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ORIGINAL ARTICLE

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# The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy

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**Abstract** *Objectives*: To assess the cardiovascular safety, tolerability and efficacy of high doses of granisetron for the treatment of nausea and vomiting in patients undergoing highly emetogenic chemotherapy. *Methods*: Patients with histologically confirmed malignant disease were given an intravenous infusion of granisetron, 160 μg/kg, over 30 min, starting 15 min after highly emetogenic chemotherapy. Patients underwent cardiac monitoring for 24 h following the granisetron infusion. Pulse, blood pressure and electrocardiogram (lead II and ambulatory) measurements were taken, and routine clinical chemistry and haematology tests performed. Blood samples for pharmacokinetic analysis were taken before the granisetron infusion, and at intervals afterwards. Adverse events were self-assessed using a symptom checklist. Self-assessment categorical rating scales were used to evaluate patient nausea, vomiting and retching. *Results*: Ten patients (eight females and two males; average age 41.5 years) completed the trial and were included in the safety and efficacy assessments. No clinically relevant changes in electrocardiogram, pulse rate, blood pressure or laboratory parameters were observed. Furthermore, in the 7 days following dosing there were no serious adverse events leading to withdrawal from the trial. A complete response (no vomiting, retching or, at most, mild nausea) was experienced by five patients. Six patients had no, or mild, nausea and an additional two patients vomited on a maximum of two occasions. Additional antiemetic rescue medication was given to three patients during the 24-h trial period. Despite considerable interpatient variability, $C_{max}$ and AUC parameters were proportionally greater than values reported for lower doses of granisetron. *Conclusions*: Granisetron administered at four times the upper recommended dose demonstrated good efficacy and tolerability with no clinically important cardiac effects.

**Keywords** Emesis · Granisetron · Highly emetogenic chemotherapy · Cardiovascular safety · Tolerability

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## Introduction

Nausea and vomiting are significant and debilitating side effects of cytotoxic chemotherapy that profoundly affect patients' quality of life and can lead to the discontinuation of potentially life-saving treatment [26, 35]. Furthermore, nausea and vomiting can result in increased mortality, morbidity and health-care costs [29]. Cytotoxic drugs have variable emetogenic potential, with highly emetogenic agents such as cisplatin inducing nausea and vomiting in more than 70% of patients [18]. However, as a result of advances in antiemetic therapy, even symptoms resulting from highly emetogenic chemotherapy can be managed effectively. Following the introduction of 5-$HT_3$ receptor antagonists, effective control of nausea and vomiting is now considered the standard of care in patients receiving chemotherapy [18].

As a class, 5-$HT_3$ receptor antagonists are generally considered to have good safety and tolerability profiles; however, there are potentially important differences among them, particularly their cardiac effects [17, 25]. For example, dolasetron, a member of this class, is associated with electrocardiographic (ECG) abnormalities and has a cardiovascular warning in its labelling (Anzemet®, dolasetron mesylate; prescribing Information. Aventis Pharmaceuticals, Kansas City, Mo.) [17, 25, 30]. Such effects are of particular concern given that the majority of cancer patients are elderly (65 years and over), and cardiovascular disease is often comorbid with cancer in older patients, a combination which is a major

cause of mortality [39, 40]. In addition, the number of comorbidities tends to increase with age, with a resulting increase in the use of concomitant medications in elderly patients and an increased risk of drug–drug interactions [11, 38, 40]. Furthermore, some cardiac complications can arise directly as a result of cancer [15, 24]. Therefore, any treatment which adds to the cardiovascular burden of patients as a result of a direct effect on the heart or as a consequence of increased drug–drug interactions following polypharmacy should be avoided. This is also a problem with particular classes of cytotoxic drugs, such as anthracyclines, which can negatively affect cardiac function [12, 16, 34]. Thus, the potential for antiemetics to have an additional impact on cardiovascular function is an important consideration.

While it is evident that 5-$HT_3$ receptor antagonists are effective in the prevention of nausea and vomiting caused by highly emetogenic treatments [20, 31, 32], a number of studies have indicated that some patients may require rescue antiemetics, frequently at higher doses, in order to gain satisfactory control of emesis [9, 13, 36]. The emetogenicity of the chemotherapy used, together with patient characteristics such as age, gender and alcohol intake, concomitant therapies and prior exposure to chemotherapy regimens all influence an individual's predisposition to nausea and vomiting [14, 33]. Some patients require higher doses of 5-$HT_3$ receptor antagonists than others in order to achieve the same level of protection. This observation is supported by Carmichael et al. who proposed that, on an individual basis, there is no apparent threshold level of plasma granisetron for effect [7]. This may indicate that the potential for successful antiemetic treatment is likely to vary from patient to patient.

