Electrocardiographic Changes After Granisetron Administration for Chemotherapy Induced Nausea and Vomiting

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Abstact- Cancer patient receive various cytotoxic drugs in association with antiemetic drugs such as $5HT_3$ receptor antagonists as their chemotherapy regimen. $5HT_3$ receptor antagonists have been reported to produce changes in ECG parameter. There are only a few studies about cardiovascular events of these drugs in patient receiving potentially cardiotoxic chemotherapies. The subject of this study is to evaluate ECG changes after administration of chemotherapeutic agents and granisetron (the most commonly used $5HT_3$ antagonist in Iran) in adults with cancer. For this clinical trial study, all cancer patients referred to department of radiation oncology of Imam Hossein Hospital since August 2005 to March 2006 were evaluated if they had inclusion criteria. Granisetron (3 mg) was infused intravenously over 30 seconds just a few minutes before chemotherapeutic agent administration. The 12-lead ECG recording was obtained before and 90 minutes after infusion of granisetron. One cardiologist determined PR, QRS, QTc intervals and heart rate of all ECGs. During the study period 54 patients fulfilled our criteria. With paired *t*-test, the PR and QTc intervals, but not QRS interval showed statistically significant prolongation after drug infusion ($P < 0.0001$), and heart rate showed statistically significant decrease ($P < 0.0001$). The ECG findings of chemotherapeutic agents and granisetron administration were prolongation of PR and QTc intervals and decrease of heart rate ($P < 0.0001$). Although these changes did not cause clinical signs, with keeping in mind that there may be possible drug-drug interactions and preexisting cardiac comorbidities in cancer patient, it seems reasonable and necessary to consider physical condition specifically cardiac condition and drug usage of each patient, while designing chemotherapy regimen and supportive drugs.

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Key words: Electrocardiography, Granisetron, chemotherapy

Introduction

Nausea and vomiting are considered as one of the most distressing side effects of currently used chemotherapeutic regimens. 5-HT_3 receptor antagonists, including granisetron are widely used in the prophylactic treatment of chemotherapy-induced nausea and vomiting (1-3). Some electrocardiographic changes have been reported in clinical use of 5-HT_3 receptor antagonists (4-7) it is important to keep in mind the adverse cardiac effects of these drugs to prevent some unexpected fatal events especially in patients with cancer and cardiac disease, or administering cardiotoxic chemotherapy such as antracyclines. The cardiac safety of granisetron has been investigated in several studies (5, 8-11). In Iran no 5-HT_3 receptor antagonists other than granisetron is available and no study has investigated the effect of granisterone on electrocardiography, so we conducted this prospective study to evaluate this subject in our patients.

Patients and Methods

This study was carried out on 54 adult patients receiving different chemotherapeutic regimens in our clinic for different types of cancer. The liver (AST, ALT, LDH, Billirubine) and renal (Cr, BUN) functions and serum electrolytes (Na, K, P, Ca) of the patients were measured at the day of assessment and any patient with abnormal testes was excluded from study. An ECG was recorded before starting first cycle of chemotherapy. After that, all patients received 3mg intravenous granisetron (Kytril; F. Hoffmann-La Roche Ltd., Basel, Sweden) in 30 seconds, five minute before administrating chemotherapy drugs. Patients with history of previous chemotherapy, any sign or symptom of heart disease, and patients

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Table 1. ECG parameters

	PR(ms)	QRS(ms)	QTc(ms)	Heart(beat/min)
pretreatment	156±22	67.4±22	432±31	81±12
post treatment	174±23	67.7±22.4	451±35	76±11
difference				
Mean±SD	18±16.3	0.37±2.7	19±30	5±7.5
percent	11.5	0.54	4.4	6.2

using any other drugs were also excluded. The maximum duration of chemotherapy in all patients was one hour. ECG was recorded again 90 minute after completion of chemotherapy administration. Each 12-lead ECG was digitized by entering the P wave onset, QRS offset, and T wave peak in lead II, QRS onset, and T wave end in each lead. If the T wave could not be determined for any a lead, no entry was recorded in that lead. QT interval was measured in each lead, and rate-corrected QT (QTc) was calculated by using Bazett's formula (12). PR interval and QRS duration were measured, and QTc were calculated in lead II. The mean values of the measurements from 3 consecutive complexes in each lead were recorded as the measurement for each parameter. Dispersions of both absolute QT and QTc measurements were calculated. The results of pre and post chemotherapy ECGs were compared with each other.

