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ORIGINAL ARTICLE

Tramadol Toxicity Induced Neurological and Renal Complications Accompanied by an Alteration in Electrocardiographic Parameters

Running Title: Complications of Tramadol Toxicity

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ABSTRACT

Introduction: In recent years, Tramadols' consumption has increased and is often associated with many serious complications which in some cases can also lead to death. In this study, we aimed to assess neurological and renal complications, and also assessed electrocardiographic changes linked to tramadol overdose. **Materials and Methods**: In this descriptive study, the data required was gathered from the patients history that had been admitted to the medical toxicology ward of Imam Reza hospital in 2006-2007. Data had being included sociodemographic data and other medical information by a self-designed form, including data such as patients' age, sex, co-ingestion of other drugs, habitual history of drug addiction, electrocardiogram (ECG) changes including duration of QRS, QT, QTC and PR Interval, pulse rate, respiratory rate, systolic and diastolic blood pressure (SBP and DBP), consciousness and seizure occurrence. Laboratory findings including blood sugar, blood urea nitrogen (BUN), creatinine (Cr) and creatine phosphokinase (CPK) along with therapeutic interventions such as dialysis admission and whether patients were referred to the nephrology ward were retrieved from patients' medical records. After the collection of data, it was registered and analyzed in SPSS software v 21. **Results**: 150 patients (64.70% male) with a mean age of 22.57 years qualified to be selected in our study. Out of these, 66% were drug addicts and 23.30% suffered from seizures. Additionally, 44% displayed an increased BUN, 4% showed Cr increase, 3.3% were hypertensive and 36.70% had tachycardia.Electrocardiographic parameters such as PR Interval, QRS, QT, and QTC were prolonged in 3.30%, 5.30%, 32%, and 17% of the patients, respectively. Furthermore, an elevated creatine phosphokinase (CPK) was noted in 38% of them, and 4% suffered from bradypnea and respiratory depression. Also, an impaired consciousness was recorded from 56.70% of the patients. Death due to cardiopulmonary arrest took place in a young addict male who had ingested 5000 mg of tramadol. **Conclusion**: Tramadol intoxication is generally common among youth and can result in seizure, tachycardia, hypertension; central nervous system and respiratory depression; increasing of BUN, Cr and CPK. A regulated marketing control of tramadol can help to prevent its side-effects and the numerous complications associated with it.

INTRODUCTION

Annually,tramdadol poisoning and toxicity primarilyaccounts for the mortality and morbidity linked to itall across the globe. Whether the exposure to it isintentional or accidental, its toxicity causes life-threatening complications (1-3). In addition, introduction of new drugs that have fatal and toxic side effects must also be taken into consideration(4).

Pain relievers play a salient role in post-operativelife satisfaction,and also benefit long-term pain management in osteoarthritis and in other chronic pains. Tramadol is an analgesic agent used to manage mild to moderate or moderate to severe pain(5), and is among the established causes of toxicity in patients with a history of drug addiction. Its ingestion in high doeses is intended as an attempt to commit suicide(5-8). It was first brought into use in 1997,Germany and from there it spread globally. The reason for its swift spread was its weak opioid agonist action and monoamine neurotransmitter reuptake inhibition(9). It centrally acts on serotonergic and noradrenergic pain receptors, and also on the

μ-opioid receptor. Its action is facilitated by a multi-modal pain relieving mechanism that acts by increasing the concentrations of serotonin,noradrenaline and μ-opioid receptor activator(10).

Tramadol addiction is seldom seen compared to other opiates viz. morphine, since development of its addiction has a low potential. Even then, a prolonged abuse, say more than several weeks to months, has a higher chance of dependency especially in people with a history of substance abuse or in those who have been using oral tramadol. A tramadol intoxication ensues from supratherapeutic dose abuse in addicts. Its symptoms include central nervous system (CNS) depression including coma, nausea and vomiting, tachycardia, cardiovascular collapse, seizures, and respiratory depression up to respiratory arrest and serotonin syndrome accompanied with fatal hyperthermia(11-14). Additionally, therapeutic dose intoxication, considering cytochrome P450 enzyme polymorphism in different patients, has also been reported particularly because tramadol is metabolized in the liver by cytochrome P450 enzyme (15).

