High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability

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This phase II trial assessed the cardiovascular safety and tolerability of high-dose granisetron for the treatment of nausea and vomiting in cancer patients undergoing emetogenic chemotherapy. Forty-one patients were given 30-min infusions of granisetron, 40 or 120 μg/kg i.v., as either a single dose or as split doses, at 6-h intervals. Subsequently, patients had the option of the alternative dosing regimen or to return to conventional antiemetic therapy. Patients were monitored for 24 h following the first granisetron infusion. Electrocardiogram (ECG; lead II and Holter monitoring) measurements were made during the study and blood samples for pharmacokinetic analysis were taken at regular intervals for 48 h after the start of the first granisetron infusion. During the first chemotherapy session, granisetron was administered as: (i) bolus doses of 80 μg/kg ($n=3$) and 120 μg/kg ($n=19$) or (ii) split doses of 2×40 μg/kg ($n=1$) and 3×40 μg/kg ($n=18$). Crossover therapy was administered to 22 patients, with granisetron doses of 120 μg/kg ($n=12$), 2×40 μg/kg ($n=1$) and 3×40 μg/kg ($n=9$). We conclude that supra-therapeutic doses up to 120 μg/kg granisetron had no clinically significant effect on ECG, pulse rate or blood pressure. The treatment was well tolerated with no significant changes in biochemistry or hematological parameters.
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Introduction

Chemotherapy-induced nausea and vomiting are debilitating side-effects of cancer chemotherapy. Apart from the detrimental effect on mortality, morbidity and healthcare costs [1], nausea and vomiting are highly distressing, and can cause patients to discontinue treatment [2,3]. Fortunately, there have been significant advances in the control of emesis; in particular, the introduction of the 5-HT_3 receptor antagonists, whose antiemetic potency has led to effective control of nausea and vomiting being deemed the standard of care in chemotherapy patients [4]. The effectiveness of the 5-HT_3 receptor antagonists is significantly enhanced by the addition of dexamethasone [5] and current antiemetic guidelines recommend this combination [6–9].

While all 5-HT_3 receptor antagonists are generally considered to have good safety and tolerability profiles, there are differences. There are differences in cardiovascular safety between available drugs; dolasetron and tropisetron are associated with electrocardiogram (ECG) abnormalities [10–12]. Cancer is prevalent in the elderly with more than 60% of patients aged over 65 years [13]. Cardiovascular disease is often comorbid with cancer in this group of patients and is a major cause of mortality [13,14]. This could be due, in part, to an age-related predisposition of patients to the cardiotoxic effects of some chemotherapeutic regimens. Furthermore, some cardiac complications can arise directly as a result of cancers, such as metastases to cardiac structures, carcinoid heart disease and dysrhythmias [15,16]. Set against this background of increasing cardiovascular risk with demographics shifting towards elderly populations, the cardiotoxic potential of antiemetics is an important consideration [17]. Elderly patients take a wide variety of prescription and over-the-counter drugs [18,19], which may increase the risk of drug–drug interactions with potentially adverse cardiovascular effects.

Although 5-HT_3 receptor antagonists have been shown to be very effective for the treatment of chemotherapy-induced emesis [20–22], studies have shown that there are some patients who require supplementary doses of these agents to gain full antiemetic control [23–25]. Predisposition to nausea and vomiting, as well as response to therapy, varies widely [26–28], and this may lead to patients requiring higher than recommended doses of antiemetic drugs.

