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Original Article

Electrocardiographic changes in patients with tramadol-induced idiosyncratic seizures

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ABSTRACT

Objectives: To assess ECG changes in patients with tramadol-induced seizure(s) and compare these changes in lower and higher than 500 mg tramadol doses as a main goal.
Material and methods: In an analytical-cross sectional manner over 1 year, 170 patients with idiosyncratic seizure(s) after using tramadol, were studied. Full data were recorded for each patient. ECGs were taken from all the patients on admission and 1 h later and were assessed for findings.
Results: 70 of 170 patients (41.2%) had used lower than 500 mg doses of tramadol while 90 patients (52.9%) were included in the high dose group. Rate of female patients in the high dose group was significantly higher. The average age of patients in the high dose group was significantly lower (22.04 vs 25.76). The high dose group had significantly higher heart rates. There was no history of cardiovascular diseases; two patients had previous history of seizure. No significant difference was shown between low dose and high dose groups from the point of ECG changes.
Discussion and conclusion: Using doses higher than 500 mg is more frequently seen in women, young people and those who have not experienced previous use of tramadol. Terminal S wave, sinus tachycardia, and terminal R wave in the lead aVR are among the most common ECG changes in tramadol users.

1. Introduction

Tramadol is a synthetic analog of codeine[1] with a 10-fold weaker affinity for opium receptors (resulting in analgesic effects) compared to morphine.[2] It is absorbed rapidly and almost completely, following oral intake.[3] There are also, slow-releasing forms of tramadol in which the free portion is being released within 12 h and the highest concentration is being achieved within 4.9 h.[4] 20% of tramadol gets bound to plasma proteins.[5] Tramadol is distributed in blood, kidney, and brain, but it cannot be found in muscles. Like morphine, tramadol is significantly accumulated in bile rather than in kidneys and liver and its clearance takes 6 h.[4] First, tramadol was claimed to be a safe agent with a low potential for being abused,[6] but later, adverse reactions were reported. Its complications are inappropriately higher in overdose. Published cases of overdoses are mainly in an acute, oral, and intentional setting. Majority of cases become symptomatic within the first 4 h and the symptoms disappear after 24 h. It is reported that up to 20% of cases need intensive care unit (ICU) admission. Tramadol overdose generally involves young people in third decade of their lives, on average.[7] Central nervous system complications are the most frequently reported manifestations ranging from agitation to deep coma.[5] Seizure has been considered to have an important role in tramadol toxicity as declared by studies and the literature.[5,7–11] Nausea/vomiting and respiratory depression have also been reported.[5,7,8] Of cardiac issues, hypotension, especially affecting systolic blood pressure (SBP) and sinus tachycardia have been listed as tramadol toxicity complications.[5,7,8,12–14]

Management of tramadol toxicity is focused on supportive care, including oxygen, fluid therapy, and diazepam for controlling agitation or seizure.

Few studies have been conducted to investigate electrocardiographic (ECG) changes after idiosyncratic seizures following

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tramadol use. Our study was performed to evaluate ECG changes in this category of patients.

2. Material and methods

This study was conducted in an analytical cross sectional manner since January 2013 to January 2014. The study was approved by ethics committee of Iran University of Medical Sciences (IUMS) and all ethical issues regarding research were fulfilled during the study. Informed consent was taken from each patient or his/her companion(s). 170 patients, admitted to a teaching Hospital because of an idiosyncratic seizure after using tramadol, were included in the study. Inclusion criteria were age between 16 and 80 years, complaints following tramadol abuse. Exclusion criteria included cardiovascular disease, proof of other drugs and substances abuse with tests and use of drugs affecting cardiovascular system before admission. A checklist including age, sex, frequency of seizures during admission, history of seizure, and dose and duration of tramadol use was filled. ECG was taken from all the patients 1 h after admission. QT interval prolongation, QRS widening, terminal S wave in the lead D_1, terminal R wave in the lead aVR, and sinus tachycardia were assessed in ECGs by trained emergency room physician. The group of patients who had used doses lower than 500 mg of tramadol, was named "low dose" group and patients who had used doses higher than 500 mg, were included in the so-named "high dose" group.[15–17] Acquired data were analyzed in SPSS V.16 with independent sample t-test for quantitative and chi-square test for qualitative comparison.

