PERGAMON

European Journal of Cancer 39 (2003) 927–931

European Journal of Cancer

www.ejconline.com

Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic: results of a pilot study

M. Aapro[a,*], J.P. Bourke[b]

[a]*Clinique de Genolier, CH-1272 Genolier, Switzerland*
[b]*Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, UK*

Received 14 January 2003; accepted 14 January 2003

Abstract

Patients with advanced malignancy are at an increased risk of cardiac arrhythmias, from their cancer and cardiotoxic treatments. Supportive care products co-administered should therefore not increase this risk. No clinically important cardiovascular effects are associated with the administration of granisetron over 30 s. To determine the effects of a rapid (1 s) injection of granisetron, 3 mg, on measures of cardiac repolarisation, a pilot study was performed in 17 patients undergoing moderately/highly emetogenic chemotherapy at two centres. All received dexamethasone, 8–12 mg, infused over 30 min, followed immediately by granisetron and then chemotherapy. Twelve-lead electrocardiograms (ECGs) performed before granisetron treatment, 2 h later and the following day (11 patients) showed no differences in QTc(end max), QTc(apex max) or QT-interval dispersion between baseline and subsequent measurements, and there were no significant secondary adverse events. On this basis, granisetron should be considered the first-choice antiemetic for patients at increased risk of cardiac complications.

Keywords: Arrhythmia; Cardiovascular; Granisetron; Antiemetic; Chemotherapy; ECG; Cardiac repolarisation; QT interval

1. Introduction

There are many reasons why the patient with advanced malignancy is at increased risk of potentially life-threatening cardiac arrhythmias. Cardiac complications such as dysrhythmias, cardiac metastases and carcinoid disease can occur directly as a result of some cancers [1,2]. Malnutrition associated with cancer can lead to QT-interval prolongation (as occurs in severe dieting, hunger strikes or protein deficiency). Furthermore, several treatments for cancer are known to be cardiotoxic—including anthracyclines (epirubicin, doxorubicin), paclitaxel, 5-fluorouracil, cyclophosphamide, and interleukin-2 [3–5]—and radiation therapy can also cause cardiac insult. The autonomic response to chemotherapy and radiation therapy (nausea, retching and vomiting) or their biochemical effects (vomiting-induced electrolyte disturbance) can have important implications, particularly in elderly patients who often have cardiovascular disease comorbid with their cancer [6,7]. It is, therefore, important to ensure that any medications co-administered to cancer patients in the supportive care context do not further increase the risk of cardiac complications, particularly arrhythmias.

Nausea and vomiting are considered to be the most distressing and debilitating side-effects of cytotoxic chemotherapy and radiotherapy, and can profoundly affect patients' quality of life [8]. Of the antiemetics currently available, 5-HT_3 receptor antagonists are widely regarded as the most efficacious and are currently recommended in the prophylactic treatment of nausea and vomiting induced by highly and moderately emetogenic chemotherapy and radiotherapy [9–11]. 5-HT_3 receptor antagonists are potent antiemetics and are generally thought to have good safety and tolerability. However, a number of studies have reported that some 5-HT_3 receptor antagonists are associated with significant changes in cardiac repolarisation, as measured by the QT-interval on the surface electrocardiogram (ECG). Prolongation or increased heterogeneity of repolarisation is the cause of polymorphic ventricular tachycardia, fibrillation and sudden cardiac death in

* Corresponding author. Tel.: +41-22-3669-136; fax: +41-22-3669-131.
E-mail address: aapro@cdg.ch (M. Aapro).

0959-8049/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0959-8049(03)00120-5

genetically inherited or acquired forms of the long QT syndrome. The fact that many drugs can have an adverse effect on cardiac repolarisation has been of considerable concern to regulatory authorities. In particular, dolasetron has been shown to increase the QTc interval, particularly when given at high doses, [12] and the prescribing information for dolasetron and tropisetron carries a cardiovascular warning. Increases in the mean QTc interval have also been reported following ondansetron administration [13]. Such factors should therefore be an important consideration in the selection of the most appropriate antiemetic agent, particularly in patients already predisposed to cardiac arrhythmias.