Although tramadol is a safer drug as opposed to other opioids like heroin, codeine and morphine as a pain reliever, it comes with its risks (16). Itsconsumption has widely increased and so has its toxic side effects. In the light of this, we aimed to assess the neurological and renal complicationsalong with electrocardiographic changes in patients with tramadol overdose admitted to the medical toxicology ward of Imam Reza hospital in Mashhad, from 21 March, 2006 to 21 March, 2007.

MATERIALS AND METHODS

This is a retrospective descriptive study, conductedfrom 21 March, 2006 to 21 March, 2007 on 150 patients, 15 years old and elder,with tramadol poisoning admitted to the medical toxicology ward of Imam Reza hospital. All research procedures were reviewed and approved by the ethical commitment and vice chancellory of Imam Reza Hospital. There was no exclusion criteriain our study.

We extracted sociodemographic data and other medical information by a self-designed form, including data such as patients' age, sex, co-ingestion of other drugs, habitual history of drug addiction, electrocardiogram (ECG) changes including duration of QRS, QT, QTC and PR Interval, pulse rate, respiratory rate, systolic and diastolic blood pressure (SBP and DBP), consciousness and seizure occurrence. Laboratory findings including blood sugar, blood urea nitrogen (BUN), creatinine (Cr) and creatine phosphokinase (CPK) along with therapeutic interventions such as dialysis admission and whether patients were referred to the nephrology ward were retrieved from patients' medical records.

STATISTICAL ANALYSES

The data was analyzed by SPSS (version 13, SPSS Inc., Chicago, IL, USA). The values of mean ± standard deviation and standard error (SE) for continuous and discrete variables, and also frequency and percentage for categorical variables were all determined by SPSS. Chi-square test was employed for analysis of variance (ANOVA), Student's t-test, and Fisher's exact test statistical comparison of qualitativeand quantitative variables with and without normal distribution.A statistical significance was considered when $P \leq 0.05$

RESULTS

A total of 175 patients with tramadol toxicity had been admitted to the toxicology ward. Out of these, 25 patients had been discharged with a self-consent, even when their medical data remained incomplete. In sum, 150 patients, including 97 men (64.7%) and 53 (35.3%) women with a mean age of 22.57 ± 6.16 (range = 15-47) years became a part of this study. The age group of 15-20 years consisted of 45.4% oftotal,which stood as the highest frequency (Table 1).

Data was incurredabout the co-ingestion of other drugs in addition to tramadol in 73 of patients (48.65%); whereas, in the remainder of patients, 73 (48.85%) did not use any other medications besides tramadol and 4 (2.7%) had missing data. An addiction history was reported in 99 (66%) of them, whileas 32 (21.3%) were non-addicts. On the other hand, data remained missing in 19 (12.7%) patients. Also, an impaired consciousness was noticed in 85 (56.7%) of patients and 65 (43.3%) were normal.

Seizure episodes were detected in 35 patients (23.3%) against 115 (76.7%). All seizures occurred 12 hours after tramadol usage which was controlled by naloxone administration. The Chi-square test showed no significant relationship between sex and seizure episodes even when 24 (16.10%) of all episodes occurred in male and 11 (7.4%) in female patients (p value= 0.62). Distribution of seizers based on addiction history showed no significant relationship either (p value= 0.258). However, the co-existence of seizure and addiction history was found in 22 (14.7%) of them with 10 (6.7%) experiencing seizures in spite of having no history of addiction. In contrast,77 (14.7%) did not suffer from seizures despite having an addiction history, and the remainder i.e.22 (14.7%) experienced neither seizure nor had an addiction history.

