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DETERMINATION OF SERUM SODIUM AND POTASSIUM LEVELS AND ECG CHANGES IN PERSONS WITH TRAMADOL POISONING REFERRED TO TOXICOLOGICAL EMERGENCY DEPARTMENT OF LOGHMAN HAKIM HOSPITAL IN TEHRAN 2012- 2013

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ABSTRACT

Determination of serum sodium and potassium levels and ECG changes in persons with tramadol poisoning referred to toxicological emergency department of Loghman Hakim Hospital in Tehran 2012- 2013

The Tramadol or Ultram an opium-like analgesic is nowadays widely abused in Iran and its unwanted side effects are such as seizures, hypotension, or intoxication are a common cause of visiting to poisoning emergency and departments. Possibility of ECG changes and consequently developing arrhythmias and other cardiac complications is new issue which potentially can enhance risk of serious cardiac arrhythmias. Therefore, with detection of these disturbances and their risks, it's hope that this study in addition to meeting its goal can contribute to the treatment of these patients, as well as a starting point for further studies in this field.

In this prospective study, all poisoned patients with Tramadol over a year of admission to Toxicological emergency department and after asking about taken drugs,only patients who were taking tramadol (n = 1402 patients) have been included in this study, and amount and timing of tramadol were determined and for clinical examination, blood samples were taken for testing serum levels of sodium and potassium. Electrocardiogram (ECG) was performed and in terms of the potential problems associated with drug toxicity as determination of PR, QRS and QTc intervals and evidence of Brugada pattern, as well as cardiac axis deviation in

favor of changes to the right and the right block has been investigated, their results along with age and gender of the patient's and results of serum potassium, sodium were recorded in the questionnaires and the obtained data, were analyzed based on statistical tests using descriptive and inferential spss software.

The overall prevalence of poisoning only with tramadol was5.87%. A total of 1402 patients were studied in which 997 patients were males (71.1% of patients) and 405 were females (28.9% of all patients). Minimum and maximum age of patients was 14 years and 53 years,respectively, with a mean age of 24.6,standard deviation (SD)13 and variance19.1.

Minimum and maximumof serum sodium level of 132 and a maximum amount of 157 patients with a mean 139.7, standard deviation 2.1 and variance of 4.4 mEq /dl were measured. Hyponatrmia in 51 patients (3.6% of patients) were measured including 38 males (2.7% of patients) and 13 females (0.9 % of total patients).Hypernatremia in1male patient (approximately 0.1% Of patients) was observed. Minimum and maximum Serum potassium were 3 and 6.1 and the mean of 4, SD of 0.27 and variance of 0. 07 MEq/dl. Hypokalemia was seen in 9 patients (0.67 %), of which 8 patients (0.6 % Of patients) were males and 2 females (about 0.1% Of all patients).Hyperkalemia in 23 patients (1.6% of all patients) was observed with 18 men (1.2% of patients) and 6 females (0.5% Of all patients).Sinus tachycardia (HR> 100 / min) was diagnosed in 463 patients (33% of cases) and 439 were male and 24 were female and sinus bradycardia ((HR <60 / min) in a male patient (0.05 % of patients) was observed.In none of the patients have seen evidence of an increase in PR interval. The QRS:120 ms or more in 91 patients (6.5% of patients) was observed, 64 were male and 27 were female. And the QTC more than 440 ms in 259 patients (18.4% of patients) were observed, of which 134 were males and 125 were females.

Evidence of axial deviation of the heart to the right (around 40 ms end at the frontal QRS complexes over 120 degrees) with a height of more than 1 mm R wave in aVR in 340 patients (24.3% of patients) were observed that 259 were males and 81 were women. Prominant S wave in lead I or aVL in 395 patients (28.1% of all patients),in 372 men and 23 women was identified.Brugada pattern in two patients, both of which were males (0.1% of total patients) was observed. Right bundle branch blocks in 73 patients (5.2% of all patients) were observed, of which 40 were males and 33 were females. .

According to this study and prior done investigations, it can be concluded that toxicity with Tramadol can be accompanied with some degrees of Na and K channels blocking in the heart and theoretically and potentially can lead to developing malignant ventricular dysrhythmias (

although has been not seen in this study) which its treatment in case of developing is like therapy for poisoning with tricyclic anti depressants and so on.

