Abstract. – Background: 5-hydroxytryptamine receptor type-3 (5-HT3) antagonists are widely used for prophylaxis of chemotherapy-induced nausea and vomiting (CINV) and regarded to have a high safety profile. However, several electrocardiographic changes and cardiac arrhythmias have been reported due to administration of 5-HT3 antagonists. Only prolongation of QT interval has been investigated as an index of potential for life-threatening arrhythmias in adult patients using 5-HT3 antagonists. Recently, increase in transmural dispersion of repolarization (TDR) has been proposed as a more reliable determinant of arrhythmogenic potential.

Aim: To assess the effects of palonosetron, a second-generation 5-HT3 antagonist, on the T-wave peak to T-wave end (TpTe) interval which has been proposed as a reliable index of spatial TDR.

Patients and Methods: A total of 50 consecutive cancer patients (aged: 57 ± 12 years) who were scheduled to receive emetogenic chemotherapy were included in the study. Baseline 12-lead electrocardiography (ECG) recordings were obtained. Then, all patients received 8 mg intravenous dexamethasone followed by a single dose of 0.25 mg intravenous palonosetron administered over 30 seconds. A second ECG was performed 30 minutes after the administration of palonosetron. Indices of cardiac repolarization and TDR before and after the administration of palonosetron were compared.

Results: In comparison with baseline there was no statistically significant change in any of the heart rate-corrected parameters, including QTc (lead V5), QT_{max}, QT_{min}, QT_{mean}, TpTe (V5), TpTe_{max}, TpTe_{min}, TpTe_{6}, and TpTe/QT (V5).

Conclusions: Palonosetron does not have any significant effect on QT, and TpTe intervals. It might be the drug of choice for prophylaxis of CINV in cancer patients receiving chemotherapy with known cardiotoxic potential or who have pre-existing cardiac disease that predispose them to drug-induced arrhythmias.

Key Words: Chemotherapy-induced nausea and vomiting, Cardiac repolarization, 5-HT3 antagonists, Palonosetron, Transmural dispersion of repolarization, Tpeak to Tend interval.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is among one of the most prevalent and disturbing side effects of chemotherapy. CINV is associated with significant deterioration in quality of life and reduces compliance to therapy in cancer patients. 5-hydroxytryptamine receptor type 3 (5-HT3) antagonists are widely used for prophylaxis of postoperative and CINV and regarded to have a high safety profile. However, several electrocardiographic changes and cardiac arrhythmias have been reported due to administration of 5-HT3 antagonists.

Palonosetron is a second generation 5-HT3 antagonist and has been proven to be more effective than other 5-HT3 antagonists. Only few investigations, including our previous study, have evaluated the proarrhythmogenic effects of palonosetron. These studies have reported that palonosetron does not prolong QT interval. However, absence of QT prolongation does not completely rule out potential for torsades de pointes (TdP) and other malgn cardiac arrhythmias. Recently, transmural dispersion of repolarization (TDR) has been proposed as a more reliable predictor of TdP. As far as we know, this new index of heterogeneity of ventricular repolarization has never been studied in 5-HT3 antagonists in the...
adult population. In this regard, the aim of this prospective study was to evaluate the acute effect of palonosetron on transmural dispersion of myocardial repolarization.

Patients and Methods

Study Patients

This prospective study was carried out between September 2011 and February 2012 in Medical Oncology Department of Selcuklu School of Medicine, Selcuk University and in Cardiology Department of Meram School of Medicine, Konya University, Konya Turkey, with the approval of the Institutional Ethics Committee. Informed consent was obtained from all participants. Prospectively recruited 50 consecutive cancer patients who were scheduled to receive emetogenic chemotherapy and used palonosetron for the prevention of acute CINV were included to the study. Patients with history and/or evidence of coronary artery disease, valvulopathy, congenital heart disease, heart failure and bundle branch block were excluded from the investigation. Other exclusion criteria were having rhythm other than sinus, using drugs that may interfere with cardiac repolarization and comorbidities including hypertension, diabetes mellitus and thyroid diseases.

Electrocardiographic Examination

12-lead ECG recordings were obtained just before the administration of palonosetron at a paper speed of 50 mm/s and a calibration of 1 mV = 20 mm. Then, all patients received 8 mg intravenous (i.v.) dexamethasone followed by a single dose of 0.25 mg i.v. palonosetron administered over 30 seconds. A second ECG was performed 30 minutes after the administration of palonosetron. Chemotherapy was initiated after the second ECG recording.