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In healthy volunteers, high-dose granisetron (up to 300 μg/kg i.v.) has been reported not to have clinically relevant effects on cardiovascular measurements including pulse rate, blood pressure and ECG [29,30]. Therefore, granisetron has no cardiovascular warnings or any limitation to its use in patients with cardiac dysfunction at clinically indicated doses [31]. However, the half-life of granisetron is longer in cancer patients compared with healthy volunteers [29,32] and with higher doses of granisetron not infrequently used in the clinical setting, some cancer patients may be exposed to much higher serum concentrations. In a previous study, the authors found no significant cardiovascular effects of granisetron at a dose of 160 μg/kg in a small cohort of patients ($n = 10$) [33]. No clinically relevant changes in ECG, pulse rate, blood pressure or laboratory parameters were recorded. The aim of the current investigation was to extend the observation of cardiovascular safety of granisetron to a larger cohort of patients ($n = 41$), and a different range of doses and dosing regimens. In addition, and in contrast to the previous study, the majority of patients were receiving cisplatin-based chemotherapy. The highly emetogenic nature of this agent increases the likelihood that increased doses of antiemetic agent may be used with such therapy.

Methods

Entry criteria included patients > 18 years of age, histologically confirmed malignant disease and a WHO performance status of ≤ 2. Patients were excluded if they had a history of cardiovascular problems; significant liver or renal dysfunction, or impaired bone-marrow function; a history of seizures or cerebral tumors; or if they were taking psychotropic drugs. All patients gave written informed consent. The design of the study conformed to the Declaration of Helsinki, 1964, and its subsequent revisions, and was approved by the relevant ethics committees.

All patients received granisetron, either given as a single dose (80 or 120 μg/kg) or split doses (2×40 or 3×40 μg/kg) as 250-ml infusions over 30 min. Antiemetic treatment started 15 min after completion of chemotherapy. Split doses were administered at 6-h intervals. Blood samples (5 ml) for pharmacokinetic analysis were collected pre-dose and at intervals from 0.5 to 48 h. For the divided-dose regimens, the pharmacokinetic schedule encompassed all infusions. An additional 'pre-dose' sample was then taken prior to each granisetron infusion and sampling resumed according to the single-dose schedule. Concentrations of granisetron were analyzed by reverse-phase high-pressure liquid chromatography with fluorescence detection as described fully elsewhere [34]. Pharmacokinetic parameters included maximum observed plasma concentration following dosing (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_d), and total plasma clearance (CL) determined using AUCDAT version 4.0 and MODFIT version 3 software on a Digital Equipment Corporation VAX 11-750 computer.

ECG lead II was displayed continuously throughout single-dose granisetron infusions and the first dose of a split-dose regimen with a physician in constant attendance. Ambulatory ECG (Holter) monitoring was commenced 10 min prior to granisetron infusions continuing until 24 h following completion. Tapes were replayed through a Reynolds Medical Pathfinder 3 system to detect and classify arrhythmias, and the reports reviewed by a cardiologist. Patients' pulse rate and blood pressure were recorded prior to the granisetron infusion, and at 0, 1, 2, 3, 4, 6 and 24 h thereafter. Routine clinical chemistry and hematology tests were performed, prior to the granisetron infusion and at 24 h. Adverse signs and symptoms were self-assessed, patients completing a checklist prior to the granisetron infusion, and at 4 and 24 h thereafter. Full details of adverse events were recorded separately and followed-up with further laboratory tests, if necessary, until causality was established.

The investigator assessed the incidence and severity of retching and vomiting at regular intervals over the first 24 h, and patients assessed the incidence and severity of any vomiting 24 h after completion of the chemotherapy and study-drug infusion. A 100-mm visual analog scale (VAS), ranging from 'no nausea at all' (0) to 'the worst nausea I have ever felt' (100) was used for the patients to rate the level of nausea prior to the granisetron infusion, and at 0, 1, 4, 6 and 24 h thereafter. Rescue medication, consisting of conventional antiemetic therapy (but excluding high-dose metoclopramide), was administered to control emesis.

Results

A total of 41 patients entered the study. The patient population consisted of 16 females and 25 males; mean age 45.5 years (range 18–67 years). Trial participants had a wide range of clinical diagnoses including: lung cancer ($n = 11$), upper gastrointestinal carcinoma ($n = 6$), ovarian carcinoma ($n = 3$), breast carcinoma ($n = 5$) and malignant melanoma ($n = 2$). The cytotoxic chemotherapy regimens were primarily cisplatin combinations (Table 1). The doses of granisetron administered to patients during cycles 1 and 2 are shown in Table 2.