Keywords: Tramadol, sodium, Ptasym, ECG, poisoning

INTRODUCTION

Tramadol hydrochloride withtrade names of Bayvmadvl, Ultram, Tramal, Trandon, Tramajyt and tralgydol is known as an opium-like analgesic that was first synthesized in 1962 and used since 1977 in Germany, also it is available in Australia and New Zealand since 1998 (12).Currently this drug is prescribed to relieve moderate to severe pain. Tramadol is an analgesic with dual mechanism. A mechanism is agonist activity similar to opioid, which is bonded with μ receptors (11).in addition to this mechanism, tramadol inhibit uptake of Serotonin (5-HT)and Norepinephrine(NE). Tramadol has 2 types L- and D- types that L- Tramadol is stronger 5 to 10 to inhibit NE uptake. While R- tramadolis stronger stronger to inhibit 5-HT uptake. Tramadol is not bonded to Alpha two andNMDA (N_ Methyl _D_ Asparatate) or benzodiazepin receptores. Bindin tramadol to μ receptors is weaker 10 times compared to morphin, 1000times compared to Metadon, and 6000 times is weaker than morphine.Compare to Imipramine, ability of tramadol to inhibit uptake of Serotonin (5-HT) and Norepinephrine (NE) is 100- 1000 times is weaker. Tramadol has an active metabolite which is called Mono- O- desmethyl Tramadol (M1), which has higher affinity toμ receptors compared to tramadol it self, but its analgesic effect on a sngle dose is negligible. Up to 68- 75 percent of oral tramadol in a single dose is absorbed which this level by repeating the dose reaches to 100%. Its effect starts an hour after taking orally and after 3-2 hours reaches to its peak in the plasma. Constant plasma concentration is achieved after two days. Tramadol is bonded a protein of approximately 20% of which in persons over 75 years, usually this amountincreases up to 25 percent. The volume of the tissue distribution of it, is about 2.7 L / Kg. Due to weakbinding withPlasma protein has less interaction with those drugs which are highly bonded to proteins (6). About 60% of oral drugs is metabolized by cytochrome p 450 _ 2D6 then after sulfurization and glucoronidation is excreted by the kidneys (90% is excreted through the kidneys). About 1% of the drug is excreted via the bile (6). The plasma half-life of tramadol and its metabolites in a healthy person is 6.3 to 7.4 hours. Tramadol crosses the placenta and its concentration reaches up to 80% of its level in maternal blood. Small amounts of tramadol and its metabolites

(1.0%) is excreted in breast milk which within 16 hours after taking is measureable (10). The therapeutic dose of tramadol is50 to 100 mg every 4-6 hours (maximum 400 mg per day) (12).Unwanted side effects of this drug, even at therapeutic doses, such as seizures, hypotension, or intoxication with is, is a common cause of visits to poisoning emergency rooms and wards. Nausea and vomiting are common in acute poisoning. Triad of opioid overdose include Miosis, respiratory depression (Bradypnea) and loss of consciousness occurs in posoning with tramadol but unlike opioid, tramadol overdose leads to increased irritability, tremors, increase in deep tendon reflexes and hypertension as well. Other symptoms include urinay retention, rhabdomyolysis, seizures, pulmonary edema, withdrawal syndrom. Seizures often is seen in the increasing of previous dose or taking large amounts of it, however the seizure may occur even with a single dose. Seizure is usually single, tonic-clonic and self-limited (16).The clinical assessment in all toxicities, after the initial emergency treatment and providing support to sustain vital signs and determining the cause of poisoning (the poison orconsumed drug), amount of consumption and exposure to drugs or toxins (the time from taking the toxin or drug till arriving to the hospital),and physical examination, we should start to do diagnostic procedures, including a request forroutine testsand specific toxicological tests, ECG and radiological investigations (if it is necessary). In assessment, diagnosis and treatment of poisoned patients, some routine tests is done which depending ont he case and patient's condition all or some of folowing examination is performed such as: ABG, Anion Gap, electrolites (Na, K, Ca, P), blood glucose, BUN, creatinine, liver function tests, CBC, PT, PTT, urine of whichare very important in primary assessment and initial treatment of poisoned patients.The electrocardiogram (ECG) is useful in evaluating patients in emergency departments and intensive care and its importance is widely clear for clinical practitioners in any field.ECGis one of available toolsto assess the poisoned patient and potentially has important role in the evaluation, monitoring, treatment and follow-up, respectively. In some intoxications clearly signs of cardiac symptoms are expected such as those are used in cardiovascular disorders, other drug may have no clear effect on cardiovascular systems in thrapeutic dose buti n the case of overdose becomes cardiotoxic, in which both cases doing ECG is inevitable.ECG should be specially considered in the initial evaluation of amnypoisoned patients. Various drugs andtoxins can lead to a