The cardiac safety of granisetron has been investigated in a number of studies, both in healthy volunteers and cancer patients [14–17]. These studies have not demonstrated any clinically important cardiovascular effects of granisetron, and it has not been necessary, therefore, to attach any cardiovascular warnings or limitations to its use. Granisetron can be administered orally or intravenously (i.v.), via a 30-s injection. Injection of granisetron over 30 s has been shown to be safe and well tolerated, and is not associated with any increase in adverse events [16]. Furthermore, the option of a bolus 30-s injection of granisetron is convenient for both patients and healthcare professionals. However, many healthcare providers seek to administer supportive care products faster than the recommended dosing and immediately prior to chemotherapy administration. Since faster injection could potentially increase the risk of adverse events, the aim of this pilot study was to determine the effects of the rapid administration of i.v. granisetron (3 mg over 1 s) on measures of cardiac repolarisation in patients receiving chemotherapy for malignant disease, by comparing 12-lead and Holter ECGs before and at several time-points after drug administration.

2. Patients and methods

This pilot study was carried out in two centres in Switzerland between September 1993 and January 1994. Patients were included if they were due to receive chemotherapy requiring antiemetic prophylaxis with a 5-HT_3 receptor antagonist. All patients were informed of the nature and purpose of the study, and written consent was obtained in all cases. The design of the study was approved by the relevant ethics committees and conformed to the Declaration of Helsinki.

An initial 12-lead ECG was performed for each patient before the start of treatment. Directly after the ECG recording, all patients received an infusion of dexamethasone, 8–12 mg, administered over 30 min, followed immediately by granisetron, 3 mg, given in 1 s as a bolus. The precise timing of the granisetron injection was recorded by an event marker. A cytotoxic chemotherapy agent was then administered, cisplatin, 60–80 mg/m^2, doxorubicin, 50 mg/m^2 or cyclophosphamide, 600 mg/m^2, being among those most commonly given. A second ECG was performed 2 h after the granisetron administration and, wherever possible, a third ECG was carried out the following day. Holter ECG monitoring was performed from 30 min before the start of the granisetron injection, continuing up to 24 h after its completion. Patients' blood pressure, heart rate and temperature were measured before the administration of granisetron, and routine haematological and biochemical tests were also performed at this time.

Each 12-lead ECG was digitised by entering the P-wave onset, QRS onset and offset, T-wave peak and T-wave end, for three consecutive complexes in each lead. The mean of these three values was then recorded as the measurement for each parameter [18–20]. If the T-wave could not be determined for any of the 12 leads, no entry was recorded in that lead. Maximum and minimum values for QT interval (apex) and QT interval (end) were then determined, as well as QT-interval dispersion (maximum minus minimum interval for both apex and end intervals about the same 12-lead ECG). Definitions of these measurements are shown in Table 1. Measurements taken before and after granisetron injection were compared by Student's *t*-test. In total, 17 patients entered the study and their demographic characteristics are shown in Table 2. 2 of the patients included

Table 1
Interpretation of the readings obtained from ECG recordings

QT-interval dispersion	Difference between the maximum and minimum QT intervals from analysis of all 12-leads of the same ECG recording—expressed as both absolute (QT) and rate-corrected (QTc) measurements. Greater QT dispersion, or variability, is considered arythmogenic
QTc (end of T-wave) interval—QTc(end max)	The rate-corrected QT interval measured from the start of the QRS complex to the end of the T-wave. The value from whichever of the 12 leads gives the greatest interval is recorded
QTc (apex of T-wave) interval—QTc(apex max)	The QT interval measured from the QRS onset to the peak of the T-wave. QTc(end) and QTc(apex) need not change in the same way, and may be measuring different aspects of myocardial repolarisation

ECG, electrocardiogram.

