Dose finding study of granisetron in patients receiving high-dose cisplatin chemotherapy

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Summary

The efficacy and safety of three different doses of granisetron (2 μg kg⁻¹, group A; 10 μg kg⁻¹, group B; 40 μg kg⁻¹, group C) were compared in a randomised, double-blind study of 157 patients due to receive high-dose cisplatin therapy (mean dose ≥ 70 mg m⁻²). In each group, up to two 3 mg rescue doses of granisetron were allowed if more than mild nausea or vomiting occurred. In group A, 30.8%, in group B 61.5% and in group C 67.9% of patients were complete responders (i.e. no vomiting or nothing worse than mild nausea) during the first 24 h. These differences are significant between groups A and B, and A and C. There were no statistically significant differences in any efficacy variable between the 10 μg kg⁻¹ and 40 μg kg⁻¹ groups, although in each case the trend favoured the higher dose. Additional rescue doses resulted in resolved or improved symptoms in 95.3% for the first rescue dose and 93.3% for the second. Over the 7 days of the study, 82.7%, 82.7% and 86.8% of patients in groups A, B and C respectively were treated with granisetron alone. Headache was the most common side-effect, reported by 9.6% of patients; the majority of headaches were mild. There was no difference between the treatment groups regarding the adverse event rate. We concluded that prophylactic doses of 10 or 40 μg kg⁻¹ lead to a safe and satisfactory degree of control of nausea and vomiting induced by high-dose cisplatin.

Nausea and vomiting are side-effects frequently associated with many cytostatic chemotherapeutic agents and are a major cause of distress to the patient (Coates et al., 1983). Cisplatin is one of the most commonly used agents, especially for treatment of testicular, ovarian, head and neck and lung cancer. Cisplatin-induced emesis has been shown to have a biphasic pattern with acute and delayed symptoms. Acute emesis with cisplatin begins approximately 6 h after chemotherapy administration and its severity is related to gender and cisplatin dose. Delayed emesis is usually less severe, related to incomplete control of acute emesis (Roila et al., 1991), and occurs 24 h to 5 days after chemotherapy (Kris et al., 1985; Gralla et al., 1981).

There is now evidence that emesis control during chemotherapy acts on the quality and cost of treatment by allowing a better compliance to scheduled drug doses. It improves patient quality of life by reducing the intensity and the number of side-effects and therefore reduces length of hospitalisation and treatment costs (Laszlo & Lucas, 1981).

Antiemetic treatment should aim to provide total control of emesis, particularly during the first cycle. With the best conventional antiemetic treatment, such as a combination of high-dose metoclopramide, corticosteroids and benzodiazepine, cisplatin-induced emesis can be controlled in up to 60% of patients (Kris, 1987). However, treatment is associated with frequent side-effects, consisting of extrapyramidal reactions and sedation (Kris et al., 1983). Research on the pathophysiology of chemotherapy-induced vomiting has demonstrated the role of serotonin (5-hydroxytryptamine). Serotonin is released by enterochromaffin cells in the upper gastrointestinal tract, where it can act on specific receptors recognised as 5-HT₃ (Borison & McCarthy, 1983). Studies on the ferret have shown the efficacy of 5-HT₃ receptor antagonists against chemotherapy-induced vomiting (Blower, 1990). Granisetron, a highly potent and selective 5-HT₃ receptor antagonist, is very effective in protecting against emesis induced by either high-dose cisplatin or moderately emetogenic agents (Tabona, 1990).

In a placebo-controlled study of 28 patients receiving high-dose cisplatin chemotherapy, granisetron was successful in protecting 13/14 patients during the first 24 h (Cupissol et al., 1990). When compared with a chlorpromazine-dexamethasone antiemetic regimen, in patients receiving moderately emetogenic chemotherapy, a significantly greater number of patients were controlled with granisetron (70% complete responders) compared with the control group (49% complete responders; P = 0.0013) (Marty, 1990).

In patients receiving high-dose cisplatin chemotherapy, granisetron was at least as effective as a metoclopramide plus dexamethasone regimen with an approximately 70% complete responder rate in both groups. No extrapyramidal side-effects were observed in the granisetron group. The side-effect rate was the same in the two groups, but in the granisetron group events were less severe and easily resolved (Chevallier, 1990).