variety of arrhythmias, such as sinus tachycardia, bradycardia, ventricular tachycardia, different types of blocks, conduction disorders, long QRS and QT, Torsade de points, and so on. If there is a branch block, the ventricles are not depolarized simultaneously, but consecutive and in tandem are depolarized.Many classes of medications preferably affect on right bundle. This leads left ventricular to depolarize slightly faster than the right ventricle. The further effect on the ECG is widening of the QRS complex and the appearance of right ventricular electrical activities that was previously hidden by the left ventricle. These changes are often the result of the effects of those drugs that block fast sodium channels (13).The fast sodium current in cardiac cells,is essentialfor the release of intracellular calcium storage and subsequent contraction of heart cells. Inhibition of fast sodium channels in His - Purkinjecells leads to delayed depolarization and conduction disturbances. This in turn leads to reduce contractility of the heart and the negative inotropic effect. Its manifestations on the ECG are prolongation of the PR intervaland the duration of the QRS, cardiac axis deviation to the right frontal screen, and Brugada pattern (incomplete right block in leads V1 to V3 with ST-segment elevation is seen). Deviation of heart toward right especially at the 40 milliseconds end of the QRS interval in limb leads is distinguishable with presence of R wave in aVR lead and a dominant S wave in leads I, aVL detectable (14).Prolonged QT interval on ECG, reflecting the increase in the excitability of the heart that this is the beginning of ventricular dysrhythmias, including Torsade de pointes. Classes of medications, that lead to inhibition of sodium channels, cause prolongation of the QT interval due to the prolongation of complex QRS. In these patients, the segment ST, remains normal. Classes of medications, that lead to block potassium channels in the heart through prolonging the Repolarization and plateau phases of cardiac cell contraction, will lead prolongation of the ST segment, QT interval prolongation. (13)

The incidence of poisoning in Western countries is not comparable to Iran, because prevalence and pattern of addiction in Iran is different,And considering that any dose of tramadol can not be viewed free of side effects and poisoning, therefore we should investigate in our country what is tramadol effect on the ECG changes and on Na, K levels(which are important electrolites on heart) regarding toxicity with it. it’s hope that we can help to more accurate assessment and treatment of these patients, with conducting this study.ASE REPORT

A study in 2007 revealed that the 33-year-old male patient with a history of depression who are alone, at his residence by the emergency, was found in a coma.In patients with several empty packages of drugs tramadol, hydroxy, gabapentin and clonazepam was the obvious initial study suggests that consuming 10 grams of tramadol. The use of drugs not specified. As a result of the bedside glucometer mg / dl55 was.Patients after the initial includes intravenous fluids and glucose and endotracheal intubation with the administration of thiopental, was transferred to the hospital and was admitted to the intensive care unit.The patient had seizures several times his initial GCS 3. Mydryatyk pupils with no reaction to light. Blood pressure mmHg 38/68, PR: 85 / min and T: 35.9, but in the case of early spontaneous breathing and respiratory disease risk, did not mention. The abnormal heart and lungs in particular, was evident.Opacities on chest radiograph was performed in the lower lobes of the lungs were observed. The electrocardiogram (ECG) patients in sinus rhythm with complete right bundle branch block plus QTc: 480 msec, read the EEG (EEG) patients showed a generalized epileptic discharges were continuous waves. CT scan of the skull was normal. The echocardiogram of the left ventricular EF of 56% and it was good.Initial blood test results were as follows:

Glucose mg / dl 162, ABG PH: 7.4, the ratio of PaO2 / FiO2: 350, mmol / lit HCO3: 18 Vlaktat 2.2 mmol / lit and hepatic function tests, bilirubin, albumin, urea, creatinine and CBC early, at normal .Patients treated with fluids, vasopressor, and was careful control of blood sugar and respiratory supportThe patient gradually deteriorated and about 12 hours after admission, the patient suddenly developed ventricular tachycardia shock was the need for more then a few minutes later, the patient was injected with 3 mg epithelial period of asystole curse IV resolved spontaneously.The patient had no evidence of cardiac ischemia in the ECG and the patient was seen in severe hypoglycemia and metabolic disorders. There was an error in the administration of medication to the patient and the ventilator is also a problem, not available. Satisfactory explanation for sudden cardiac arrest, the doctors found the patient.The patient underwent echocardiography of the left ventricle Hypvkynzy EF: 25% was observed. On admission the patient Tvksykvlvzhyk routine tests of blood and urine was requestedThe results obtained using GC-MS urine significant peak of tramadol and desmethyltramadol and also small amounts of hydroxy, gabapentine and clonazepam