One of the investigators (M.T.) who was blinded to clinical and patient information made all the ECG analysis by using a magnifying glass. Three consecutive beats were used for analysis and at least 10 leads were analyzable in all ECGs. Intervals between two consecutive R-waves were defined as RR interval. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave. The end of the T wave was defined as intersection of the terminal limb of the T wave with the isoelectric baseline. The longest and the shortest QT intervals across 12 leads were defined as the maximum QT (QT$_{max}$) and the minimum QT (QT$_{min}$) intervals, respectively. They were corrected according to heart rate by using the Bazett Formula and defined as corrected QT$_{max}$ (QT$_{maxc}$) and corrected QT$_{min}$ (QT$_{minc}$), respectively. Bazett formula was preferred to provide uniformity and enable comparison with other studies [Bazett: QTc = QT/(RR)$^{1/2}$]. QT dispersion (QT$_{disp}$) was defined as the difference between QT$_{max}$ and QT$_{min}$.

For the T-wave peak to T-wave end interval (TpTe) measurement, time interval between peak of T wave, i.e., the time point in which T wave had highest amplitude and end of T wave which also was defined as the crossing point of T wave and isoelectric line was noted as a function of time (Figure 1). TpTe was also corrected according to heart rate and referred as TpTe$_{c}$. The longest and the shortest TpTe intervals across 12 leads were defined as the maximum TpTe (TpTe$_{max}$) and the minimum TpTe (TpTe$_{min}$) intervals, respectively. TpTe dispersion (TpTe$_{disp}$) was defined as the difference between TpTe$_{max}$ and TpTe$_{min}$. TpTe/QT and TpTe/QT ratios were calculated. Abnormal ECG recordings with ambiguous T waves, distorted, flat or with high noise levels by any means were excluded. Since it is recommended to measure TpTe intervals separately in all leads rather than taking the average, all the leads were examined. Although statistical analyses were
performed for all the leads, precordial lead V5 was used as a representative of all measurements.

To determine the intraobserver variability, measurements of 20 randomly selected cases were repeated by the investigator. Agreement between measurements of QT andTpTe intervals obtained from lead V5 were assessed using the Bland and Altman method. The 95% limits of intraobserver agreement for QT interval were 19.4 and 21.4 milliseconds (msc), which means that there was a 95% probability that the repeated measurements differed no more than 19.4 to 21.4 msc from the first measurement. The 95% limits of intraobserver agreement for TpTe were 13.5 and 16.5 msc, respectively.

**Statistical Analysis**

Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Significances of the differences between the parameters before and after palonosetron treatment were tested by the paired samples t-test. For comparison of two dependent groups with a medium effect size of 0.50 at an α level of 0.05 and a power of 0.80 a minimum of 34 subjects were required. A p value less than 0.05 was considered to be statistically significant. Data were analyzed by using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Mean age of the patients was 57±12 years (range: 25-81). Of the 50 patients enrolled in the study 50% (n=25) were men and 50% (n=25) were women. Administration of i.v. palonosetron resulted in a significant decrease in mean heart rate (p =0.01). The mean heart rate did not decrease below 50/minute and no symptom occurred in any of the patients. Systolic and diastolic arterial blood pressures were similar. In comparison with baseline QT (obtained from lead V5), QTmax and QTmin intervals increased significantly after the administration of palonosetron. However, there was no statistically significant change in any of the heart rate-corrected parameters, including QTc (lead V5), QTmaxc, QTminc, QTcd, TpTe (lead V5), TpTe_max, TpTe_min, TpTe_q and TpTe/QT (lead V5) (Table I). Results were similar when QT and