Granisetron labelling carries neither cardiovascular warnings nor limitations to its use in patients with cardiac dysfunction. Furthermore, no clinically important cardiovascular changes (pulse rate, blood pressure, ECG, QTc interval) have been observed with intravenous (i.v.) granisetron at doses as high as 300 μg/kg in healthy volunteers [6, 37]. Nevertheless, it is conceivable that adverse effects on cardiac function could occur at high doses of granisetron in cancer patients. This trial focused on the cardiovascular safety of high-dose granisetron in patients receiving highly emetogenic chemotherapy.

## Methods

Patients included in this open study were over 18 years of age, had a histologically confirmed malignant disease and a performance status of two or less according to the World Health Organization (WHO) criteria. Patients were excluded if they had:

- Current symptoms of ischaemic heart disease, cardiac arrhythmias or a significant conduction disturbance
- History of myocardial infarct within the previous 6 months
- Significant liver or renal dysfunction, or impaired bone-marrow function

All patients gave written informed consent, and were aware that they were free to withdraw from the trial at any time. The design of the study conformed to the principles of the Declaration of Helsinki, 1964, and its subsequent revisions, and was approved by the ethics committee.

All patients received granisetron, 160 μg/kg, given as a single 250-ml infusion lasting 30 min starting 15 min after chemotherapy was completed. Blood samples (5 ml) for pharmacokinetic analysis were collected predose and at intervals from 0.5 to 48 h after chemotherapy. Concentrations of granisetron in blood plasma were analysed by reverse-phase high-pressure liquid chromatography with fluorescence detection as previously described [10]. The pharmacokinetic parameters determined included $C_{max}$, area under the plasma concentration-time curve between zero and infinity (AUC), the terminal elimination half-life ($t_{1/2}$), volume of distribution (V) and total plasma clearance (CL) which were determined using AUCDAT version 4.0 and MODFIT version 3 software on a Digital Equipment Corporation VAX 11-750 computer.

Patients were monitored for 24 h following the granisetron infusion. ECG lead II was displayed continuously throughout the granisetron infusion with a physician in constant attendance. Ambulatory ECG (Holter) monitoring was performed, recording onto cassette tape from 10 min before the start of the granisetron infusion and continuing until 24 h after its completion. Tapes were replayed through a Reynolds Medical Pathfinder 3 system to detect and classify arrhythmias. Patients' pulse and blood pressure were recorded prior to and at completion of the granisetron infusion and subsequently at 1, 2, 3, 4, 6 and 24 h thereafter. Routine clinical chemistry and haematology tests were performed prior to granisetron and at 24 h after the granisetron infusion. Adverse signs and symptoms were self-monitored with completion of a checklist prior to the granisetron infusion and at 4, 24, 48 and 72 h.

Nausea was rated by patients prior to granisetron and at 6, 12, 18, 24, 48 and 72 h using both a 100-mm visual analogue scale (VAS), ranging from "no nausea at all" to "the worst nausea I have ever felt" and a categorical rating scale of severity of nausea (0 = none, 1 = slight, 2 = moderate, 3 = severe). The incidence of vomiting was recorded by the study investigators up to 72 h after the start of the granisetron infusion. In addition, patients were asked to assess the incidence and severity of their own vomiting 24 h after the study drug infusion. Rescue medication consisting of conventional antiemetic therapy (but excluding high-dose metoclopramide) was administered to control emesis at the discretion of the supervising physician.

Full statistical analyses of efficacy were not considered appropriate given the small number of patients treated. However, descriptive statistics were used, where appropriate.

## Results

Ten patients entered the study. The patient population consisted of eight females and two males with an average age of 41.5 years (range 28–56 years). Patient details, including chemotherapy, are shown in Table 1. All ten patients who entered the study received highly emetogenic chemotherapy as detailed in Table 1.