revealed no drug or other Xenobiotic were observed. The quantitative concentrations of tramadol were determined in blood samples admission to 23.9mg / L (therapeutic range 0.1- 0.8 mg / L), respectively. Other results on blood samples at the time was later revealed elevated concentrations. Desmethyl tramadol peak concentration at 12 hours after admission (at the time of cardiac arrest), respectively.Hydroxy, gabapentin and clonazepam in the urine by GC-MS in combination with tramadol was detected because the drugs were found at low levels, unfortunately, few measurements were performed.Laboratory concluded that considering that patient's blood concentrations of tramadol mg / L 9/23, which is 30 times greater than the upper limit of the normal range is about 15 times the therapeutic and toxic levels (1-2 mg / L) and 10 of possibly fatal (2 mg / L) is a drug, the drug most likely associated with refractory shock caused by the patient's heart Vasystvl.Although other drugs consumed, blood pressure may fall Dprsvn CNS are involved, it is unlikely that these drugs are the cause of cardiac arrest (9).. In another study called: Isolated tramadol overdose associated with brugada ECG patten, who in 2010 published a case report of a patient's electrocardiogram was hospitalized due to poisoning tramadol, Brugada syndrome were observed. This syndrome is a genetic disorder or acquired disorder that represents ECG to block sodium channels in the heart. .This syndrome, ventricular arrhythmias, syncope and sudden death can be. Brugada syndrome ECG changes in wave height coved ST 2 mm or more in the pre-cordial leads right (V1 and V2) and the T-wave inversion. .Acquired forms of Brugada syndrome with electrolyte abnormalities such as hyperkalemia or poisoning effect of the sodium channel blocking properties of the heart, such as drugs, antiarrhythmics, Type I, lithium, tricyclic antidepressants and cocaine-associated.This case report is to describe a 47-year-old man who attempted to use 3 grams of tramadol was a suicide attempt. He did not have a seizure at his ECG changes were observed in Brugada syndrome. (7)Another study entitled:

Electrocardiographic Manifestations Of Tramadol Toxicity With Special Referace To Their Ability For Predication Of Seizures on Bymarmsmvm just because tramadol 479, were studied retrospectively.Heart rate of 100 per minute in 6/30 percent and QRS 120 ms and 440 ms at 5.7 percent and QTC more than 6.24 percent of the more than 1 mm and height of the R wave in aVR 1.22% and the terminal 40 ms of the QRS frontal surface above 120 ° C at 31.7%, and complete or

incomplete bundle branch block right in 6/4 of patients,In this study, no significant differences between patients who did and those who did not have seizures after hospitalizationGiven the age and sex of vital signs and ECG findings were observed.The results of these studies indicate that tramadol toxicity may,The fast sodium and potassium channel blockers leads to a widening of the QRS complex series of changes in the ECG and heart-to-right axis deviation increase in the corrected QT intervalWhich can be potentially life-threatening arrhythmias is to make progress. (4).

METHOD AND MATERIAL

In this prospective study, all poisoned patients with Tramadol over a year of admission to Toxicological emergency department and after asking about taken drugs,only patients who were taking tramadol (n = 1402 patients) have been included in this study, and amount and timing of tramadol were determined and for clinical examination, blood samples were taken for testing serum levels of sodium and potassium. Electrocardiogram (ECG) was performed and in terms of the potential problems associated with drug toxicity as determination of PR, QRS and QTc intervals and evidence of Brugada pattern, as well as cardiac axis deviation in favor of changes to the right and the right block has been investigated, their results along with age and gender of the patient's and results of serum potassium, sodium were recorded in the questionnaires and the obtained data, were analyzed based on statistical tests using descriptive and inferential spss software.

Findings

The total number of patients admitted to the emergency Toxicological 23877 people during the year 1402 the number of patients (incidence rate of 87.5% of the clients) who were enrolled in this study were taking tramadol and studied in which 997 patients were males (71.1% of patients) and 405 were females (28.9% of all patients). Minimum and maximum age of patients was 14 years and 53 years, respectively, with a mean age of 24.6, standard deviation (SD) 13 and variance 19.1.The mean age of the patients were male 2/3 - / + 1.24 and 7.4 in women - / + 8.24 years.

Minimum and maximum of serum sodium level of 132 and a maximum amount of 157 patients with a mean 139.7, standard deviation 2.1 and variance of 4.4 mEq /dl were measured. Sodium concentration in male patients 1.6 - / + 139 and the average concentration of sodium in female patients was 2.2 - / + 140 mEq dL was observed. Hyponatrmia in 51 patients (3.6% of patients) were measured including 38 males (2.7% of patients) and 13 females (0.9 % of

total patients). Hypernatremia in 1 male patient (approximately 0.1% Of patients) was observed. Minimum and maximum Serum potassium were 3 and 6.1 and the mean of 4, SD of 0.26 and variance of 0. 07 MEq/dl. Potassium concentration in male patients 26/0 - / + 1.4, and the mean concentration of potassium in women 27 /. - / + 4 mEq dL was observed.Hypokalemia was seen in 9 patients (0.67 %), of which 8 patients (0.6 % Of patients) were males and 2 females (about 0.1% Of all patients). Hyperkalemia in 23 patients (1.6% of all patients) was observed with 18 men (1.2% of patients) and 6 females (0.5% Of all patients). Minimum and maximum heart rate of 53 to 153 beats per minute with a standard deviation of 9/12 and 5/94 variance. The mean heart rate in male patients 10 - / + 1/87 and in women 11 - / + 86 beats per minute.Sinus tachycardia (HR> 100 / min) was diagnosed in 463 patients (33% of cases) and 438 were male and 25 were female and sinus bradycardia ((HR <60 / min) in a male patient (0.05 % of patients) was observed. In none of the patients have seen evidence of an increase in PR interval. The QRS:120 ms or more in 91 patients (6.5% of patients compared to 7.5% in prior study) was observed, 64 were male and 27 were females. And the QTC duration more than 440 ms in 259 patients (18.4% of patientscompared to 24.6% in prior study) were observed, of which 134 were males and 125 were females.