The results of the 24-h ECG monitoring are summarized in Table 3. There were no clinically significant changes in lead II ECG recordings during the trial and no clinically important findings resulting from the analysis of ambulatory ECG recordings. The minor ECG features described in Table 3 did not correspond with the peak

Table 1 Chemotherapy regimens administered during the trial

Chemotherapy regimen	No. of patients ($n=41$)
Cisplatin containing	39
Cisplatin $>50\,mg/m^2$	34
Doxorubicin/etoposide/ifosfamide/vincristine/mesna	1
Doxorubicin/ifosfamide/mesna	1

Table 2 Granisetron doses administered during the trial

	Granisetron dose (μg/kg)			
	1×80	2×40	1×120	3×40
Session 1 ($n=41$)	3	1	19	18
Session 2 ($n=22$)	0	1	12	9
Total no. of treatments	3	2	31	27

Table 3 Results of the 24-h ECG monitoring during the first session as reviewed by an independent cardiologist for individual patients

ECG feature	No. of patients ($n=41$)
Normal/physiological recordings	17
Junctional coronary sinus rhythm	1
Intermittent type I AV block (Wenckebach)	1
Occasional VEBs	2
Frequent VEBs (considered benign)	1
Occasional VEBs and APBs	1
Occasional salvos of AF (at night)	1
Four-beat AF	1
Occasional atrial extrasystoles + 10-beat run SVT	1
SVT (up to 20 beats) with salvos of SVT and VEBs	1
SVT–two brief runs	1
Very brief bigeminy, occasional VEBs and APBs	1
Sinus tachycardia	1
Technical failures	3
No recording	8

AV, atrioventricular; VEB, ventricular ectopic beat; APB, atrial premature beat; AF, atrial fibrillation; SVT, supraventricular tachycardia.

plasma concentration; there was no pattern in the timing of these events and they usually occurred when the granisetron plasma concentration had declined to below 10% of the peak value. There were no conduction disturbances associated with the granisetron infusion. Likewise, there were no clinically important changes in heart rate or blood pressure observed during the study. There were no abnormalities in hematology or clinical chemistry that could not be explained by patients' malignant disease or chemotherapy.

Adverse events were collected using checklists filled in by the patients and are summarized (Table 4). The most frequent adverse events associated with granisetron treatment were somnolence, headache, and chills and fever. For the 31 patients who received a single dose of granisetron, the majority of adverse events reported by patients were graded as mild, though four patients reported severe thirst, and one patient reported severe headache, somnolence, blurred vision, partial transitory deafness and taste perversion. For the 27 patients who received split doses ($3\times40\,\mu g/kg$) of granisetron the majority of self-reported adverse events were again mild, though two patients reported severe somnolence, and in addition symptoms of pain, glossitis, emotional lability, paresthesia, taste perversion and urine abnormalities were each reported as severe by one patient. None of these adverse events were attributed to the granisetron infusion by the study investigators.

Table 4 Summary of the most common treatment-emergent adverse events as reported by patients using a symptom checklist

Adverse event	No. (%) of patients
Single dose of granisetron (80 or 120 μg/kg; $n=34$)	
somnolence	17 (50)
headache	11 (32)
chills and fever	9 (26)
sweating	9 (26)
asthenia	8 (23)
thirst	7 (20)
confusion	6 (18)
eructation	6 (18)
Split dose of granisetron ($3\times40\,\mu g/kg$; $n=27$)	
somnolence	16 (59)
headache	7 (26)
chills and fever	7 (26)
dizziness	6 (22)

A summary of the granisetron pharmacokinetic parameters is shown in Table 5.

