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Efficacy and Safety of Granisetron in the Prevention of Chemotherapy-induced Emesis in Paediatric Patients

Jean Lemerle, Diego Amaral, David P. Southall, James Upward and Robert D. Murdoch

In an open ascending-dose study, granisetron, a specific 5-HT$_3$ receptor antagonist, was admininistered to 24 paediatric patients (17 male, 7 female, mean age 6.2, range 3–15 years) who were receiving moderately or highly emetogenic chemotherapy for malignant disease. Single doses of 10, 20 and 40 μg/kg were administered by intravenous infusion 1 h before chemotherapy. Each dose level was studied in a group of 8 patients. With the 40 μg/kg dose, 5 of 8 patients experienced no nausea or vomiting in the 24 h after granisetron treatment. With 20 μg/kg, a similar response was seen, but with 10 μg/kg only 2 of 8 patients experienced complete antiemetic protection despite additional prophylactic chlorpromazine in this group. Granisetron was very well tolerated, and there were no clinically important changes in pulse rate, blood pressure or Holter electrocardiogram. It is concluded that granisetron was very well tolerated by paediatric patients. In addition, there was clear evidence of a major antiemetic effect for at least 24 h after a single intravenous dose of 20 or 40 μg/kg.
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INTRODUCTION

NAUSEA AND VOMITING are among the most distressing and debilitating side-effects of the chemotherapy regimens used for the treatment of childhood cancers. The currently available antiemetics do afford benefits but none is completely satisfactory: side-effects may be troublesome, particularly sedation and extrapyramidal effects [1], and combination of treatment [2–5] and complex dosing regimens may be required to achieve optimal antiemetic activity [6].

Granisetron is a selective 5-HT$_3$ receptor antagonist. In adult patients it has been found to be well tolerated in single doses of up to 160 μg/kg [9]. Furthermore, a single dose of 40–160 μg/kg has been shown to provide a major degree of antiemetic protection for a full 24 hours, even in patients who have received high doses of cisplatin [7–9].

The present study was the first evaluation of granisetron in paediatric patients. It was undertaken to assess the tolerability and efficacy of the agent in children receiving moderately or

Table 1. Patients receiving the most emetogenic of the chemotherapy regimens

Granisetron dose (μg/kg)	Total daily dose: Cisplatin (25–30 mg/m²)	Ifosfamide (1.8–4.7 g/m²)	Doxorubicin (42–47 mg/m²)	Cytarabine (60–110 mg/m²)
10	2	3	0	2
20	0	3	1	0
40	1	2	2	1

Other drugs used alone or in combination: vincristine, actinomycin, methotrexate, etoposide, carboplatin, procarbazine, cyclophosphamide, bleomycin, prednisone and hydrocortisone.

highly emetogenic chemotherapy for the treatment of malignant disease.

PATIENTS AND METHODS

Patient selection

24 paediatric patients who were attending the Institut Gustave Roussy for the treatment of malignant disease were studied. Of these 24 patients, 17 were male. Their mean age was 6.4 (range 3–15) years and body surface area 0.85 (S.D. 0.33) m^2. Female ranges were comparable with a mean age of 6.0 (3–15) years and body surface area 0.81 (0.21) m^2. 19 patients had previously had one or more courses of chemotherapy with 7 receiving in excess of five courses. All had a WHO status of zero. Patients presented with the following conditions: 7 patients with rhabdomyosarcoma, 7 with non-Hodgkin lymphoma, 4 with neuroblastoma, 2 each with osteogenic sarcoma and malignant teratoma and 1 each with nephroblastoma and Hodgkin's disease. Informed consent was obtained from each child's parents or legal guardian before entry into the study. The study was approved by the Ethics Committee of the Institute Gustave Roussy.

Study design

This was an open ascending-dose study. Each patient received a single dose of 10, 20 or 40 μg/kg of granisetron. 8 patients were studied at each dose level; the dose levels were studied sequentially. Granisetron was administered, as an infusion via a central venous catheter or a peripheral vein, over 30 minutes. The infusion was started 1 h before the administration of the cytostatic drugs. Details of cytostatic therapy are given in Table 1.

Assessment of safety

Pulse rate and blood pressure were measured before and after the infusion of granisetron and then hourly for 6 h; further measurements were made at 12, 18 and 24 h after the infusion.

A Holter recording of the electrocardiogram (ECG) was made for 6 h before the administration of granisetron and for 24 h afterwards. Haematology (full blood count together with red cell parameters) and clinical chemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, chloride, creatinine, sodium, potassium, total protein and urea) were evaluted before and 24 h after treatment.

Evaluation of antiemetic efficacy

At the end of each hour, a score was given by a trained observer according to the following system, recording only the most severe symptom: no nausea, retching or vomiting (0), nausea or debility (1), retching (defined as gagging or dry vomiting) single or multiple episodes (2), a single episode of vomiting (3) and multiple episodes of vomiting (4). A total score for the 24 h was calculated at the end of the study by summation. The antiemetic efficacy was defined as follows: complete response (0) major response (1–6) minor response (7–12) and no response: (> 12).

