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ORIGINAL ARTICLE

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An open study to assess the safety, tolerance and pharmacokinetics of an intravenous infusion of granisetron given at 3 mg over 30 s in patients receiving chemotherapy for malignant disease

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Abstract Granisetron is a highly potent and selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist indicated for the prevention of cytotoxic-induced nausea and vomiting. Clinical trials have demonstrated granisetron to be effective and well tolerated at a standard dose of 40 μg/kg or 3 mg given i.v. as a 5-min infusion. In this study, the efficacy and safety of granisetron given as a 30-s infusion was assessed. A total of 21 patients, scheduled to undergo chemotherapy, received a single 3-mg i.v. dose of granisetron over 30 s, completed at 1 h before chemotherapy administration. Patients were allowed two further i.v. doses of granisetron at 3 mg within the 24-h assessment period. Changes from baseline values in vital signs were analysed prior to granisetron administration and at 30 s as well as 1, 10, 15, 30 and 60 min after granisetron administration. Holter ECG recordings were taken for 6 h prior to and 1 h after administration. No significant change was found in vital signs at 30 s or 1 min after granisetron infusion. There was a small but statistically significant fall in diastolic blood pressure as compared with baseline and a non-significant trend in favour of a reduction in heart rate at 10 and 15 min. No ECG abnormality was recorded post-infusion that had not been present pre-infusion. None of these changes was considered to be clinically relevant. The treatment was well tolerated. The most frequently reported adverse events were constipation ($n = 6$) and headache ($n = 5$). Maximal plasma levels of granisetron were within the range of 44.57–410 ng/ml except in one patient. The median values recorded for peak concentration (C_{max}) and area under the curve (AUC) were 195 ng/ml and 71.2 ng h ml^{-1}, respectively. In conclusion, granisetron at 3 mg was shown to be safe and well tolerated when given as a 30-s i.v. infusion to patients receiving chemotherapy for malignant disease.

Key words Granisetron · Tolerance · Rapid infusion · Pharmacokinetics

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Introduction

Nausea and vomiting have been described by patients as the most distressing of all the side effects of chemotherapy [1]. These symptoms may be so severe that patients may delay or even refuse further, possibly curative, treatment. Effective antiemetic treatment is therefore an important part of the drug regimen for these patients. Conventional antiemetic treatment commonly involves multiple medication and is often associated with adverse effects. For example, the combination of high-dose metoclopramide, a dopamine antagonist, plus dexamethasone can be associated with distressing extrapyramidal symptoms and sedation, leading to a reduction in patients' quality of life. Another drawback of many conventional antiemetic regimens is their complicated and sometimes lengthy administration schedules.

Following research that implicated the involvement of the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor in the emetic response, the development of selective 5-HT$_3$ receptor antagonists such as granisetron produced a major advance in emetic control. The 5-HT$_3$ receptor antagonists granisetron, tropisetron and ondansetron have been shown to be effective agents in the control of acute emesis induced by cytostatic agents, although their role in delayed emesis has not yet been defined [2–4].

Intravenous granisetron is currently given as a single, 5-min infusion ending 5 min prior to the scheduled start of chemotherapy. A 3-min infusion has been investigated in volunteers [5] and in a placebo-controlled, ascending dose study conducted to assess its tolerability, safety and pharmacokinetic profile over a range of doses (50–160 μg/kg) [6]. No dose-related effect or clinically significant change in blood pressure, pulse or ECG time interval was noted, and no abnormality of cardiac rhythm was observed. Recent preliminary data have shown good tolerability for a 30-s infusion [7], but a full clinical assessment of the safety and tolerability of such a rapid infusion of granisetron remains to be performed.

It was the aim of this study to assess the safety, tolerability and pharmacokinetics of granisetron, given as a 3-mg i.v. infusion over a 30-s period to patients undergoing chemotherapy with a variety of emetogenic cytotoxic agents. Holter ECG recordings for 6 h prior to drug administration and 1 h post-dosing were used to monitor the safety of this rapid method of granisetron dosing.

Patients and methods

Study design

An open, non-comparative study design was employed to investigate 21 patients with malignant disease who were scheduled to receive emetogenic cytotoxic chemotherapy.