Discussion

In addition to symptomatic toxicities, some cytotoxic agents are associated with a cardiotoxic risk. Additionally, with an ageing population there is an increased incidence of comorbid cardiovascular and malignant diseases. In a recent Italian study of elderly non-small cell lung carcinoma patients, cardiovascular problems were found to be the most common comorbidities, with an average prevalence of 60.3% [35]. Therefore, the potential cardiac side-effects of supportive-care drugs, such as the 5-HT_3 receptor antagonists, need to be carefully considered. Although these side-effects are considered minimal at currently recommended doses [30,36–38], the consequences of administering 5-HT_3 receptor antagonists at higher doses not infrequently used in patients undergoing chemotherapy are unclear. It is thus beneficial to determine safety and tolerability of granisetron over a broad spectrum of doses. This trial provides useful data regarding the tolerability and cardiac safety of high doses of granisetron in cancer patients, and extends the observations of our previous study [33].

No firm conclusions can be drawn regarding the efficacy of the high doses of granisetron used in this patient population, in view of the varied population studied.

Table 5 Summary of pharmacokinetic parameters for single-dose granisetron therapy in both sessions (due to incomplete data collection for split-dose granisetron therapy, no derived parameters were obtained for this group)

Parameter	Granisetron dose (μg/kg)	No. of patients	Range	Mean	CV (%)
C_{max} (ng/ml)	80	3	48.5–66.4	57.6	16
	120	28	31.2–477.0	95.9	85
AUC (ng/ml/h)	80	3	265.0–1858.0	1016.0	79
	120	28	66.6–4897.0	715.0	130
V_d (l)	80	3	61.2–176.0	129.0	47
V_d (l/h)			1.22–3.21	2.27	44
V_d (l)	120	28	78.0–357.0	180.0	42
V_d (l/h)			1.23–5.46	2.72	41
CL (l/h)	80	3	2.15–19.00	8.64	105
CL (l/h/kg)			0.04–0.30	0.14	96
CL (l/h)	120	28	1.57–92.80	27.7	91
CL (l/h/kg)			0.02–1.80	0.44	101
$t_{1/2}$ (h)	80	3	5.43–25.70	16.9	61
	120	28	1.51–34.7	8.58	83

C_{max}, maximum plasma concentration; AUC, area under the plasma concentration–time curve between zero and infinity; $t_{1/2}$, terminal half-life; V_d, volume of distribution; *CL*, total plasma clearance; CV, coefficient of variation.

However, the control of nausea and vomiting was at least as effective as that which can be achieved with conventional antiemetic treatment. In addition, despite high response rates to recommended doses, 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 [23]. However, clinical studies show a trend towards increased antiemetic efficacy with increasing doses of granisetron [21,23,39–42]. 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 [24,25].

As demonstrated previously with single doses of granisetron, 160 μg/kg [33], granisetron dosed as either 80 or 120 μg/kg single doses or split doses of 2×40 or 3×40 μg/kg infusions administered over 30 min in this study were well tolerated by patients undergoing emetogenic chemotherapy. No adverse events experienced by the patients treated in this study were attributed to the granisetron infusions. Importantly, there were no clinically relevant changes in pulse rate, blood pressure or cardiac rhythm, and no significant changes in hematology or clinical chemistry inconsistent with the patients' underlying malignant diseases or its treatment.

The data generated from this trial are in agreement with other studies with granisetron indicating that it is not associated with significant cardiovascular adverse events. A comparative study of i.v. granisetron, 10 μg/kg, ondansetron, 32 mg, and placebo in 12 healthy volunteers showed that granisetron did not cause any significant ECG changes including QTc, PR and QRS intervals [30]. However, in the ondansetron-treated subjects, the QTc interval was increased significantly compared to both the placebo and granisetron groups [30]. Indeed, doses of granisetron up to 300 μg/kg have been tested in healthy volunteers with no adverse effects on ECG parameters and all subjects remained well with no adverse symptoms throughout the study [29]. In addition, our own observations of the effect of high-dose granisetron, 160 μg/kg, in a small cohort of patients undergoing moderately emetogenic chemotherapy revealed no evidence of clinically significant cardiovascular effects [33]. Here, we extend our previous observations to a broader range of granisetron concentrations in a larger group of patients who are principally receiving highly emetogenic cisplatin chemotherapy.