No significant changes in lead II ECG recordings were observed during the trial. Furthermore, there were no clinically important findings resulting from the analysis of the ambulatory ECG recordings and there was no evidence of conduction disturbances (Table 2). There were three reports of sinus tachycardia from the ECG recordings. However, the changes predated the granisetron infusion and pulse rate recordings did not show any significant change associated with drug administration and no clinically

**Table 1** Clinical diagnosis and chemotherapy treatment for each patient

| Patient number | Clinical diagnosis | Chemotherapy drug | Chemotherapy dose |
|---|---|---|---|
| 1 | Metastatic breast carcinoma | Doxorubicin | 1.06 mg/kg |
| | | Ifosfamide | 131 μg/kg |
| 2 | Malignant melanoma | CB10-277[a] | 170 mg/kg |
| 3 | Breast carcinoma | Doxorubicin | 1.07 mg/kg |
| | | Ifosfamide | 133 μg/kg |
| 4 | Metastatic malignant melanoma | Dacarbazine | 15.4 mg/kg |
| | | Vindesine | 76.9 μg/kg |
| 5 | Metastatic carcinoma/unknown primary | Bleomycin | 500 μg/kg |
| | | Cisplatin | 1.42 mg/kg |
| 6 | Floor-of-mouth carcinoma | Doxorubicin | 1.10 mg/kg |
| | | Cisplatin | 1.37 mg/kg |
| 7 | Metastatic breast carcinoma | Doxorubicin | 750 μg/kg |
| | | Ifosfamide | 77.5 μg/kg |
| 8 | Metastatic breast carcinoma | Doxorubicin | 797 μg/kg |
| | | Ifosfamide | 149 μg/kg |
| 9 | Ovarian cystadenocarcinoma | Doxorubicin | 1.20 mg/kg |
| | | Cisplatin | 2.20 mg/kg |
| 10 | Ovarian cystadenocarcinoma | Carboplatin | 10.7 mg/kg |

[a]A dacarbazine analogue (experimental compound)

**Table 2** Ambulatory (Holter) ECG monitoring results for the 24 h after granisetron infusion (*APB* atrial premature beat, *PAC* premature atrial contraction, *PVC* premature ventricular contraction, *SVT* supraventricular tachycardia, *VE* ventricular ectopic beat, *VPB* ventricular premature beat)

| Patient number | Trace quality | Dominant rhythm | Atrial arrhythmias | Ventricular arrhythmias | Conduction disturbance | Comments of cardiologist |
|---|---|---|---|---|---|---|
| 1 | No recording | | | | | |
| 2 | Good | Sinus rhythm | Nil | Nil | Nil | Normal sinus rhythm |
| 3 | Good | Sinus rhythm evidence of sinus tachycardia throughout | Nil | Nil | Nil | Daytime tachycardia; settling at night |
| 4 | Good | Sinus rhythm | Nil | Occasional VPBs | Nil | Physiological recording with occasional VEs |
| 5 | No recording | | | | | |
| 6 | Good | Sinus rhythm | Occasional PAC | Nil | Nil | Normal |
| 7 | Good | Sinus rhythm | Nil | PVCs up to 4/min | Nil | Fairly frequent ventricular ectopics at times; mainly during night |
| 8 | Good | Sinus rhythm | Sinus tachycardia at times | Rare VEs | Nil | I think the computer report of SVT is wrong: the P-waves during tachycardia (shown) are normal—this is more likely to be sinus tachycardia |
| 9 | Fair incomplete recording (15 h) | Sinus tachycardia throughout | Nil | Nil | Nil | Sinus tachycardia of around 110/min |
| 10 | Good | Sinus rhythm | Very occasional APBs | Very occasional VEs | Nil | A few atrial and ventricular ectopics. A physiological recording |

important changes in blood pressure occurred. No unexpected abnormalities in haematology or clinical chemistry were seen.

Adverse events were collected by means of checklists completed by the patients and events that were identified as treatment-emergent are summarized (Table 3). The most common adverse events were chills and fever (though these were not considered to be related to the granisetron treatment), somnolence and taste perversion, each reported by four patients. All adverse events were either mild or moderate in severity, with the exception of single reports of chills, fever, diarrhoea, thirst, somnolence, sputum production and taste perversion. None of the adverse events was considered related to the granisetron infusion.

A complete response (no vomiting, retching or, at most, mild nausea) was achieved by five patients. Six patients had no, or mild, nausea and eight patients had no vomiting or vomited a maximum of twice. Additional antiemetic rescue medication was given to three patients during the 24-h trial period; two patients received oral dexamethasone, 4 mg every 20 h after granisetron, and another patient received a single dose of oral metoclopramide, 10 mg.