In these trials granisetron was administered as a 40 μg kg⁻¹ single dose, with the option of two additional doses of 40 μg kg⁻¹ to be used as rescue for breakthrough symptoms. This schedule has been compared with 160 μg kg⁻¹ dosage in patients receiving highly and moderately emetogenic chemotherapy. In both cases there was no significant difference between the two groups regarding emesis control at 24 h, efficacy over a period of 7 days, time to first emetic episode or the adverse event frequency (Soukop, 1990). The present study was initiated in order to further investigate the efficacy and safety of lower dosages of granisetron.

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Patients and methods

Study design

The aim of this study was to compare the efficacy and safety of three different doses of granisetron in patients receiving cisplatin therapy for the first time. Each patient was randomly assigned in a double-blind fashion to receive a single intravenous dose of 2, 10 or 40 μg kg⁻¹ granisetron. The study was conducted at 17 centres in three countries (France, Germany and South Africa).

Patients

Eligible patients were inpatients due to receive cisplatin-containing chemotherapy for the treatment of histologically confirmed malignant disease and who had given their written informed consent.

Chemotherapy was to be delivered on a single day and to contain cisplatin at a minimum dosage of 75 mg m⁻² given as an infusion over a period of 3 h. Other cytostatic agents were permitted after cisplatin, but only those that would not be routinely covered by antiemetic therapy.

Patients were excluded from the study if they had marked hepatic or renal dysfunction, cardiovascular disease, active peptic ulcer, gastrointestinal tract obstruction or brain tumour or had a history of chronic nausea or vomiting. Patients were also excluded if they received corticosteroids. If medications with a CNS effect were taken, their daily regimen was not to be changed for the week before the study day. The study was conducted according to the Declaration of Helsinki and approval for the study was obtained from local ethics committees.

Antiemetic therapy

Patients received granisetron as a single infusion over 5 min to be completed 5 min before the start of cisplatin therapy. If moderate or severe nausea or vomiting occurred, up to two additional 3 mg granisetron infusions were allowed. These two administrations could not be given within 10 min of one another. If this treatment failed to maintain control of emesis, patients were withdrawn from the study and treated with conventional antiemetics of the physician’s choice.

Efficacy assessments

Efficacy was measured by the patient, the clinician and by recording the use of additional antiemetics. Patients were asked about their subjective assessment of nausea and vomiting. Nausea was recorded on a four-point scale as either none, mild, moderate or severe, and episodes of vomiting were recorded on a four-point scale as either no vomiting, one episode of vomiting, 2–4 episodes of vomiting or more than four episodes of vomiting. Patients’ appetites were also recorded and compared with their appetites in the week before chemotherapy commenced. The evaluations were done prior to the start of chemotherapy and thereafter at 6, 12, 18 and 24 h.

The clinician’s objective assessment of emetic control was given at the end of the first 24 h of the study and rated as very good, good, average, poor or very poor. The need for additional granisetron or other anti-emetics was recorded, including the reason (nausea or vomiting) and outcome (resolved, improved or no improvement). During the following 6 days, the use of any other antiemetics was recorded.

Efficacy was defined according to the following classification:

Complete response
No vomiting and nothing worse than mild nausea over the 24 h after the start of cytostatic chemotherapy.

Major response
One episode of vomiting and/or moderate/severe nausea over the 24 h after the start of cytostatic chemotherapy.

Minor response
Two to four vomiting episodes (regardless of nausea) over the 24 h after the start of cytostatic chemotherapy.

Failure
More than four emetic episodes (regardless of nausea) over the 24 h after the start of cytostatic chemotherapy.

Clinical and laboratory monitoring

Objective clinical assessment of alertness and general well-being was recorded before and at the start of therapy and then at 6, 12, 18, 24 h after the start of cisplatin infusion. Blood pressure, pulse rate and temperature were recorded at the same time points and at the screening examination and at the follow-up visit at 7 days. The usual haematological and clinical chemistry laboratory analyses were performed on blood and urine samples at the screening visit, on the treatment day and at the follow-up visit.

Adverse events

Patients were asked directly at the screening visit, on the treatment day and at the follow-up visit if they felt different in any way since the start of the treatment and any adverse events were recorded. Adverse events were also recorded by spontaneous reports from patients and direct observation by the staff.

For each event reported, the physician was required to give duration, severity, outcome and treatment given, and to assess the relationship to granisetron as unassessable, unrelated, probably unrelated, probably related, related. Adverse events were analysed for frequency. A serious adverse event was defined as any event that was fatal, life-threatening, disabling or incapacitating or resulted in hospitalisation, prolonged a hospital stay, or was associated with congenital abnormality, carcinoma or overdose. Serious adverse affects were studied separately.