| Table I. Comparison of heart rate, arterial blood pressure and electrocardiographic indices of cardiac repolarization and transmural dispersion before and after the administration of palonosetron. |
|----------------|----------------|-----|
|                | Baseline (n=50) | After palonosetron (n=50) | p   |
| Heart rate (bpm) | 83 ± 15         | 77 ± 13                    | 0.01|
| RR interval (msc) | 747 ± 153       | 799 ± 147                  | 0.03|
| SBP (mm Hg)      | 126 ± 12        | 127 ± 12                   | 0.44|
| DBP (mm Hg)      | 79 ± 10         | 80 ± 8                     | 0.57|
| QT (V5)          | 360 ± 36        | 376 ± 30                   | <0.001|
| QTc (V5)         | 419 ± 24        | 423 ± 26                   | 0.40|
| QTmax            | 381 ± 29        | 396 ± 34                   | <0.001|
| QTmaxc           | 444 ± 21        | 446 ± 25                   | 0.58|
| QTmin            | 329 ± 28        | 341 ± 30                   | <0.001|
| QTminc           | 383 ± 23        | 384 ± 24                   | 0.77|
| QTd              | 52 ± 15         | 55 ± 19                    | 0.24|
| TpTe (V5)        | 61 ± 18         | 62 ± 20                    | 0.71|
| TpTec (V5)       | 83 ± 19         | 85 ± 19                    | 0.66|
| TpTe_max         | 97 ± 24         | 95 ± 21                    | 0.55|
| TpTe_min         | 104 ± 45        | 102 ± 18                   | 0.77|
| TpTe_maxc        | 70 ± 44         | 67 ± 15                    | 0.61|
| TpTe_q           | 34 ± 13         | 35 ± 18                    | 0.69|
| TpTe/QT (V5)     | 0.23 ± 0.06     | 0.22 ± 0.05                | 0.29|
| TpTec/QTc (V5)   | 0.23 ± 0.05     | 0.23 ± 0.05                | 0.33|

Bpm: beat per minute; DBP: diastolic blood pressure; msc: millisecond; QTc: corrected QT interval; QTcd: corrected QT dispersion; QTd: QT dispersion; QTmax: maximum QT interval; QTmin: minimum QT interval; QTmaxc: corrected maximum QT interval; QTminc: corrected minimum QT interval; SBP: systolic blood pressure; TpTe: Tpeak to Tend interval; TpTec: corrected Tpeak to Tend interval; TpTe_max: maximum TpTe interval; TpTe_min: minimum TpTe interval.
TpTe measurements were obtained from other leads. To avoid redundancy, only the statistical analyses of parameters obtained from lead V₅ were demonstrated.

**Discussion**

As far as we know, this is the first study investigating changes in transmural dispersion of myocardial repolarization after administration of a 5-HT₃ antagonist in adult population. In this context, electrocardiographic changes associated with use of a second generation 5-HT₃ antagonist, palonosetron, was evaluated. Our principle finding was that 30 minutes following the i.v. administration of palonosetron, heart rate decreased, but none of the cardiac repolarization indices changed significantly.

Twelve-lead ECG is a noninvasive measure for the evaluation of proarrhythmic potential of drugs. This practical tool is widely used in clinical trials and daily practice to identify drug-induced cardiac arrhythmias. The QT interval in the ECG represents the duration of depolarization and subsequent repolarization of ventricles. Delayed cardiac repolarization, which can be measured as prolongation of the QT interval, has been proposed to play a pivotal role in the genesis of cardiac arrhythmias. Most drugs that cause TdP prolong the QT interval. However, prolongation of QT interval should not be regarded as synonymous with drug torsadogenicity. Many studies have reported that drugs which cause prolongation of QT interval rarely lead to TdP in the absence of TDR. It has been very recently reported that 25% of the patients with diagnosis of genetically-confirmed long QT syndrome and who do not have prolonged baseline QTc are under risk for life-threatening arrhythmias. According to these findings it has been suggested that increase in TDR rather than prolongation of the QT interval is the main underlying mechanism of arrhythmogenesis induced by drugs.

Ventricular cells show distinct repolarization properties in the different regions. Under normal conditions, repolarization of the epicardium is completed first and depicted by the peak of the T wave. A group of cells located in the midmyocardium which also have extensions to subendocardium and subepicardium show some unique electrophysiological properties and are referred as M cells. Repolarization of M cells is latest and depicted by end of the T wave. Discrepancy between the timing of complete repolarization of distinct regions are described as TDR. The time interval from the peak of T-wave to its end is referred as TpTe interval and suggested to be a reliable noninvasive marker of spatial TDR. When compared to QT and QTcd, TpTe interval is shown to be a more reliable index as a predictor of TdP under a variety of conditions, such as coronary artery disease, hypertrophic cardiomyopathy, organic heart disease and long QT syndrome. It has been also reported that prolonged TpTe has potential for enhancement of sudden cardiac death in community-based studies. TpTe/QT ratio and TpTe/d are other markers shown to be associated with malignant ventricular arrhythmias.