Evidence of axial deviation of the heart to the right (around 40 ms end at the frontal QRS complexes over 120 degrees) with a height of more than 1 mm R wave in aVR in 340 patients (24.3% of patientscompared to 22.1% in prior study) were observed that 259 were males and 81 were women. Prominant S wave in lead I or aVL in 395 patients (28.1% of all patients), in 372 men and 23 women was identified. Brugada pattern in two patients, both of which were males (0.1 % of total patients) was observed. Right bundle branch blocks in 73 patients (5.2% of all patientscompared to 4.6% in prior study) were observed, of which 40 were males and 33 were females.

Frequency tables ECG poisoned patients with tramadolreferred to Loghman hospital based on gender between 2012- 2013

t a b u l a t i o n

a l l y					
		s e x			
		1	2	"	
n Q R S	QRS duration < 120 msec	3 7 8	9 3 3	1 3 1 1	
	QRS duration 120 msec and >	2 7	6 4	9 1	
"		4 0 5	9 9 7	1 4 0 2	

***sex duration QTc Crosstabulation

m a i n a l l y					
		s e x			
		1	**2**	"	
duration QTc	**QTc duration < 440 msec and**	**2 8 0**	**8 6 3**	**1 1 4 3**	
	QTc duration > 440 msec	**1 2 5**	**1 3 4**	**2 5 9**	
"		**4 0 5**	**9 9 7**	**1 4 0 2**	

p e t t y c r i m e w a v e i n a V R * * * s e x C r o s s t a b u l a t i o n

m a i n a l l y					
		s e x			
		1	2	"	
petty crime wave in aVR	petty crime and Hight apart aVR and< 1 mm	3 2 4	7 3 8	1 0 6 2	
	petty crime and Hight apart aVR > 1 mm	8 1	2 5 9	3 4 0	
"		4 0 5	9 9 7	1 4 0 2	

B r u g a d a p a t t e r n * * * s e x C r o s s t a b u l a t i o n

m a i n a l l y					
		s e x			
		1	2	"	
pattern Brugada	"Well Brogada pattern	4 0 5	9 9 5	1 4 0 0	
	pattern Brugada	0	2	2	
"		4 0 5	9 9 7	1 4 0 2	

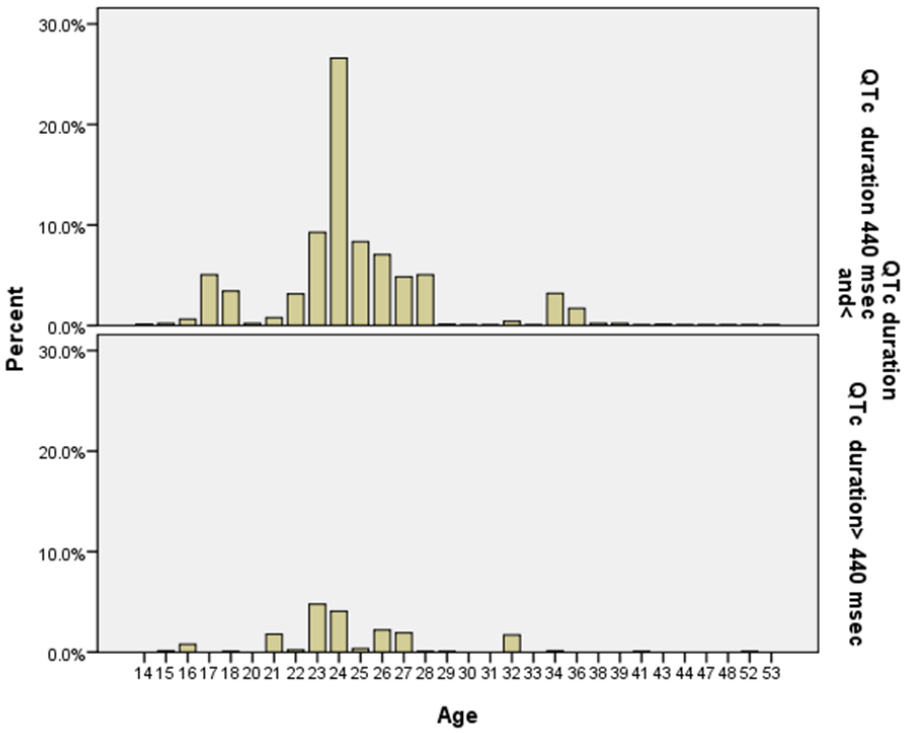

Figure 1: Distribution of EKG changes in QT based on age at referral to Loghman hospital with tramadol toxicity in 2012- 2013