Statistical analysis

The target size for each treatment group was 60 patients, giving a power of at least 80% to detect a difference of 26% in the percentage of complete response between any pair of dose groups. An interim analysis was planned to be performed on the results of the first 60 patients to allow any ineffective dose to be dropped from the study.

A chi-square test was used to test for differences between the three treatment groups for proportion of adverse events, complete responses and good/very good global efficacy assessments. A Cox log-rank test was used to test for differences between the three treatment groups for time to first nausea, first moderate/severe nausea, first vomiting or retching, less than complete response, use of granisetron rescue medication and use of conventional antiemetic medication.

A two-tailed significance level of 4.8% was used to test whether the result is significant for the chi-square test on complete response, as this was tested in the interim analysis. In all other cases a two-sided significance level of 5% was used to determine whether the event was to be regarded as significant.

If there was sufficient evidence to suggest a significant difference between the three treatment groups, three pairwise comparisons were made between the 2 and 10 μg kg⁻¹, 2 and 40 μg kg⁻¹ and 10 and 40 μg kg⁻¹ groups. To maintain the two-tailed significance level of 5%, the Bonferroni correction was used. That is, for each pairwise comparison a two-tailed significance level of 1.600% for complete response and 1.667% for all other items was used to determine if the result was to be regarded as statistically significant. All patients were included in the efficacy and safety analysis.
Results

Demography

One hundred and fifty-seven patients were enrolled in this trial. Fifty-two patients received granisetron at a dose of 2 μg kg⁻¹, 52 at a dose of 10 μg kg⁻¹ and 53 at a dose of 40 μg kg⁻¹. Demographic data are given in Table I. There were 87 male and 70 female patients, with a greater proportion of males in the 2 μg kg⁻¹ group than in the 40 μg kg⁻¹ group. Age and alcohol usage were well balanced among the three groups. The main primary disease sites were head and neck (37 patients), ovary (24 patients), lung (21 patients) and cervix (18 patients) (Table II), and were fairly evenly distributed among the three groups.

All patients received cisplatin-containing chemotherapy. The mean dose of cisplatin was 95.9 mg m⁻² in the 2 μg kg⁻¹ granisetron group (range 60–150 mg m⁻²), 96.2 mg m⁻² in the 10 μg kg⁻¹ granisetron group (range 75–120 mg m⁻²) and 99.3 mg m⁻² in the 40 μg kg⁻¹ granisetron group (range 75–200 mg m⁻²). One patient in the 2 μg kg⁻¹ group in fact received 60 mg m⁻² cisplatin in violation of the protocol.

Efficacy during the first 24 h

The efficacy in the first 24 h is presented in Table III. At the end of the first 24 h, 30.8% of patients in the 2 μg kg⁻¹ granisetron group (group A), 61.5% in the 10 μg kg⁻¹ granisetron group (group B) and 67.9% in the 40 μg kg⁻¹ granisetron group (group C) were complete responders. In total, three patients were classified as complete responders who received additional doses of granisetron in the first 24 h (two in the 10 μg kg⁻¹ group and one in the 40 μg kg⁻¹ group).

Efficacy over 7 days

Nine patients (17.3%) from group A, nine patients (17.3%) from group B and seven patients (13.2%) from group C were complete responders. In total, the efficacy was similar for the three groups.

There were significant differences between these three groups regarding the proportion of complete responders. Using the Bonferroni correction, a significant difference was found between groups A and B (P = 0.002) and between groups A and C (P = 0.001) but not between groups B and C. Moreover, 28 patients (53.8%), 40 patients (76.9%) and 45 patients (84.9%) in the respective groups experienced no more than one episode of vomiting or retching.

The same results (significant differences between A and C and between A and B) were observed when analysing time to less than a complete response and time to the first vomiting. For all cases first events tended to occur earlier in the 2 μg kg⁻¹ dose group. With respect to time or first moderate/severe nausea, there was a significant difference between group A and C but not between A and B or between B and C.

Thirty-two patients (61.5%) from group A, 22 patients (42.3%) from group B and 17 patients (32.1%) from group C received a rescue medication (granisetron or other agents) during the first 24 h. The use of any rescue medication and time to rescue were significantly different between groups A and B (P = 0.002) and between groups A and C (P < 0.001) when using the Bonferroni correction. Details about additional granisetron use are given in Table IV. Thirty patients in group A, 19 in group B and 15 in group C received one additional dose of granisetron. This resulted in resolution of emesis in 86.7%, 63.1% and 60.0% of cases respectively. A second additional dose was given to 40%, 57.9% and 46.7% of patients in groups A, B and C and produced resolution of symptoms in 41.6%, 81.8% and 28.6% of patients respectively (Table V).