Although, their clinical safety has been established in a large number of studies, several adverse cardiac events are reported due to administration of 5-HT₃ antagonists. Consequently, considerable interest has been raised regarding effects of these antiemetic agents on ECG parameters and many investigations have been designed both in healthy subjects and cancer patients. Several of these studies have reported that 5-HT₃ antagonists induce significant, but asymptomatic changes in ECG parameters including PR interval, QRS complex and QT interval. In their study comparing patients who received droperidol and ondansetron for postoperative nausea and vomiting, Charbit et al showed that both of the drugs induced clinically relevant QTc interval prolongations. As a conclusion they suggested that regarding safety profile ondansetron might not be superior to low-dose droperidol – an antiemetic agent with black box warning for QT interval prolongation and TdP. Chan et al confirmed the findings of the former study in the same patient population. In contrary, Buyukavci et al reported that i.v. granisetron but not ondansetron caused clinically asymptomatic, but significant acute prolongation of mean QTc and QTcd intervals in children receiving high-dose methotrexate therapy. In their single-blind study comparing the electrocardiographic effects of i.v. dolasetron mesylate and ondansetron in healthy volunteers Benedict et al showed that both of the drugs prolonged the QTc interval.

Palonosetron has been proven to be a more effective antiemetic agent than other 5-HT₃ antagonists. This effect can be explained by its unique pharmacological characteristics. It has a higher affinity to 5-HT₃ receptors and a half-
life. Prolongation of cardiac repolarization in the course of treatment with 5-HT$_3$ antagonists has been attributed to the blockage of voltage-dependent K$^+$ channels. Effect of palonosetron on K$^+$ channels has never been specifically evaluated. We hypothesized that, with its different structure and specific binding characteristics, palonosetron might have more accentuated effects on cardiac repolarization. However, in our study administration of i.v. palonosetron did not cause any significant acute change in repolarization (QT$_{c}$, QT$_{cd}$) or transmural dispersion indices (TpTe, TpTe$_d$ and TpTe/QT). Our findings are concordant with three previous studies evaluating the effects of palonosetron on conventional cardiac repolarization indices. In one of these investigations, our group has hypothesized that higher 5-HT$_3$ receptor affinity of palonosetron makes it possible to show adequate antiemetic effects within lower serum concentration limits which is not high enough for cardiac ion blockage. Therefore, palonosetron does not effect cardiac repolarization when administered 0.25 mg intravenously, a dose which has been shown to be effective with many clinical trials.

We have found a significant, but modest decrease in heart rate after the administration of palonosetron. This finding was concordant with previous reports. 5-HT$_3$ receptors are mainly located on vagal afferent nerve terminals in gastrointestinal system. It has been demonstrated that they exert positive chronotropic effect. Inhibition of this positive chronotropic effect is suggested to be responsible for heart rate decreasing effects of 5-HT$_3$ antagonists.

Consequently, we suggest that palonosetron might be the drug of choice for prophylaxis of CINV in cancer patients receiving chemotherapy with known cardiotoxic potential or who have pre-existing cardiac disease that predispose them to drug-induced arrhythmias.

**Study Limitations**

Our study has several limitations. Firstly, all of the patients received palonosetron in a single fixed dose. We can not completely rule out potential arrhythogenic effects of prolonged use leading to higher cumulative doses. However, our data confirm the safety of single-dose regimen which was previously shown to be adequate to control CINV. Secondly, to eliminate potential effects of chemotherapeutics on repolarization indices, second ECG recordings were obtained 30 minutes after the administration of palonosetron, just before the initiation of chemotherapy. Hence, long-term effects of palonosetron on ECG are yet to be elucidated.

**Conclusions**

Palonosetron does not have any significant impact on cardiac repolarization and transmural dispersion indices at clinically relevant doses. Therefore, palonosetron is a rational choice of CINV prophylaxis in cancer patients predisposed to a repolarization abnormality.

**References**

Effect of palonosetron on transmural dispersion


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