Additional antiemetic therapy

In this initial safety study all patients due to receive 10 μg/kg granisetron prior to chemotherapy were given chlorpromazine at antiemetic doses (7–25 mg intravenous bolus) prophylactically. 2 patients receiving 20 μg/kg granisetron also received chlorpromazine, as a result of severe nausea and vomiting in previous courses of chemotherapy.

Statistical analysis

Antiemetic efficacy was assessed by repeated measures analysis of variance. Hypothesis testing was performed at the 5% significance levels. Analyses were carried out using procedure GLM of the SAS statistical package [11].

RESULTS

Safety

Granisetron was well tolerated. In the 24 h study period, no unwanted effects were noted on clinical observation or on assessment of pulse rate, blood pressure, haematology or clinical chemistry. Analysis of the Holter ECG showed no evidence of any effect on the cardiac rhythm: all recordings were normal but isolated ventricular arrhythmias (supraventricular and ventricular premature beats, and SVES) were infrequently observed. These were not clinically important and did not exceed the frequency observed in the normal population [13–15]. Headache and constipation, seen in other studies, were not observed.

Table 2. Time to first emesis response

Time in relation to start of dosing with granisetron (h)	Dose of granisetron (μg/kg): 10	20	40
≤6	5	0	1
6–12	1	4	0
12–18	0	0	1
18–24	0	0	1
>24*	2	4	5

*>24 hours indicates that no emesis was recorded.
10 vs. 20 μg/kg, $P = 0.082$; 20 vs. 40 μg/kg, $P = 0.058$; and 10 vs. 40 μg/kg, $P = 0.044$.

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Table 3. Emesis response

Dose granisetron (μg/kg)	Response			
	Complete	Major	Minor	None
10	2	2	3	1
20	4	3	0	1
40	5	2	1	0

Efficacy

The majority of patients received at least one drug which is considered highly or moderately emetogenic (Table 1). The more emetogenic drugs were represented evenly in the three treatment groups.

Results for the 24 h study period are shown in Tables 2 and 3. 5 of the 8 patients who received 40 μg/kg of granisetron did not vomit or experience nausea (a complete response) while a further 2 patients vomited only once and experienced a major response.

With the 20 μg/kg dose of granisetron, 4 patients experienced a complete and 3 a major response. With the 10 μg/kg dose, there was a complete response in 2 patients and a major response in a further 2. The time of onset of symptoms with the three dose levels of granisetron is shown in Table 2: the 40 μg/kg dose produced a significant delay in the onset of symptoms ($P = 0.044$) compared to the 10 μg/kg dose. Doses of 20 μg/kg granisetron just failed to reach significance relative to 10 μg/kg dosage.

DISCUSSION

In this first study of granisetron in a mixed paediatric population, doses of 10, 20 and 40 μg/kg showed clear evidence of antiemetic efficacy. Complete and major antiemetic responses were obtained in 7 of the 8 treated with either 20 or 40 μg/kg granisetron. The duration of activity of the 40 μg/kg dose apppeared longer than 10 μg/kg with a significant increase in time to breakthrough symptoms. Of the patients receiving 40 μg/kg only 1 experienced symptoms within the first 12 hours following chemotherapy compared with 6 patients who received 10 μg/kg even though the lowest dose group received prophylactic treatment with chlorpromazine. These differences could not be explained on the basis of differing proportions of patients on highly emetogenic drugs or anticipatory nausea or vomiting despite previous courses of chemotherapy in 19 of the 24 patients treated.

A randomised multi-institutional trial where granisetron is compared to the combination of chlorpromazine and dexamethasone in terms of efficacy and tolerance in children has been initiated and will provide further information on the efficacy of granisetron in children receiving emetogenic chemotherapy.

Earlier studies of 40 μg/kg granisetron in adult patients [7] receiving highly emetogenic regimens have shown a 50% complete control of emesis and a further 36% of patients remaining free of nausea and vomiting for longer than 12 hours. Similarly Joss *et al.* [12] reported that 48% of patients were complete responders following granisetron at 40 or 100 μg/kg and a further 45% of patients experienced between 1–5 vomiting episodes in the 24-hour period following chemotherapy. All of these patients received cisplatin at greater than 50 mg/m^2. Soukop *et al.* [9] reported "complete" control of symptoms in the first 24-hour period in 57 and 60% of patients receiving 40 or 160 μg/kg granisetron, respectively, in a multicentre study of 296 patients receiving cisplatin at greater than 49 mg/m^2.

Granisetron in doses of 10–40 μg/kg was very well tolerated by these children with malignant disease undergoing chemotherapy. There were no clinically important changes in any vital signs, clinical chemistry and haematology, which could not be explained on the basis of their disease state or chemotherapy history. In adults much higher single intravenous doses have been safely given, up to 300 μg/kg in volunteers [10] and up to 160 μg/kg in patients [9], but the present study represents the first experience in the paediatric age group.

In conclusion, granisetron, when given in doses up to 40 μg/kg by intravenous infusion, was very well tolerated by children receiving moderate or highly emetogenic chemotherapy for malignant disease. A single prophylactic dose of 20 or 40 μg/kg provided excellent antiemetic control in the majority of patients.

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