The results were analyzed with the SPSS.11 (SPSS inc., Chicago, IL) The data were expressed as mean ± standard deviation. The mean values of ECG parameters obtained at different times were compared with t-test and Mann-Wiethney test. $P < 0.05$ was considered significant

Results

Fifty-four patients (48 female and 6 male) entered the study from June 2005 to March 2006 with a median age of 47±12 (25-80). Thirty-onepatients were under 50 and remaining equals or above 50. The most common type of cancer was breast cancer. Chemotherapy regimens contained an antracycline in 17 (31.4%) patients. It is shown in table 1 that the average PR interval was prolonged about 18 units (11.5%) that was significant ($P< 0.0001$). QRS duration showed no significant changes ($P < 0.3$). QTc interval was prolonged significantly in comparison with pre chemotherapy values (19 units, 4.4%, $P < 0.0001$). Heart rate was decreased 5 beat per minute in average (6.2%) that was significant ($P < 0.0001$). Type of chemotherapy drugs (anthracycline *vs*. no anthracycline), type of cancer (breast cancer *vs.* other cancers) and age of patients (less than 50 *vs.* equals or more than 50) had no effect on ECG changes after granisetron administration.

Discussion

This study showed that the intravenous granisetron, administered to prevent the chemotherapy induced nausea and vomiting, can prolong PR and QTc intervals and decrease heart rate. Cardiac effects of the 5-HT_3 receptor antagonist antiemetics, including dolasetron, ondansetron, and granisetron, reviewed by several authors (7, 13). Generally small reversible and clinically insignificant changes are reported in ECG parameters after administration of antiemetics which are most prominent within 1 to 2 hours. Most of the studies in this field are carried out in healthy volunteers.

A 2 mg dose of oral granisetron has no proarrhythmic activity in healthy subjects (14). Cardiac effects of granisetron (3 mg intravenously), followed by administration of cardiotoxic chemotherapy including doxorubicin or epirubicin were evaluated by Jantunen *et al.* (1996) in patients with cancer (6).

Table 2. ECG parameter changes

		PR(ms)	QRS (ms)	QTc(ms)	Heart rate(beat/min)
Type of chemotherapy	Without antracycline(N=17)	19±14	0	19±27	5.5±11
	With antracycline(N=37)	18±17	0.54±3.2	23±23	4.9±5.3
Type of cancer	Breast (N=41)	18±16	0.48±3.1	19±31	5.4±5.1
	the other (N=13)	18±14	0	18±27	4±12
Age	<50 (N=31)	19±17	0.37±2.1	19±26	5.2±7.1
	>50 (N=13)	19±16	0	22±19	5.5±12

They observed only asymptomatic increases in the PR interval but no significant change in QRS duration, cardiac rhythm, or QTc intervals.

Watanabe *et al.* (1995) observed significant ECG changes including sinus bradycardia, integral change of P waves, junctional escape beat and atrioventricular block with granisetron in patients with bone and soft tissue sarcomas (5). However, those changes were determined after several courses of chemotherapy and not in the first course.

It seems that the cumulative doses of the chemotherapeutic agents administered to those patients may have a role in development of these ECG changes. We observed a significant increase in PR and QTc interval and a decrease in heart rate 90 minute after single-dose granisetron infusion. However, all those changes were clinically asymptomatic. These changes may return to baseline after many hours as shown by Bendict (15).

In another study of single-dose intravenous dolasetron, which is one of the 5-HT_3 receptor antagonist antiemetics, versus intravenous ondansetron, the assessments revealed that both of the agents result in prolongation for the PR, QRS, QT and QTc intervals (16).

Serotonin antagonist antiemetics, including granisetron prevent vomiting by blocking the serotonin (5-HT) receptors on afferent vagal nerves in the gastrointestinal tracts. These drugs theoretically carry a risk for cardiac interaction as a result of vagal innervation of the heart (5). 5-HT has positive chronotropic effect and can be inhibited by 5-HT_3 receptor antagonists including granisetron, so heart rate usually decrease by using these drugs (17, 18). We also found decreasing the heart rate in our patients.

Human cardiac Na channels blockage by granisetron, ondansetron, and dolasetron is a concentration-dependent phenomenon (19). This may indicate that these drugs may result in some cardiac repolarization problems if adequate plasma concentrations are reached. In our patients who received granisetron, the QTc dispersions showed a significant increase at 90 minute of infusion. It has been shown that the QTc dispersion may be affected by heart rate (20). Although our patients remained asymptomatic, and we did not see any significant arrhythmias associated with prolonged repolarization, saying nonsustained arrhythmias were absent need Holter monitoring.

This study suggests that 3 mg of granisetron adversely affects cardiac repolarization when administered intravenously in adult cancer patients and the changes are not associated with clinical symptoms. This might indicate that the cancer patients receiving chemotherapy with known cardio toxic potential have to be observed in terms of new arrhythmias during the first few hours of drug administration.

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