Patient selection

Patients of either sex were included if they were over 18 years old, had malignant disease and were scheduled to receive either cisplatin or various other emetogenic cytotoxic agents, either as monotherapy or in combination, and had a performance status of 2 or less (WHO criteria). All patients gave their written or witnessed verbal informed consent to participate and were free to withdraw from the study at any time. The design of the protocol conformed to the Declaration of Helsinki (1964) and its subsequent revisions, Tokyo (1975), Venice (1983) and Hong Kong (1989). The study was approved by the Central Oxford Research Ethics Committee.

Patients were excluded who had a history of ischaemic heart disease, myocardial infarction or cardiac arrhythmias or exhibited conduction disturbance at the time of entry; had significant electrolyte disturbances; showed marked liver or renal dysfunction; had a symptomatic primary or secondary brain tumour; were taking drugs known to have cardiovascular activity; had pre-existing nausea and/or vomiting; or were scheduled for treatment with other antiemetic drugs (except corticosteroids, which were part of the chemotherapy regimen), radiotherapy or other investigational new drugs during the period of study.

Pre-treatment examinations

A complete medical history was taken and a physical examination was performed. A 12-lead ECG was performed at the screening visit to exclude patients with cardiac arrhythmias or significant conduction disturbance.

Chemotherapy

Most patients received one or more of the following drugs for up to 5 consecutive days, either as monotherapy or in combination: cyclophosphamide, carboplatin, cisplatin, dacarbazine, ifosfamide or etoposide. No other cytotoxic treatment could be given prior to administration of these drugs on day 1. Patients were excluded if their chemotherapy regimen involved a cumulative dose of Adriamycin (doxorubicin) or daunorubicin in excess of 200 mg or of epirubicin in excess of 400 mg. Patients returned to the clinic 7 days after completion of the chemotherapy cycle for a follow-up safety assessment and for physical and laboratory examination.

Materials

Intravenous granisetron was supplied by SmithKline Beecham and presented as 5-ml glass ampoules containing 5 mg of active drug. For the purposes of administration, 3 ml (3 mg of active drug) was withdrawn from the ampoule into a syringe and diluted with 0.9% sterile saline to a final volume of 15 ml.

Antiemetic treatment

Patients received a single, 3-mg i.v. infusion of granisetron (15 ml) over 30 s, completed at 1 h prior to the commencement of chemotherapy. Two further 3-mg doses of granisetron (each derived in a 5-min infusion) could be given, if required, during the 24-h assessment period if nausea and vomiting were not controlled.

Assessment of safety and pharmacokinetics

An ECG was recorded continuously by Holter monitoring onto a cassette tape for a minimal period of 6 h immediately prior to granisetron dosing as well as during and for 1 h following granisetron administration. The tapes were assessed to detect and classify any arrhythmias. A continuous ECG (lead II) was displayed during the infusion of granisetron and for 30 min thereafter.

Vital signs (pulse, supine diastolic and systolic blood pressure, and body temperature) were recorded at the following times on the screening day; 6-h prior to granisetron infusion, immediately prior to granisetron administration, then at 30 s as well as 1, 2, 5, 10, 15, and 30 min and 1 h after granisetron infusion. Post-chemotherapy vital signs were assessed every 6 h for up to 24 h. Vital signs were also recorded on any subsequent day of granisetron treatment and at the follow-up visit.

Blood samples were taken for routine haematology and clinical chemistry analysis on the screening day, on the chemotherapy day prior to granisetron administration and at the follow-up assessment.

All adverse events, except nausea and vomiting, reported by the investigating team or by the patient either spontaneously or in response to direct questioning were evaluated and recorded on the case-record forms. The severity of the event and its relation to the study drug were assessed by the observer and the events were classified according to the WHO body-system classification and by the preferred term. Severe and serious adverse events were considered on an individual basis.

For the purpose of pharmacokinetic assessments, blood samples (5 ml) were taken via an indwelling catheter at the end of the granisetron infusion (30 s) and at 1.5, 3, 5, 10 and 30 min as well as 1, 2 and 4 h after the start of the granisetron infusion. Blood samples were centrifuged and plasma was stored at −20°C prior to assay for granisetron concentration. Samples were assayed using high-performance liquid chromatography (HPLC) with fluorescent detection [8] or by the current approved method for the analysis of granisetron in plasma.