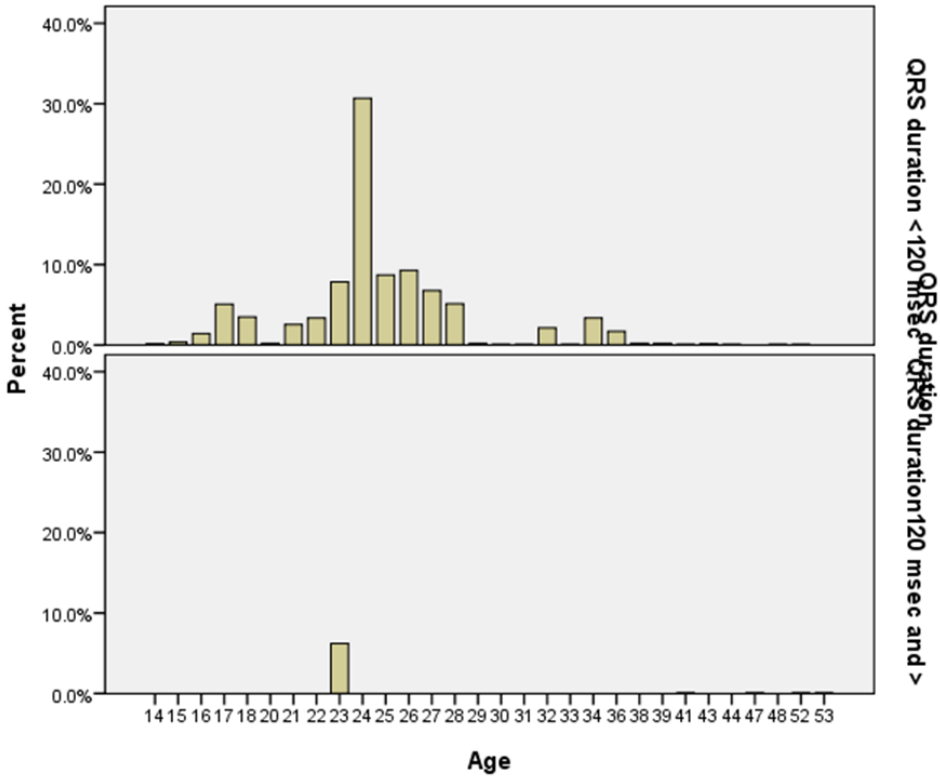

Figure 2: Distribution of EKG changes in QRS based on age at referral to Loghman hospital with tramadol toxicity in 2012- 2013