The pharmacokinetics are summarized in Table 4. There was considerable interpatient variation in both

**Table 3** Summary of treatment-emergent adverse events classified by body system for all patients

| Body system | Adverse event | Symptom severity (number of patients) | | | | Total (%) |
|---|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | Unknown | |
| Body as a whole | Asthenia | | 1 | | | 1 (10) |
| | Chills and fever | 2 | 1 | 1 | | 4 (40) |
| | Abdominal pain | | 1 | | | 1 (10) |
| Digestive system | Eructation | 3 | | | | 3 (30) |
| | Flatulence | | 1 | | | 1 (10) |
| | Dry mouth | 1 | | | | 1 (10) |
| | Diarrhoea | | | 1 | | 1 (10) |
| Metabolic/nutritional | Thirst | 1 | | 1 | | 2 (20) |
| Nervous system | Confusion | 1 | | | | 1 (10) |
| | Dizziness | 1 | 1 | | | 2 (20) |
| | Somnolence | 2 | 1 | 1 | | 4 (40) |
| | Tremor | 1 | | | | 1 (10) |
| Respiratory system | Respiratory disorder | 1 | | | | 1 (10) |
| | Sputum increased | | | 1 | | 1 (10) |
| Skin/appendages | Sweating | 1 | | | | 1 (10) |
| Special senses | Taste perversion | 3 | | 1 | | 4 (40) |
| Urogenital system | Urine abnormality | 1 | | | 2 | 3 (30) |

**Table 4** Summary of pharmacokinetic parameters ($C_{max}$ maximum observed plasma concentration, $AUC$ area under the plasma concentration–time curve between zero and infinity, $t_{1/2}$ terminal elimination half-life, $V$ volume of distribution, $CL$ total plasma clearance, $CV$ coefficient of variation)

| Parameter | Range | Number of patients | Mean | % CV |
|---|---|---|---|---|
| $C_{max}$(ng/ml) | 51.2–208 | 10 | 105 | 44 |
| AUC (ng/ml·h) | 175–1454 | 9 | 546 | 84 |
| V (l) | 52.0–331 | 9 | 160 | 51 |
| V (l/h) | 1.30–5.34 | 9 | 2.84 | 45 |
| CL (l/h) | 4.4–54.9 | 9 | 29.5 | 68 |
| CL (l/h/kg) | 0.11–0.91 | 9 | 0.52 | 64 |
| $t_{1/2}$(h) | 1.63–11.7 | 9 | 5.52 | 62 |

$C_{max}$ and AUC, but these were in keeping with previously reported data using lower dose levels. In particular, $C_{max}$ and AUC values (mean ± coefficient of variation) from this study using granisetron, 160 μg/kg (105 ng/ml ±44% and 546 ng·h/ml ±84%) were approximately twice the corresponding values from a study using granisetron, 80 μg/kg (67.7 ng/ml ±59% and 359 ng·h/ml ±79%) [1].

## Discussion

The choice of appropriate cytotoxic therapy is influenced by a number of factors, with efficacy the prime factor. However, the toxicity profile is also important, with particular chemotherapeutic agents associated with a substantial cardiotoxic risk. Set against the background of a demographic shift towards ageing populations and an associated increased incidence of comorbid cardiovascular and malignant disease, it is particularly important that the potential cardiac effects of supportive care therapies (e.g. 5-$HT_3$ receptor antagonists) be considered carefully. Although the effects of many of these agents have been studied at therapeutic doses [3, 6, 8, 22], the consequences of administering such agents at higher doses in patients undergoing chemotherapy are unclear. This trial provides useful data regarding the safety and tolerability of high doses of granisetron, which may be required to treat patients with refractory disease.

The i.v. infusion of granisetron, 160 μg/kg, administered over 30 min, was well tolerated by patients undergoing highly emetogenic chemotherapy. Furthermore, there were no serious adverse events within 7 days following the granisetron infusion and none of the adverse events was attributed to the drug. There were no clinically important changes in pulse rate, blood pressure or cardiac rhythm and no changes in haematology or clinical chemistry that were inconsistent with the nature of the patients' malignant disease and/or its treatment. Thus, these results indicate that granisetron can be safely administered to cancer patients at doses up to 160 μg/kg.

The pharmacokinetic results of this study, when compared to those observed previously at lower doses, are consistent with granisetron kinetics being linear up to 160 μg/kg, although a large interpatient variation was observed. However, this is also consistent with observations from previous trials [1]. In particular, the data suggest that variability in clearance is the principle determinant of intersubject variations in the pharmacokinetic behaviour of this drug.

In view of the small number of patients, no firm conclusions can be drawn regarding the efficacy of the high doses of granisetron used. However, clinical studies consistently show a trend towards increased antiemetic efficacy with increasing doses of granisetron [5, 19, 23, 28, 32, 36]. Some data demonstrate that patients experiencing unsatisfactory control of nausea and vomiting with granisetron can respond to supplementary doses, or doses of granisetron that are higher than those generally

used [36]. Furthermore, some patients refractory to other 5-$HT_3$ receptor antagonists respond well to granisetron, again sometimes at doses that may be higher than those in general use [9, 13].