Statistical assessment

The paired *t*-test was used to investigate changes in vital signs from baseline values. Summary statistics were calculated for demographic data and for vital-signs data at the time points indicated in the previous section. Mean values and 95% confidence intervals (CI) were also presented in graphical form for the period ranging from baseline to the last recorded value prior to cytotoxic infusion.

Results

In all, 12 men and 9 women entered the study. The mean age of the patients was 53.9 years (range, 29–71 years) and their mean weight was 67.8 kg (range, 42.3–92.8 kg). The characteristics of the patients are given in Table 1. Of the 21 patients, 17 were chemo-naive and 4 had previously received chemotherapy.

All patients had malignant disease, with primary sites being as follows: breast (5), colon (1), head and neck (1), lung (7), ovary (1), rectum (1), stomach (2), testis (2) and urethra/bladder (1). Although the time elapsing between the end of granisetron administration and the start of chemotherapy was not always 1 h, the primary safety data were collected at 30 min following granisetron administration and, therefore, the eligibility of the data was unaffected.

Efficacy

In the first 24 h, 17 of 21 patients (81%) experienced no episode of vomiting; 4 patients experienced between 1 and 4 episodes of vomiting during the same period.

Safety

Electrocardiography

All surface ECGs were analysed for changes in intracardiac conduction, and none was found. Some abnormalities in cardiac rhythm were found to be present both pre- and post-granisetron infusion by Holter and ECG (lead II) monitoring; these included supraventricular ectopics and ventricular premature beats, supraventricular ectopics, occasional supraventricular ectopics and occasional ventricular ectopics. Other abnormalities were seen pre- but not post-infusion, namely, a ventricular ectopic, a salvo of supraventricular ectopics and a supraventricular ectopic and broad-complex ventricular tachycardia.

Table 1 Demographic characteristics

Number of patients	21
Mean age (years)	53.9 ± 10.8
Range	29–71
Mean weight (kg)	67.8 ± 12.5
Range	42.3 – 92.8
Mean height (cm)	170.2 ± 8.3
Range	154–182
Sex	
M	12
F	9

Vital signs

Changes in vital signs from baseline were analysed statistically at various time points after the start of granisetron administration. No significant change was found in vital signs at 30 s or 1 min after infusion of granisetron, but at 10 and 15 min there was a very small but statistically significant fall in diastolic blood pressure (DBP) and a non-statistically significant trend in favour of a reduction in heart rate. None of these changes was considered to be clinically relevant and may reflect a decrease in the patients' anxiety following drug administration.

Adverse events

No clinically relevant adverse experience of the cardiovascular system was observed. During the study, 16 patients (76.1%) suffered 29 adverse events (Table 2). Adverse events related to the gastrointestinal system were experienced by 10 patients, 6 of whom (28.6%) experienced constipation. In all, 6 patients experienced events associated with the central and peripheral nervous system, and 5 of these (23.8%) experienced headache. All other adverse events were experienced on only one occasion or by one patient, except for fever and hot flushes, which were experienced by two patients each. Serious adverse events occurred in two patients. These comprised fever and thrombophlebitis in one patient and abdominal pain, sepsis, granulocytopenia and thrombocytopenia in another.

Table 2 Most commonly experienced adverse events

	n (%)
Any event	16 (76.1)
Constipation:	
Mild	3
Moderate	2
Severe	1
Total	6 (28.5)
Headache:	
Mild	3
Moderate	1
Total	5 (23.8)

Table 3 Pharmacokinetic parameters

	C_{max}(ng/ml)	$AUC_{(0-4)}$(ng h ml^{-1})[a]
Mean (CV %)	233 (96%)	90.9 (47%)
Median (range)	195 (44.6–1127)	71.2 (54.5–212)

[a] $n = 16$

Pharmacokinetics

Granisetron was detectable in plasma samples from all patients at between 30 s and 1.5 min after the start of the granisetron infusion. The pharmacokinetic parameters are summarised in Table 3. The peak plasma concentration (C_{max}) of granisetron was reached at between 30 s and 3 min after the start of the infusion, falling rapidly thereafter. In 18 patients (85.7%), granisetron plasma concentrations fell to half their peak value by 5 min after the start of the infusion. The C_{max} varied between 44.6 and 410.8 ng/ml in all patients but one, whose plasma concentration reached a value of 1127.1 ng/ml at 30 s from the start of the infusion (Table 3). It fell rapidly within 1 min to a value of 192.3 ng/ml. The corresponding $AUC_{(0-4h)}$ value of 107 ng h ml^{-1} recorded for this patient was not very different from the mean $AUC_{(0-4h)}$ value. The high C_{max} value obtained in this patient was not associated with any adverse event.

