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INVESTIGATING TYPE OF TISSUE CHANGES AND ITS ASSOCIATED FACTORS IN BODIES WERE SENT TO TEHRAN LEGAL MEDICINE ORGANIZATION IN DEA TH FROM POISONING TRAMADOL (2008-2013)

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ABSTRACT

'One of the most common causes of death in the world is caused by poisoning. Recently the abus e of prescription drugs has increased and Tramadol is also no exception. In order to evaluate the histological changes and its associated factor resulting in tramadol toxicity, tissue changes due to age, sex, history of addiction, the involved member, the occurrence of death from tramadol was assessed.

The present study was a Cross-sectional study on all bodies in biological fluids positive tramadol or had a clinical history of tramadol and has been sent to Tehran Legal Medicine Organization d uring the last five years (2008-2013).

Investigating the demographic indicators of deceased and toxicology reports with pathologic org ans of registered in the records of examinations of the corpses referred to Tehran Legal Medicine Organization. Finally the data was analyzed through SPSS software.

In this study, 49 corpses were examined, according to sex was 39 men (79/5%) and 10 women (2 0/5%). Most of the corpses were aged 25-34 years (40.8%) with a mean of 27 years. Among all examined corpses 41 subjects (83/6%) have been dead without any history of Tramadol use and

none of them had a history of using irritants in their file.

Among the symptoms before the death with cardiopulmonary arrest (67/3%) was the most obvio us sign is seen on the deceased and gastrointestinal symptoms did not observed. Pathological cha nges in the macroscopic and microscopic examination of examined organs; the most common fin ding was related to the liver and brain sample so that the brain edema in 25 subjects (51%) and d egeneration of hepatocytes (32.7%) samples were observed. Changes in both brain and liver tissu e samples showed a significant relationship (p-value <0.05), with the recent history of taking tra madol. In toxicology study the contents of the stomach and gallbladder tissue and urine samples and blood. The most subjects positive for tramadol in gastric biopsies of 28 patients (57.1%) and the lowest reported 12 cases (24.4%) in the gallbladder and the tissue sample is observed.

The death rates among tramadol poisoning that referred to dissection and were examined was am ong young men. The highest rate of positive samples of gastric contents in the samples deceased, the best sample that will help us would be the stomach contents. And the best sample to study th e pathological changes among corpses poisoned with tramadol would be the liver and brain samp le that had most changes in our investigations.

Key words: poisoning, tramadol, tissue changes, Toxicology

INTRODUCTION

One feels that one is always faced with a vari ety of diseases associated with is feeling of p ain that involved all neural and physiological system of human. Therefore, from long time ago several measures are taken to reduce the sense of pain. These measures are including the use of analgesics or narcotics (opioids) a nd synthetic drugs. (1)

There is almost no field of medicine that deal s with sedative drugs. After the official anno uncement of the ban prescribed injectable for m of diclofenac, tramadol drug marketed as a n alternative sedative in Iran.

Tramadol is a synthetic sedative in our count ry and in the world that is also used in variou s fields of medicine. Since its introduction in 1977 in the Germany, after that the drug was used in other countries. (2) About ten years a go, it is formally entered the Iranian market. Now is easily accessible to our patients and i s available without prescription. It is now ma inly used as sedative for moderate and severe pain. (3) Although this was an opioid drugs but there was no legal restrictions on the sale and distribution. According to the cultural st atus in Iran of the desire for rapid relief of pa in landmarks market competition between ph ysicians and especially general practitioners

prescribe this drug without historical precede nce to the extent society.(4)

Studies in the USA have shown that out of e very 7 people in the US who use Tramadol, 1 person is drug-dependent. (5) at first it seem s that drug-dependent is very low risk but thr ough using the Tramadol some side effects si milar to morphine such as nausea and vomiti ng is observed long-term use of the drug dep endence was also observed.(6)

The other side effect of Tramadol pill abuse as psychosis and brain disorders, personality diplopia, and inability to make decisions, lac k of balance, dry mouth would be pointed wo uld be pointed and usually the pill consumers become aggressive and uncontrollable (7) T he risk of seizures with concurrent administr ation of SSRI and TCA family medicine tra madol and alcohol and other substances that have effect through CNS and history of seizu res goes higher. (8)

Many of these causes made the WHO expert committee of abuse materials put the tramad ol in list of specific drugs under international control (4) currently; the abuse of these subs tances among the youth is developing. (9) in a study Tarmian and et al (2005) on the univ ersity students of six university in Tehran ha ve reported that abuse of tramadol was 5%. (10)

But in recent years, tramadol has developed s o that according to the statistics of Iran drug control headquarters rate of abuse of tramado l (26/5%) among the used drug is in the first raw. (11)

In a study conducted on 190 patients in Ame rica about the Tramadol toxicity, the prevale nce of clinical symptoms due to toxicity wer e reported as follows decreased level of cons ciousness (27.4%), nausea and vomiting(21/ 1%), tachycardia (17/4%), seizures (13/7%) hypertension (5/8%) and movement disorder s (4/2%) make up the symptoms.