The current study indicated that granisetron, 160 μg/kg, is not associated with any cardiac related safety problems. Comparative studies with granisetron and other 5-$HT_3$ receptor antagonists have demonstrated differences between the drugs in this class to induce ECG changes. In a trial of 12 healthy subjects in which ondansetron, 32 mg i.v., granisetron, 10 μg/kg i.v., and placebo were compared, there were no changes in QTc, PR or QRS intervals on the ECGs of patients who received granisetron, in comparison with the ondansetron group who had a significantly longer QTc interval after dosing, compared with either granisetron or placebo [6]. In another study, i.v. granisetron, 3 mg, and i.v. dolasetron, 1.8 and 2.4 mg/kg, were compared in patients ($n = 474$) receiving high-dose cisplatin chemotherapy. The dolasetron-treated patients had significantly greater increases in QTc and PR intervals 1–2 h after dosing compared with patients treated with granisetron, and there were no significant differences between the groups for QRS duration [3]. Moreover, no significant differences between placebo- and granisetron-treated healthy volunteers were observed in PR, QRS or QTc intervals at doses of granisetron up to 300 μg/kg, and all subjects who received this high dose of granisetron remained well and asymptomatic throughout the study [37]. The absence of an effect of granisetron on the ECG is reflected in the prescribing information for granisetron (Kytril®, Roche Laboratories, Nutley, N.J.), which does not include any cardiovascular warning for use of the drug.

This contrasts with trials of other 5-$HT_3$ antiemetics. In a study of i.v. dolasetron ($n = 198$), 1.8 or 2.4 mg/kg, versus i.v. ondansetron ($n = 206$), 32 mg, for acute cisplatin-induced emesis, prolongation of the PR, QRS, QT, and QTc intervals was recorded for both antiemetics, with greater average changes from baseline in PR, QRS and QTc intervals with dolasetron compared to ondansetron [21]. In another study ($n = 696$) in which 8 days treatment with dolasetron, 2.4 mg/kg i.v. then 200 mg orally, was compared with ondansetron, 32 mg i.v. then 8 mg orally three times daily, in patients receiving chemotherapy, ECG changes in both groups of patients were identified: prolongation of the QTc interval developed in 41% of dolasetron-treated and 19% of ondansetron-treated patients [27]. QRS prolongation was reported in 24% and 9% of dolasetron- and ondansetron-treated patients, respectively. In a study of patients ($n = 45$) receiving i.v. ondansetron, 32 mg, or dolasetron, 2.4 mg/kg, PR, QRS, QT and QTc interval prolongation was found [4]. Increases in the PR, QRS and QT intervals after administration of each agent and QTc after dolasetron were significant ($P < 0.05$). Furthermore, ondansetron significantly slowed heart rate by a mean eight beats per minute ($P < 0.05$).

Since prolongation of the QTc interval has been shown to be an independent risk factor for sudden death [2], and is also a risk factor for torsades de pointes, a hard-to-treat arrhythmia that can be fatal, such effects may have serious consequences. Thus the prescribing information for dolasetron states that the agent should be administered with caution in patients who either have or may develop prolongation of cardiac conduction intervals, particularly QTc. Furthermore, the prescribing information for tropisetron also states that this 5-$HT_3$ antiemetic agent can prolong the QTc interval and that caution should be exercised in patients with cardiac rhythm or conduction disturbances. As a consequence, patients with cardiac abnormalities have been excluded from participation in clinical trials of dolasetron and tropisetron. In contrast, the prescribing information for granisetron and ondansetron do not include any such warnings, and both agents have shown a good safety profile in clinical practice. A recent review examining the cardiotoxic potential of 5-$HT_3$ receptor antagonists has thus concluded that dolasetron has a greater effect on ECG intervals compared with either granisetron or ondansetron, with ondansetron having a more pronounced effect on ECG intervals compared to granisetron [25].

The current study demonstrated that high-dose granisetron can be safely administered to patients receiving highly emetogenic chemotherapy. The best choice of antiemetic agent in this patient population should be one associated with the lowest risk of serious adverse events, including the use of the agent at a high dose. Examination of the current information regarding the cardiac safety of 5-$HT_3$ antiemetics [25], along with the results of the present study, indicate that granisetron may have the least potential for adverse cardiac events in this setting.

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