3. Results

170 patients were included in the study; In low dose group there were 70 (41.2%) patients, including 68 men and 2 women, while 90 (52.9%) of patients, including 76 men, 13 women and unknown sex of one patient, entered the high dose group. Dose of tramadol used, has not been recorded for 10 patients (5.9%).

Table 1
Basic patients' characteristics.

	Low dose group	High dose group	p-value
Age	25.76 ± 7.30	22.04 ± 6.21	0.001
Gender	68 males (97.14%), 2 females (2.85%)	76 males (85.39%), 13 females (14.60%)	0.012
Systolic blood pressure	124 ± 14.25	120.90 ± 15.17	0.190
Diastolic blood pressure	77.94 ± 8.20	75.40 ± 10.55	0.103
Respiratory rate (RR)	23.31 ± 2.61	22.76 ± 2.61	0.106
Pulse rate (PR)	101.06 ± 20.03	92.94 ± 17.80	0.009

There was no difference in respiratory rates (RRs) between two groups but a significant difference between pulse rates (PRs) of two groups has been observed. PRs were lower in the high dose group compared to the low dose group (92.94 ± 17.80 vs. 101.06 ± 20.03; $p = 0.009$) (Table 1).

There was not even one positive history of heart disease in the participants. 157 patients denied any history of cardiac problems and in 13 patients there was no recorded document supporting their cardiac history. Two cases had a positive previous history of seizure; one of them was due to previous use of tramadol.

Number of seizure attacks was 1.18 ± 0.615 and 1.26 ± 0.604 in the low and high dose groups, respectively ($p = 0.169$). Fig. 1 shows the frequency of seizure attacks in patients after tramadol use.

The time interval between using tramadol and occurrence of seizure(s) was measured in both groups. It was 150 min in the low dose group, compared to 235 min in the high dose group; there was no statistically significant difference between two groups ($p = 0.113$).

The positive history of previous tramadol use was significantly more frequent in the low dose group ($p = 0.002$), as 47 of patients reported previous use of tramadol, while 21 of them denied any history of previous use (compared to 38 and 48 patients, respectively, in the high dose group).

Overall, 68 patients (42.5%) showed sinus tachycardia and 4 patients (2.4%) had sinus bradycardia; sinus tachycardia was significantly much more frequent in the high dose group (47 vs. 21 patients; $p = 0.005$).

There was no statistically meaningful difference between two groups from the point of bradycardia (3 patients in the high dose group vs. just 1 patient in the low dose group; $p = 0.632$).

The most frequent ECG changes were terminal S wave, sinus tachycardia, terminal R wave in the lead aVR, T wave inversion, right bundle branch block (RBBB), and QRS widening, respectively. No left bundle branch block (LBBB), QT interval prolongation (Fig. 2), second or third degree atrio-ventricular (AV) block were seen. Table 2 demonstrates ECG changes in details.

4. Discussion

Seizure is a critical issue in tramadol toxicity. While population-based reports speculate the frequency of seizure from 8 to 14%,[5,7] hospital reports declare a higher risk for seizure, from 15 to

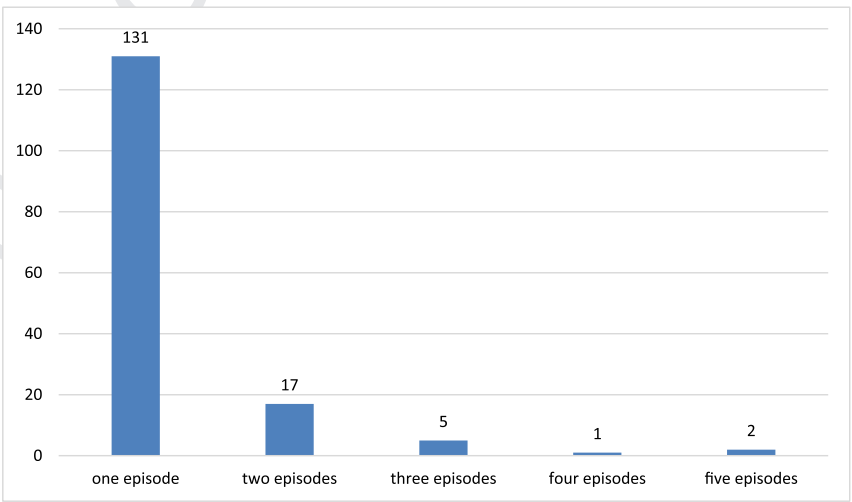

Fig. 1. Number of seizure episodes in the individuals.

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