Discussion

The primary objective of this study was to assess the safety and tolerance of granisetron given as a 3-mg infusion over a period of 30 s. A total of 21 patients were monitored intensively, including Holter ECG recording for 6 h prior to and 1 h after granisetron administration and measurement of the SBP, DBP and heart rate on the day of administration. During the first 24 h, 17 of 21 patients (81%) did not experience vomiting; the remaining 4 patients experienced between 1 and 4 episodes of vomiting during the same period.

It is well known that the antiemetic domperidone, a dopamine antagonist, can cause cardiac arrest and arrhythmias when given i.v. at high doses [9–13]. The recent discoveries that 5-HT_3 receptors have been found in human atrial tissue [14] and that some 5-HT_3 receptor antagonists have been found to cause a dose-dependent prolongation of the QT interval have led to concerns that all 5-HT_3 receptor antagonists may have unwanted arrhythmogenic potential. 5-HT_3 receptor antagonists derived from tropane, such as zatosetron and tropisetron, are known to cause a dose-dependent increase in the QT interval on the surface ECG [15]. However, more recently, such an effect has been observed with ondansetron, a 5-HT_3 receptor antagonist unrelated to tropane [16]. It is possible, therefore, that the ECG effect is related to a general property shared by 5-HT_3 receptor antagonists rather than to the properties of the tropane structure. It was therefore noteworthy that in the present study the ECG abnormalities were either present both pre- and post-infusion or seen only pre-infusion. These were not considered to be clinically significant or to be related to granisetron. There was no intracardiac conduction defect found on the surface ECGs, and the PR and QT intervals were unchanged. Small, non-clinically significant decreases in blood pressure were detected at 10 and 15 min after the end of the infusion.

The results of the pharmacokinetic profile showed wide interpatient variability in granisetron plasma concentrations. The mean maximal plasma level was 233 ng/ml, within the range of 44.6–410.82 ng/ml (with the exception of one patient, whose value exceeded the top of the range), and the mean AUC was 90.9 ng h ml^{-1}. As expected, the maximal plasma levels were higher than those previously seen following a 30-min infusion of a similar dose (40 μg/kg) in patients [17, 18] and healthy volunteers [19], where mean plasma concentrations of around 30–40 ng/ml have been reported. Similar interpatient variations in plasma levels of granisetron were noted in healthy subjects and patients receiving 30-min infusions. The mean AUC value for granisetron given as a 30-min infusion was approximately 250–350 ng h ml^{-1}. Comparable data are not available for rapid infusion of ondansetron; however, in studies of standard infusions of clinical doses of ondansetron (8 or 32 mg) in healthy volunteers, peak plasma concentrations of 95 ng/ml (8 mg) and 123 ng/ml (32 mg) were shown. Studies of ondansetron have shown efficacy to be correlated with a high AUC value [20], but this has not been shown for granisetron [18].

For standard infusions of granisetron (40 mg/kg; 30 min) the half-life is around 4 h in healthy volunteers [17, 18] and longer in patients (around 9 h), due to a lower clearance rate in patients. This longer half-life allows for once-daily dosing in patients. However, standard infusions of clinical doses of ondansetron (8 or 32 mg) in volunteers have demonstrated a half-life shorter than that of granisetron, i.e. around 3–4 h owing to a higher clearance rate.

In the study reported herein, 81% of patients were completely protected from vomiting, suggesting that administration by bolus injection retains efficacy comparable to that of the 30-min infusion. Granisetron was well tolerated and the higher plasma levels achieved did not result in a reduction in tolerance to the drug. In all, 16 patients recorded 29 adverse events during the study. The most commonly reported adverse events were constipation and headache. Both are thought to be related to 5-HT_3 receptor antagonist therapy. Previous clinical studies of granisetron have reported an incidence of approximately 4% for constipation and

14% for headache [21]. Serious adverse events occurred in two patients but were not considered to be related to granisetron.

In conclusion, the results of this study demonstrate that granisetron (3 mg) given as a 30-s i.v. bolus infusion to patients receiving chemotherapy for malignant disease is both safe and well tolerated.

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