To investigate the relationship between CPK level and seizure occurrence, Chi-square test was brought to use and a significant relationship was found with P value<0.001. In patients with seizure episodes, 8 (5.3%) had normal a CPK, 25 (16.7%) had an elevated CPK, and 2 (1.3%) had missing data. On the other hand, the non-seizure group comprised of 63 (42%) patients with normal a CPK, 32 (21.3%) with an elevated and 20 (13.3%) with no available data.

Statistical analysis of co-ingestion of tricyclic antidepressants (TCAs), antipsychotic drugs, benzodiazepines (BZD), and selective serotonin reuptake inhibitors (SSRIs) with tramadol showed a significant correlation between BZD and tramadol (P value= 0.031) in Chi-square test, but not with other drugs. The p-values obtained in analysis of TCA through Chi-square test were equal to 0.06, while those for Fisher's exact test for antipsycotic and SSRI drugs were 0.413 and 0.053, respectively. Lab data, ECG changes and other paraclinical data have been categorized in

The mean ingested dose in patients with seizure and no seizure was 1897 ± 2037 mg and 1400 ± 1574 mg, respectively. But no significant difference was detected between these

groups based on the T-test with a P value= 0.198. Also, the mean ingested dose in men (2419 ± 2379 mg) was seen to behigher than that of women (1010 ± 732 mg).Even then,no significant difference had been found between these groups based on the T-test with P value= 0.082. Also, a minimum dosage of 250 mg was seen in the seizure group.

Analysis of variance between the mean ingested dosage and pulse rate change confirmed the existence of a significant relationship between them. But, no significant relationship between the respiratory rate changes and the mean ingested dose was noticed. Mean dosage in patients with a normal heart rate was 1110 ± 818 mg, 2325 ± 2571 mg in tachycardia, and 1882 ± 2001 mg in bradycardia (P value= 0.021). Moreover, mean dosage in patients with normal respiratory rates was 1347 ± 1500 mg, 1227 ± 1400 mg in tachypnea and 5400 ± 3750 mg in bradypnea patients (P value=0.72).(Table 2).

Table 1. Frequency of age-group distribution

age group(years)	number	percent
15-20	68	45.4
21-25	53	35
26-30	19	12.7
31-35	2	1.4
36-40	4	2.7
41-45	2	1.4
46-50	2	1.4
total	150	100

DISCUSSION

Tramadol abuse and intoxication is a major problem, especially in Southest Asian countries. Increased consumption of analgesic drugs to relieve pain and their benefits such as long-term life satisfaction lead to an approved therapeutic usage of tramadol internationally despite of all its inevitable complications. Mohamed F. Khodeary et al. in 2016 evaluated dosage and time-related side effects linked to tramadol usage since in recent years, its increased usage has lead to it being asource of a hazardous socioeconomic problem. They found hepato-renal toxicity and poisoning incidences, particularly among young Egyptian adults (17). This confers with our study which also demonstrated that young people in the age group of 15-20 years and men are most vulnerable to tramadol toxicity.

Its overdose can result in seizures in intoxication dosage and dizziness, drowsiness, fatigue, cephalgia in therapeutic use. Regarding F. Taghaddosinejad et. al. in 2011 detected seizure attack within 20 minutes to 12 hours after tramadol ingestion. Possible pathology backs to its monoamine uptake inhibition caused by O –Desmethyltramad as its metabolite. (18) In study of P. Layegh et. al. in 2017 siezure had been accured even in therapeutic dose. They suggested taking MRI in a tramadol-consumption seizure may lead to hypersignal area and frontal lesion. (19)K. Kroenke et. al. in a review study suggested that patients who experienced serotonin syndrome and seizure consequent on tramadol co-ingestion with tricyclic or SSRI antidepressant, a monoamine oxidase inhibitor, an antipsychotic drug, or other opioids may be at increased risk (20). we have detected same result in the specialty of BZD co-ingestion (18-21).