Table 2
Demographic characteristics of patients included in the study

Patients (*N*)	17
Mean age (range) (years)	54.5 (38–72.8)
Sex	
M	11
F	6
Type of cancer	
Lymphoma	1
Pancreas	1
Breast	3
Hepatoma	1
Gastro-intestinal (including colon)	3
Lung, small cell	3
Lung, non-small cell	1
Kaposi's	1
Testicular	1
Sarcoma	1
Squamous cell, penis	1

M, male; F, female.

were studied twice each when receiving consecutive courses of chemotherapy.

3. Results

Comparisons between the ECG results obtained before the infusion of granisetron and 2 h after, following 19 instances of rapid injection of the drug (two events each for 2 of the 17 patients), are given in Table 3. There were no differences in rate-corrected QT intervals (QTc(end max), QTc(apex max) or QT-interval dispersion) from 12-lead ECG data between baseline and any time after the administration of the granisetron bolus. When QTc(end) intervals from continuous Holter single-lead ECG recordings were compared, there were no systematic changes between measurements taken 30, 15 and 5 min prior to granisetron injection and those obtained at the same time intervals afterwards ($P = 0.62$; $P = 0.41$; $P = 0.94$, respectively). Because of difficulties in identifying the timing of granisetron administration precisely on some recordings, this analysis was possible in only 11 of the subjects. However, the results from these 11 patients indicate that rapid injection of granisetron produced no systematic change in the QTc intervals. Moreover, there was no evidence of polymorphic ventricular tachycardia or *torsade-de-pointes* (the classical prolonged repolarisation-related form of non-sustained ventricular tachycardia) on Holter ECG recordings in any patient.

Patients were also monitored for neurologic and gastrointestinal adverse events. Overall, granisetron was well tolerated and no serious adverse events were observed that could be related to the study drug. In addition, there was no evidence that injecting granisetron immediately before chemotherapy caused any reduction in the antiemetic efficacy that is normally associated with the administration of the drug 30–60 min before or after chemotherapy.

4. Discussion

The key finding of this study is that rapid injection of granisetron, 3 mg, does not cause clinically significant changes in the QT parameters analysed. Granisetron does not prolong or increase the heterogeneity of cardiac repolarisation as assessed by surface QT-interval and dispersion of QT interval analyses. This contrasts with findings obtained with other 5-HT_3 antagonists, which have been shown to cause measurable prolongation in these variables. In addition, rapid injection of granisetron immediately before chemotherapy is well tolerated, providing effective prophylaxis against emesis, with increased convenience for patients and healthcare providers. To date, this is the only study to report on the effect of administering granisetron, 3 mg, within 1 s. There appears to be no correlation between decreasing the injection time and an increase in cardiovascular risk. The results of this pilot study suggest that rapid injection of granisetron was not associated with cardiac arrhythmias or other adverse cardiac events and that, in contrast to the effects of other 5-HT_3 antagonists on the QT-interval, granisetron does not have arythmogenic potential.

Other studies have reported on the cardiac effects of granisetron administration performed over 30 s and 5 min. In an open study of i.v. granisetron, 3 mg over 30 s, in 21 patients, surface ECGs performed before and

Table 3
ECG intervals before and 2 h after 1-s injection of granisetron (3 mg)[a]

	QT-interval dispersion (ms)	QTc-interval dispersion (ms)	QTc(end max) interval (ms)	QTc(apex max) interval (ms)
Pregranisetron	84±33	84±33	478±54	370±40
2 h postgranisetron	81±34	81±34	467±55	367±40
t-Statistic	0.43	0.429	1.21	0.396
Degrees of freedom	18	18	18	18
P value (two-tailed probability)	0.67	0.67	0.24	0.697
95% confidence interval	−11 to +16.75	−11.1 to +16.7	−8.2 to +30.3	−10.9 to +15.9

[a] Values are expressed as means±standard deviation.

after granisetron administration showed no changes in intracardiac conduction [16]. The authors concluded that granisetron, 3 mg, given as a 30-s i.v. bolus to patients receiving chemotherapy for malignant conditions, is safe and well tolerated. A later trial of granisetron, 3 mg, given as a 5-min constant-rate infusion and followed by doxorubicin or epirubicin injection, showed no statistically significant change in cardiac rhythm, QRS duration or QTc intervals, further emphasising the cardiovascular safety of granisetron [17].