The examined patients were aged 9 months t o 80 years and Most of the consumption and subsequent poisoning, self-immolation were reported. (12) In a retrospective study on 126 patients in America, symptoms of tramadol overdose in order included lethargy, nausea, vomiting, tachycardia, agitation, seizures, co ma, increased blood pressure and loss of con sciousness signs of respiratory distress has b een. Symptoms due to toxicity with tramadol was more due to inhibitory effect of tramado l of reuptake of catechol amines and serotoni n to cause narcotic effects of this drug and re stless, hyper Keynesian chills, tachycardia, c hanges in blood pressure and increase the lev el of consciousness can be indicative of a ser otonin syndrome. This study showed that the toxicity of tramadol had greater nervous syst em toxicity than cardiovascular system. (13)

In a case study in Ireland in 2007, that introd uces serious complications of tramadol toxici ty including cardiac arrest, and severe liver f ailure which ultimately resulted in the death of the patients

In the two presented cases, the only cause of death was pure tramadol. For detection of tra madol in serum MS-GC method was used th at could be measured metabolite of tramadol, Mono de -methyl tramadol. In this study, ser um levels of terāputik of 100-300 ng/ml were considered.

The following changes were also seen in a st udy of autopsies of corpses including; 1-blee ding in the air sacs of the lung tissue 2-Acute tubular necrosis of kidney 3- Perry Central I schemia **of** liver is reported and Tramadol le vel of blood, liver, kidney was in order 4/5m g/l, 6/5mg/l and 5/2mg/l was recorded. (14)

In a study conducted in Imam Khomeini Hos pital in Kermanshah in 2008, the incidence o f death of subjects reported less than 30 year s old. In a study of Izadi and et al (2010) in I sfahan the average age reported less than 25 years old. The most common symptoms of tr amadol poisoning have been mentioned as lo ss of consciousness. Also, in this study the us e of tramadol was more common among men . (15)

In the study by T.matthiesen and T.woherma nn in 1997 the most common symptoms befo re the death were neurological symptoms. (1 6)

In a paper of case report by B.debacher and F.renaryly and et al (2010) among two dead s ubjects due to the overdose of tramadol throu gh the qualitative and quantitative toxicology testing urine and blood samples were analyz ed. Only one of the two samples was positive and the level of tramadol has been reported as fatal. (17)

METHODS

This is a cross-sectional study. The study po pulation was considered for the all corpses in biological fluids were positive for tramadol or recently had history of clinical use of tram adol referred to Legal Medicine Organization in Tehran during the last five years (2008-20 13).

The examined sample through use of lab kits to determine the poison the quality of Gc-m ass and TL-C on all the corpses sent to the di ssection was performed during 2008-2013 w ere identified. The inclusion and exclusion cr iteria for the study were used that criteria for inclusion was a positive test for tramadol in biological fluids (blood or urine or tissue of s tomach and gallbladder) or a recent history o f clinical use of tramadol. The exclusion crite ria was including the other reason for death e xcept the death with tramadol or poisoned c orpses in biological fluids (urine or blood, or

stomach or gallbladder willing) had negative test in their file or lack of recent history of tr amadol use contained in the report file. Thro ugh the Compilation information form of req uired data were extracted from the files in Ka hrizak forensic dissection of Tehran and reco rded in forms and then the data were analyze d with SPSS-16 software and is shown in for m of diagram and curve

FINDINGS

This study investigated all files of corpses se nt to Kahrizak forensic dissection of Tehran during 2008-2013were diagnosed with defini te cause of death in drug toxicity has been de alt with Tramadol.

A total of 49 cases of inclusion and exclusio n criteria, and finally a definite cause of deat h tramadol intoxication, were selected. Based on the findings 49 corpses on the sexual diff erentiation of the 39 men (79.5%) and 10 wo men (20.5%) were examined. Most of the cor pses aged 25-34 year0000000000s old (40/8 %) with average of 27 years old.