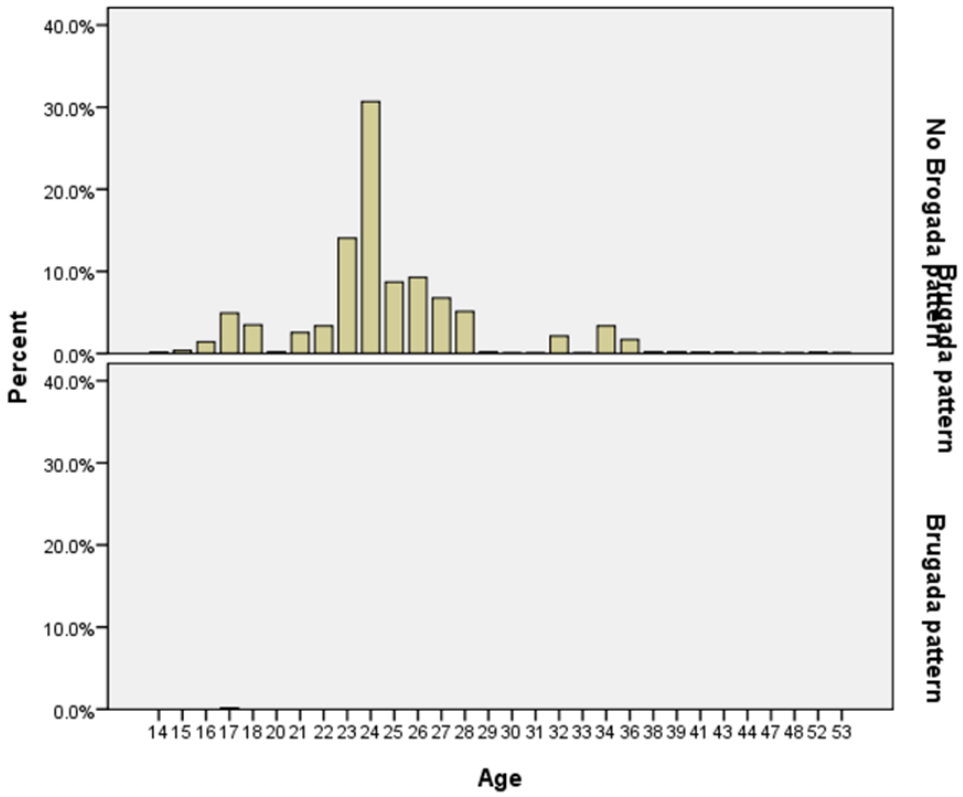

Figure 3: Distribution of EKG changes in Burugada pattern based on age at referral to Loghman hospital with tramadol toxicity in 2012- 2013

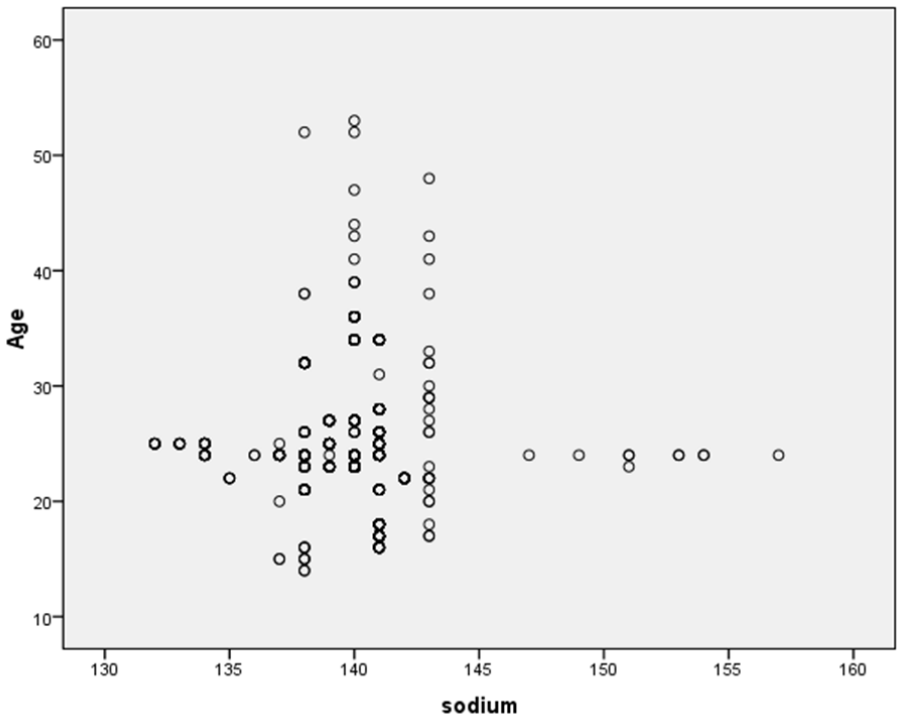

Diagram 1: the distribution of Serum sodium abundance according to age in patients with tramadol poisoning referred to the Loghman hospital in 2012- 2013