Our study results shows cardiovascular dysregulation (hypertension, palpitations, tachycardia, orthostatic hypotension) and ECG changes (12). Ghamsari A et al. in 2016 assessed ECG changes in tramadol poisoned patients, and noticed sinus tachycardia, a deep S wave in leads I and aVL, right axis deviation, and a long QTc interval (10). Likewise, our study also revealed pulse rate changes with a higher tramadol mean dosage in poisoned patients. Even though the ECG duration time changed in some cases, but statistical analysis did not find any significant relationship. It is noteworthy to mention that an even more extensive and elaborate study needs to be done to clarify this indifference (22).

Other tramadol ovrdose complication in this study are respiratory depression, increasing of BUN, Cr, and CPK, and in rare cases can even lead to an inevitable death. Also, its therapeutic use's side effects involve nausea, increased sweating, emesis, xerostomia, constipation, and diarrhea (23).

No data regarding the patients' psychiatry history was identified and whether tramadol overdose was intentional or accidental remained unclear. Ahmadi et al. in 2011 investigated the epidemiologic background of tramadol poisoning in a medical toxicology ward and their survey confirmed that single and young people gullible to suicide are more likely to consume tramadol in high doses. Seizure was described as a common complication in these patients, specifically in men (23).

CONCLUSION

Based on the results of our present study, tramadol overdose can ensue these complications: seizures, tachycardia, hypertension, central nervous system and respiratory depression, increasing of BUN, Cr, and CPK, and in rare cases can even lead to inevitable death. Also, side-effects ofits therapeutic use involve nausea, dizziness, drowsiness, fatigue, cephalgia, increased sweating, emesis, xerostomia, constipation, diarrhea, and cardiovascular dysregulation (palpitations, tachycardia, orthostatic hypotension), especially in young adults. Its advantages as a pain reliever and disadvantages as a possible abuse potential drug make it essential to superintend its market sales and also apprehend early signs of its toxicity to prevent any further serious damage.

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Table 1. Laboratory data and paraclinic parameters change

Parameter	Lower than Normal (N)	Normal(N)	Higher than Normal (N)	No Data (N)	Mean	Normal Range
DBP [a] (mmHg)	_	145 (96.7%)	5 (3.3%)	_	73	60-90
SBP[b] (mmHg)	27 (18%)	118 (78.7%)	5 (3.33%)	_	120	80-140
PR[c] (N/minute)	7 (4.7%0	88 (58.6%)	55 (36.7%)	_	95 ± 22	60-100
RR[d] (N/minute)	6 (4%)	132 (88%)	12 (8%)	_	12	12-20
Cr[e] (mg.dl)	_	144 (96%)	6 (4%)	_	0.94	0.7-1.4
BUN[f] (mg.dl)	_	84 (56%)	66 (44%)	_	25.71	7-25
CPK[g] (U.L)	_	57 (38%)	71 (47.3%)	22 (14.7%)	351 ± 545.77	55-165
Blood Sugar (mg.dl)	13 (8.2%)	98 (65.3%)	30 (20%)	9(6%)	104 ± 39.53	75-110
QT (ms)	_	84 (56%)	48 (32%)	18 (12%)	340 ± 25	350-440
QRS (ms)	_	124 (82.7%)	8 (5.3%)	18 (12%)	80 ± 13	≤ 100
PR[j] Interval(ms)	_	127 (84.7%)	5 (3.3%)	18 (12%)	160 ± 24	120-200

[a] Diastolic Blood Pressure; [b] Systolic Blood Pressure; [c] Pulse Rate; [d]Respiratory Rate; [e]Creatinine; [f] Blood Urea Nitrogen; [g]CreatinePhosphokinase; [h] QT Corrected [d]Respiratory Rate; [e]Creatinine; [f] Blood Urea Nitrogen; [g]CreatinePhosphokinase; [h] QT Corrected

AUTHOR CONTRIBUTION

All authors contributed equally

CONFLICT OF INTEREST

The authors declare that there was no conflict of interests in this study

ETHICAL STANDARDS

This study was approved by Mashhad University of medical sciences ethics committee.

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