The clinician’s global assessment of efficacy was good or very good in 63.5%, 76.9% and 86.5% of cases. Using the Bonferroni correction, a significant difference was found between groups A and C (P = 0.007) but not between groups A and B or between groups B and C. Only two patients in the 2 μg kg⁻¹ granisetron group and one patient in the 40 μg kg⁻¹ group were withdrawn from the trial for lack of antiemetic efficacy. The clinician had assessed the patient’s well-being as ‘well’ in most of the cases with no major difference between the three treatment groups.

Table I Demographic data

| Granisetron dose | 2 μg kg⁻¹ | 10 μg kg⁻¹ | 40 μg kg⁻¹ |
|------------------|-----------|-----------|-----------|
| Males            | 33        | 28        | 26        |
| Females          | 19        | 24        | 27        |
| Mean age (years) | 57.8      | 51.0      | 54.8      |
| Age range (years) | 28–79    | 17–79     | 23–74     |
| Mean height (cm) | 166.4     | 165.4     | 167.2     |
| Mean weight (kg) | 66.6      | 63.7      | 66.2      |
| No alcohol consumption | 22 | 24 | 22 |

Table II Primary disease site

| Granisetron dose | 2 μg kg⁻¹ | 10 μg kg⁻¹ | 40 μg kg⁻¹ |
|------------------|-----------|-----------|-----------|
| Head and neck    | 10        | 17        | 10        |
| Ovary            | 7         | 9         | 8         |
| Lung             | 7         | 5         | 7         |
| Cervix           | 3         | 7         | 8         |
| Urethra bladder  | 3         | 2         | 5         |
| Melanoma         | 4         | 3         | 2         |
| Oesophagus       | 4         | 2         | 1         |
| Breast           | 1         | 1         | 4         |
| Others (13 sites)| 11        | 6         | 8         |
| Total            | 52        | 52        | 53        |

Table III Twenty-four hour efficacy

| Granisetron dose | 2 μg kg⁻¹ | 10 μg kg⁻¹ | 40 μg kg⁻¹ |
|------------------|-----------|-----------|-----------|
| Complete response| 16 (30.8%)| 32 (61.5%)| 36 (67.9%)|
| Major response   | 12 (23.1%)| 8 (15.4%) | 9 (17.0%) |
| Minor response   | 17 (32.7%)| 9 (17.3%) | 5 (9.4%)  |
| Failure          | 7 (13.5%) | 3 (5.8%)  | 3 (5.7%)  |
| No nausea        | 23 (44.2%)| 31 (59.6%)| 35 (66.0%)|
| No vomiting      | 20 (38.5%)| 34 (65.4%)| 39 (73.6%)|

*P < 0.001 for 2 vs 10 μg kg⁻¹ and 2 vs 40 μg kg⁻¹.

Table IV Summary of additional granisetron use

| Granisetron dose | 2 μg kg⁻¹ | 10 μg kg⁻¹ | 40 μg kg⁻¹ |
|------------------|-----------|-----------|-----------|
| (n = 52)         | (n = 52)  | (n = 53)  |
| Rescue therapy, no. of additional doses | 0 | 22 (42.3%) | 33 (63.5%) | 38 (71.7%) |
| 1                | 30 (57.7%) | 19 (36.5%) | 15 (28.3%) |
| 2                | 12 (23.1%) | 11 (21.1%) | 7 (13.2%)  |
| 3                | 1 (1.9%)   | 1 (1.9%)   |            |
| 4                | 1 (1.9%)   |            |            |

Table V Effect of additional granisetron doses

| Granisetron dose | 2 μg kg⁻¹ | 10 μg kg⁻¹ | 40 μg kg⁻¹ |
|------------------|-----------|-----------|-----------|
| (n = 52)         | (n = 52)  | (n = 53)  |
| Rescue therapy, no. of additional doses | 1 | Resolved | 26 | 12 | 9 |
| 2                | Improved  | 3         | 5         | 6 |
| 3                | Failure   | 1         | 2         | 0 |
| 4                | Resolved  | 5         | 9         | 2 |
| 5                | Improved  | 6         | 1         | 5 |
| 6                | Failure   | 1         | 1         | 0 |
needed other rescue medication. Thus, 82.7%, 82.7% and 86.8% respectively were treated with granisetron alone over the 7 day study period. Using the Bonferroni correction, time to first use of any additional antiemetic therapy during this period was significantly different between groups A and B (P = 0.005) and between groups A and C (P < 0.001), but not between groups B and C.

