of approximately 60% are maintained for up to eight cycles of chemotherapy with granisetron as the antiemetic [17].

In the present study, there was a significant trend in favour of granisetron plus dexamethasone in terms of times to less than complete response, to first episode of moderate/severe nausea, to first episode of vomiting and to use of rescue antiemetic medication. This reflects other findings that control of delayed emesis following moderately emetogenic chemotherapy is significantly better with a combination of a 5-HT$_3$ receptor antagonist plus dexamethasone than with either agent alone or with standard antiemetic regimens [14–16, 24–26, 38].

In conclusion, these results show that a single dose of dexamethasone, 20 mg, added to granisetron enhances the efficacy of granisetron alone in controlling nausea and vomiting following moderately emetogenic chemotherapy. Furthermore, the improved efficacy is maintained for up to 5 days, as evidenced by longer times to breakthrough nausea and vomiting and decreased use of additional antiemetics. Granisetron plus dexamethasone is preferred by patients. There do not appear to be any differences in the safety profiles of granisetron alone and with the addition of dexamethasone.

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