After administration of i.v. granisetron at higher than usual doses (50 μg/kg) in one small study, ECG changes were reported in 4 of 12 patients who were receiving multiple chemotherapy agents for bone and soft-tissue sarcomas, administered over more than nine cycles [21]. However, cardiac function and timing of ECG changes in relation to granisetron administration were not reported in detail. It is difficult to compare the results of this study with others because of the large number of chemotherapeutic agents and high dose of granisetron employed. However, these results conflict with other findings in which patients who received high doses of granisetron (up to 160 μg/kg) experienced no clinically important effects on ECG, pulse or blood pressure [22].

A further study has compared the cardiovascular effects of granisetron, 10 μg/kg, infused over 5 min or 30 s and with those of i.v. ondansetron, 32 mg, administered over 15 min [15]. No clinically important cardiovascular changes were associated with any of the regimens, although the mean post-dose QTc interval was longer for ondansetron than for placebo or granisetron for all 12 subjects in whom these data were analysed. In addition to the 5-min infusion time for granisetron, 30-s i.v. bolus administration thus also appears to be safe and well tolerated.

Other 5-HT_3 antagonists, by contrast, are known to produce greater changes than granisetron in ECG parameters. In particular, minor, asymptomatic, transient prolongations in some ECG intervals have been detected on computer-generated tracings after single i.v. doses of dolasetron, 2.4 mg/kg, and ondansetron, 32 mg [23,24]. Dolasetron predominantly altered ECG parameters of ventricular depolarisation (QRS duration), whereas ondansetron affected ventricular repolarisation (prolonged JT interval). Both agents, at the doses used, caused significant increases in the QT interval compared with placebo [24]. Other studies, in 123 patients [25] and 319 patients [26] receiving various chemotherapeutic agents, have demonstrated a trend for increased ECG intervals with increasing dolasetron doses. A recent review of the cardiotoxic potential of 5-HT_3 receptor antagonists has concluded that ondansetron has a greater effect on ECG intervals than granisetron, and that the cardiotoxic potential of dolasetron is greater still [2]. In consequence, both dolasetron and tropisetron carry cardiovascular warnings as part of their labelling.

The small number of patients included in this pilot study is a limitation shared by all *in vivo* studies into cardiovascular changes associated with 5-HT_3-receptor antagonists. Assessment of QT-interval prolongation provides a *marker* of cardiac repolarisation, rather than a direct measure. The fact that chemotherapy is given in addition to granisetron, thus increasing the arythmogenic potential of the drug 'cocktail', makes it difficult to isolate the QT effects of granisetron. This does, however, provide a realistic context in which to test the arythmogenic potential of the drug, as it matches the clinical setting. It is also helpful to remember that the administration of multiple medications and/or radiation therapy can give rise to cardiac insult in patients with or without pre-existing cardiac conditions. Thus, an understanding of the possible risk factors in a true clinical setting should go hand-in-hand with comparisons between different agents when determining the most appropriate therapy for individual patients.

This pilot study shows that granisetron does not adversely affect cardiac repolarisation, even when administered i.v. as a 1-s bolus in patients with various malignancies just prior to chemotherapy. The results provide further important safety data on granisetron. On this basis, granisetron should now be considered the antiemetic of first choice, for patients known to have coexisting cardiac disease or those receiving chemotherapy or concomitant medications with known cardiotoxic potential.

Acknowledgements

Support of this paper was provided by Hoffman-La Roche.

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