**Clinical monitoring and laboratory tests**

Double-flagged change in vital signs occurred for 13 patients (four, four and five patients in groups A, B and C respectively). No case was considered as study drug related by the clinician. No major changes were seen in laboratory results between predose and follow-up time.

**Adverse events**

The adverse event incidence and most frequent adverse events reported are presented in Table VI. Headache was the most commonly reported event, and the incidence of this or any other event did not appear to be related to the randomised prophylactic dose of granisetron. Headache was considered as mild and responded to corrective therapy except in one patient who rated headache as severe, however this was present before the start of granisetron therapy. Severe or serious adverse events were reported for four patients in group A, six patients in group B and one patient in group C. All but one were considered by the investigator to be unrelated to the study drug (see below). Two patients died. In one case, the cause of death (acute hepatopathy) was considered by an independent expert to be related to halothane compounds given prior to granisetron as general anaesthesia for an endoscopy. The second patient who died during the study period developed severe aplasia. The clinician considered the death to be related to toxic shock, septicemia and chemotherapy toxicity. No relationship was found in this study between adverse event rate and administered dose of granisetron.

**Discussion**

Cisplatin chemotherapy is associated with vomiting in 93% of patients when given at more than 80 mg m⁻² (Gralla et al., 1981; Cuppisol, 1990). Nausea and vomiting are considered as separate phenomena, and nausea can occur in the absence of vomiting. In a French crossover trial which studied antiemetic treatment, it was noted that the patients’ preference criteria were more closely related with the effect of antiemetics on nausea, while for the physicians judgment was based on vomiting or retching (Bonneterre et al., 1991). In the paper presented here, complete response includes an assessment of both vomiting (absent) and nausea (no more than mild), and this seems to be very important as far as patients’ quality of life is concerned.

Use of a single dose of granisetron as antiemetic treatment, resulted in, respectively, 30.8%, 61.5% and 67.9% complete response rates for the 2, 10 and 40 μg kg⁻¹ groups. In the same groups 42.3%, 65.4% and 71.7% of patients respectively did not receive any additional granisetron. There was a significant difference between the 2 μg kg⁻¹ group and the other two groups. Although results were numerically better in the 40 μg kg⁻¹ group, there was no significant difference between the 10 and 40 μg kg⁻¹ groups. When nausea and vomiting were examined as independent variables it can be seen that 40 μg kg⁻¹ was better at controlling both these symptoms compared with lower doses and the difference was greater than when complete response was presented.

These results in the 40 μg kg⁻¹ group are similar to those obtained in other granisetron studies. In high-dose cisplatin studies, granisetron given as a single dose of 40 μg kg⁻¹ gives complete response rates of between 55% and 75% (Chevallier, 1990; Soukop, 1990). This response rate does not seem to be improved significantly by increasing the dose of granisetron to 160 μg kg⁻¹ (Soukop, 1990). In a Canadian double-blind trial in which 149 patients were enrolled, granisetron was administered as an 80 μg kg⁻¹ single dose and compared with a high-dose metoclopramide—dexamethasone—diphenhydramine combination. In both groups 46% of the patients were free of vomiting for 24 h. This similarity to metoclopramide-dexamethasone was also seen at 40 μg kg⁻¹ (Chevallier, 1990), which demonstrates that prophylactic doses greater than 40 μg kg⁻¹ are not more efficacious.

In this study, granisetron was effective when used as rescue therapy. After the first emetic episode (nausea or vomiting 95.3% of patients and after the second event 93.3% had their symptoms resolved or improved. There was evidence to suggest a difference in the three treatment groups regarding the first use of additional granisetron therapy (P < 0.001). No significant difference was found between the three groups regarding additional granisetron efficacy.

Treatment was well tolerated. In no case was granisetron associated with severe adverse events. The usual granisetron-related side-effects such as headache and constipation were as frequent as in other studies (Chevallier, 1990; Marty, 1990; Smith, 1990; Soukop, 1990; Venner, 1990) and there was no relationship between granisetron doses and adverse event rate.

**Conclusion**

In this study, prophylactic doses of 10 or 40 μg kg⁻¹ granisetron given intravenously were clinically and statistically more effective than a dose of 2 μg kg⁻¹ in preventing cisplatin-induced emesis. It can be concluded that at the two higher dose levels, granisetron leads to a safe and satisfactory degree of control of nausea and vomiting induced by high-dose cisplatin.

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