In a comparative study in 474 patients receiving high-dose cisplatin chemotherapy, comparing the ECG effects of i.v. dolasetron, 1.8 and 2.4 mg/kg, and granisetron, 3 mg, there were significantly greater increases in PR and QTc intervals in dolasetron treated patients 1–2 h after dosing, compared with the patients who received granisetron [36].

The labeling for other 5-HT_3 receptor antagonists, i.e. dolasetron [11] and tropisetron [10], carries cardiovascular warnings. Although no randomized trial data currently exists for the effects of tropisetron on cardiovascular parameters, the prescribing information states that it can prolong the QTc interval and that caution is needed in patients with cardiac rhythm or conduction disturbances [10]. The prescribing information for dolasetron states that this agent should be administered with caution in patients who either have, or may develop, prolongation of cardiac conduction intervals, particularly QTc. Many comparative studies have been done to compare the ECG effects of dolasetron and ondansetron. Although the prescribing information for ondansetron does not contain any warnings for patients at increased risk of cardiac arrhythmias, studies have demonstrated that it has some effects on the ECGs of

cancer patients. Treatment with either ondansetron, 32 mg, or dolasetron, 1.8 or 2.4 mg, caused prolongation of cardiac conduction intervals (PR, QRS, QT and QTc intervals), but dolasetron-treated patients developed greater average changes from baseline in PR, QRS and QTc intervals compared with ondansetron [43]. In another study, ondansetron, 32 mg, and dolasetron, 2.4 mg/kg, resulted in significant prolongation of PR, QRS, QT and QTc intervals from baseline following administration ($p < 0.05$) [44]. Increases in PR, QRS and QT intervals after administration of both drugs, and an increase in the QTc interval after dolasetron were significant ($p < 0.05$). Furthermore, ondansetron significantly slowed heart rate by a mean 8 beats/min ($p < 0.05$). In another study, 41 and 24% of patients, respectively, experienced prolongation of the QTc and QRS interval following dolasetron treatment, compared with 19 and 9% of ondansetron-treated patients, respectively ($n = 696$) [45]. Overall, dolasetron is considered to result in greater cardiac effects compared with either ondansetron or indeed granisetron [46–48].

Prolongation of the QTc interval is potentially serious, as it has been linked to sudden death [17], and is an associated risk factor for torsades de pointes, a hard-to-treat and potentially fatal arrhythmia. Consequently, patients with cardiac impairment have been excluded from the large published clinical trials of dolasetron and tropisetron [43,45,47,49–53].

The small sample size of patients receiving granisetron in this study, 80 μg/kg, and an incomplete dataset for the split-dose granisetron therapy (Table 5) limits the discussion of granisetron pharmacokinetics to patients who received granisetron, 120 μg/kg. Large inter-patient variations were recorded for all pharmacokinetic parameters following granisetron, 120 μg/kg, particularly in AUC (66.6–4897.0 ng/ml/h). Despite this, however, the C_{max} and AUC values, as well as the range of inter-patient variation, are consistent with previously reported data from clinical trials using lower doses of granisetron in cancer patients [32,37]. Specifically, the C_{max} values in this study for granisetron, 120 μg/kg, are about 50% greater than those measured following granisetron, 80 μg/kg, by Addelman *et al.* (95.9 ng/ml ± 85% versus 67.7 ng/ml ± 59%, respectively) [32]. Differences in drug clearance may be responsible for most inter-patient variation in the pharmacokinetic behavior of the drug. This variation is also reflected in the range of elimination half-life of granisetron (1.51–64.7 h).

Conclusions

The current investigation has shown that high-dose granisetron is not associated with any clinically significant cardiovascular complications and the results suggest that i.v. granisetron can be safely administered to patients up to doses of 120 μg/kg. This trial also supports the view that healthcare providers need not pre-screen cancer patients for possible cardiac impairment prior to granisetron therapy. Granisetron may, therefore, be an appropriate antiemetic choice for patients receiving emetogenic chemotherapy who are at risk of cardiac impairment.

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