Among all the examined corpses 41subjects (83/6/%) had no history of using tramadol and none of them had the history of irritants in t heir files. In term of addictive drug use, 8 su bjects (16/3%) had history of drug addiction that only one of them mentioned simultaneou sly use of tramadol.

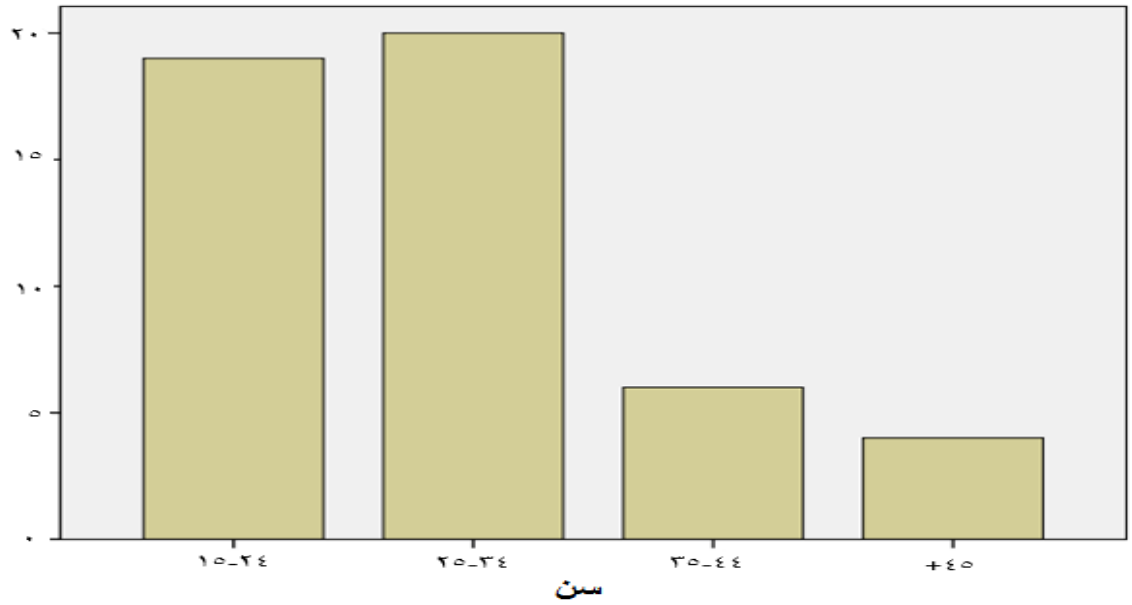


Figure 1: Prevalence of age poisoning with tramadol sent to Kahrizak forensic dissection of Tehran (2008-201 3)

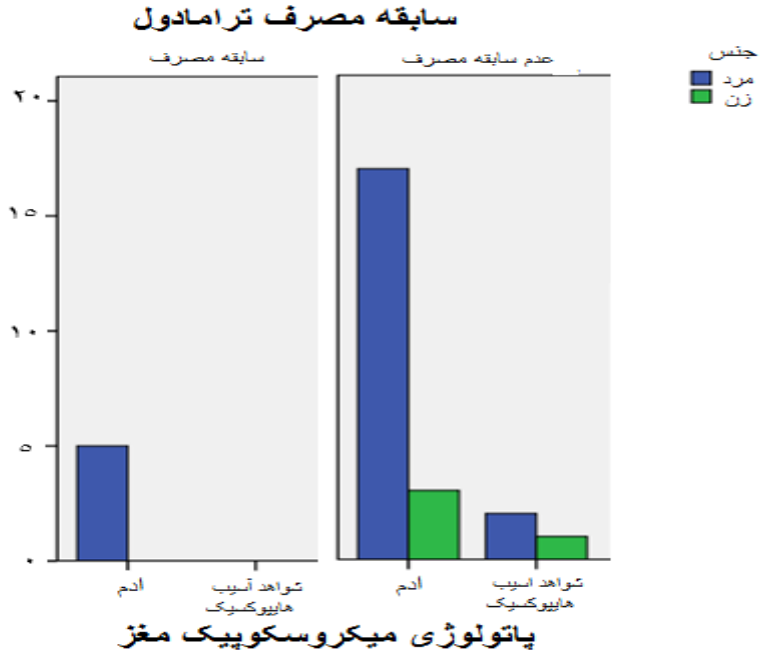
Symptoms before death were categorized as cardiac arrest, respiratory arrest, seizures, shortness of breath, stomach and loss of consciousness and pupil size. Most symptoms were seen with card-iopulmonary arrest (67/3%), seizures (49.2%), loss of consciousness (46.9%), dyspnea (12.2%) and no gastrointestinal symptoms were observed among deceased. mydriatic pupil were reported in 16.3% of the dead who had no history of tramadol use.