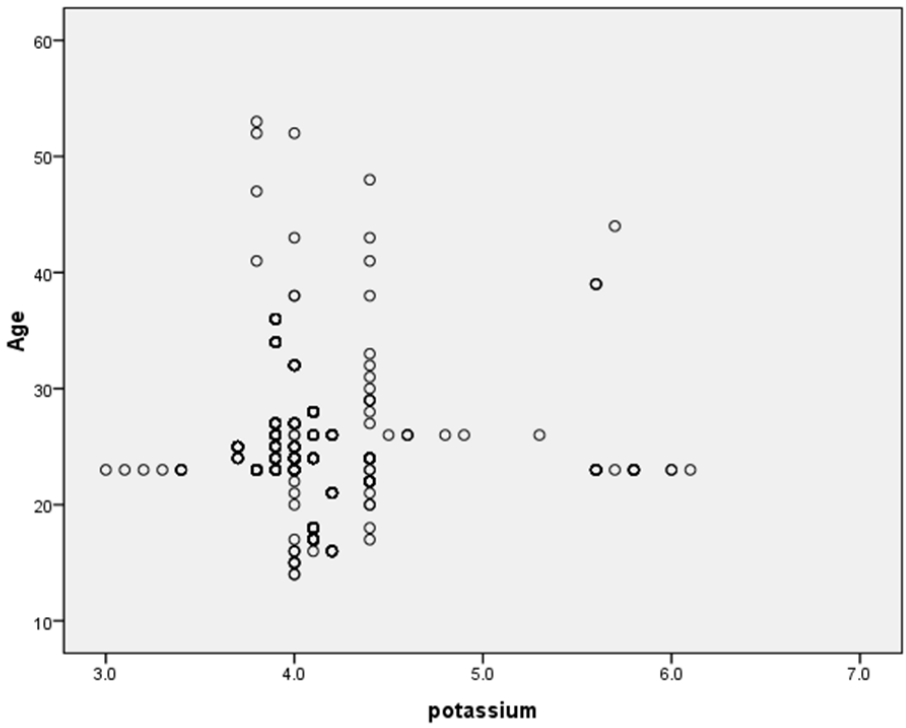

Diagram 2: the distribution ofSerum potassium abundance according to age in patients with tramadol poisoningreferred to the Loghmanhospital in 2012- 2013

DISCUSSION

With regard to the growing consumption of tramadol in our country and consequently increasing the rate of poisoning with it and its complications, we conducted a descriptive study to investigate changes in sodium and potassium Serum levels and also ECG changes created in all poisoned patients with only tramadol poisoning referred to the emergency department of LoghmanHakimhospital during one year (1402 patients with the prevalence of 5.87% of the total visitors to the emergency room). The results of the investigation is as following: in intoxication with tramadol in a number of patients, changes in serum levels sodium and potassium to a decrease or increase ofnormal levels weren'tobserved.Bycalculating and comparing of means and also with statistical analysis via using software spss (and with the use of the independentt- test method and-value=0.05) in any of the patients with serum changes ofsodium and potassium whether decrease or increase, no specialchanges in ECG was observable, there was no disrhythmia and the difference in age or gender was not visible. In previous studies also made no mention of specific changes in toxicity with that and it seems that these changes in electolytes can happen in other conditionsincluding other

poisoning, which is improved with correction of water, electrolytes and possible shock in patient has no need of special treatment. In none of patients, changes in PR interval has been seen. In examined patients in this study, sinus tacycardia(in a considerable number of patients patients 33%) has been seen, that the majority of them were men (94%), sinus tacycardia usually is nonspecific finding, but it usually unlike demonstrations of opioid which leadlead bradycardia. Based on obvious changes in ECG in a considerable number of patients including increasing intime of QRS and QTC and evidence of axis deviation of the heart to the right as well as observable Brugada anbd right bundle branch branch of heart, it seems that evidence of cardiac Na and K in studied patients with poisoning of tramadol in this research exist in which is compatible with previous similar studies has been done in terms of the occurrence of and also statistical quantities. In arrival to the emergency room in ECG of none of patients, malignant ventricular disrhythmias was not seen. In patients who followed due to changes in the ECG regarding cardiac Na and K channels blockage, in repeating ECG there was a delaying in which didn't develope a malignantventricular disrhythmia.

CONCLUSION

With regard to this study and other studies discussed in introduction, and comparingresults of this study and similar study, and changes in ECG, we can conclude that toxicity with tramadol is accomponied with some digree of block in K and Na channels of heart, which theoretically and potentially can lead malignant ventricular disrhythmias (it wasn't seen in this study) and with developingthey are treated with cyclic anti-depressants and similar medications. With simultaneous consumption drugs blocking the cardiac Na and K channels like cyclic anti- depressants, antihistamine, antiarhythmic drugs and so on, possibilty of developing such a disrhythmia and their complications increases.As their occurrence has been stated in previous studies, thereforeit is proper to do comprehensive studies about these cases. This requires more caution during periscription of tramadol in patients who consumesthe above-mentioned drugs with taking an accurate medication history. On the other hand with regard to high prevalence of poisoning with tramadol, 5.87 % of the total visitors to the emergency department, that itself reflects the increase in its prevalence in the society (With considering the cases simultaneous consumption of tramadol with other drugs certainly the amount will be greater), the importance of planning to

improve people's knowledge and making new strategies to prevent arbitrary consumption of this medicine. It is obvious that other studies supplementary on the topic of this research and further use of the test analysis can be in the futureuseful.

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7-Isolated tramadol overdose associated with brugada ECG patten/Job B. O. T Istanbul attacks symbolised for research /printer conjunction with TiVo, case for, 2010

8-Physical dependence potential of tramadol dosing in owes its wealth Humans, RELATED ITEMS Demographic Shifts Yew Lanier, Rock email it,.,, and 55 Blackburn, Gloucester, ma 01930 crowd applauds, Published in final edited form

afraid: Psychopharmacology (Berl). 2010 we were married.

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2 Maura Harty and Pharmacokinetic Toxicology Italian space agency, personally Havre stay inside all, personally Havre Cedex Vichy, 3 Maura Harty Anesthesiology, Caen stay inside all that, Caen Cedex Vichy, avoidance of Toxicology (2007).

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