Table1- frequency of symptoms before death due to tramadol poisoning referred to Kahrizak forensic dissection (2008-2013) according to gender

male	female	Frequency percentage	frequency	symptoms
26	7	67/3%	33	Cardiac arrest
13	8	42/9%	21	Convulsion
7	16	46/9%	23	Decrease of consciousness
39	10	0	0	Gastrointestinal symptoms
5	1	49/2%	21	Shortness of breath

In this study, we examined four organs, brain, lung, liver, kidney and heart microscopic and macroscopic. Among Macroscopic findings in the lung, the most common finding was 27 subjects (55.1%) had an elastic consistency that contains rich edema in cut was announced. Among the Microscopic tissues, lung had the most finding (14.3%) simultaneously atelectasis, edema and pulmonary bleeding was observed. And also, 5 subjects 10.2%) had a histological signs of pneumonia in Pathologic study. And only 2 subjects (4.1%) were seen evidence of pulmonary aspiration. Among Macroscopic pathologic findings in the brains of 17 patients (34.7%) had cerebral vasculature. Microscopic findings in the brains of 25 patients (51%) had brain edema and in only 3 patients (6.1%) were seen evidence of hypoxic damage.

Figure2- investigating the frequency of Microscopic pathologic changes in the brain in intoxication with tramadol reference to the dissection according to gender and history of tramadol use (2008-2013)



پاتولوژی میکروسکوپیک مغزMicroscopic patholo gy of brain

ادمedema

شواهد آسیب هایپوکسیک Evidence of hypoxic inju ry.

سابقه مصرفHistory of use

سابقه عدم مصرف lack of History of use

جنسgender

زنfemale

مردmale سابقه مصرف ترامادولthe history of tra madol use

In Macroscopic examination of liver patholo gy 22 patients (48%) reported they had Firm liver that none of them had history of liver di sease before. In Microscopic view of a decea sed liver, 16 patients (32.7%) have been hepa tocytes degeneration changes and other findi ngs were in order 5 subjects (10/2%) Inflam matory cells, 3 patients (6.1%) Perry Central necrosis of the liver and 2 patients (4.1%) ha d hepatic steatosis.

Table 2- Microscopic findings in liver among tramadol poisoning reference to the Kahrizak dissection 2008-2013 according to age

Lack of tramadol use	Tramadol use	Male	Female	Frequency percentage	Frequency	Microscopic findings in liver
3				38/8%	19	Natural findings
			4	32/7%	16	Changes degeneration of hepatocytes
			0	10/2%	5	Inflammatory cell
0				4/1%	2	Steatosis
			0	6/1%	3	Perry Central liver necrosis

In Macroscopic examination of the heart, only 1 patient (2%) had increase in heart size with slight narrowing of the Coronary arteries. In Microscopic examination of heart pathology 4 patients (8.2%), atherosclerosis, and in 2 cases (4.1%) simultaneously inflammatory cells, hypertrophy and atherosclerosis Subendocard bleeding at the same time has been reported. Toxicology studies of blood, among 44 samples, only one case (2%) were positive for the presence of tramadol. And urine toxicology study, of the 44 samples were examined in 27 cases (24.5%) were positive. Toxicology studies gallbladder and tissues, 12 samples (24.5%) have been reported positive. In examining the stomach contents of 28 samples (57.1%) were positive.

DISCUSSION

This study investigated the demographic characteristics and tissue changes in death due to poisoning with tramadol in corpse s were sent to the Tehran Legal Medicine Organization. In our study the most cases of death was due to tramadol in males 39 subjects aged 25-34 years with average age of 27 years old have been seen.

There was a significant relationship between the age and Biographies of tramadol use P-value< (0.05). As it was mentioned in the introduction, in study in Imam Khomeini hospital in Kermanshah in 2008 the incidence of mortality was noted in patients less than 30 years. Also in a study in Isfahan Izadi and et al (2010) the reported average age was less than 25 years old which is compatible with our study.

In term of gender, among 49 dead subjects 39 subjects (79.5%) were men and 10 subjects (20.4%) were women that there was a significant relationship between gender and consumption of tramadol P-value<0.003.

In this study, tramadol was more common among men and had significant relationship with tramadol use (15) Also, this study was consistent with our study.

In term of history of drug abuse, 8 subjects (16.3%) had a history of drug addiction that only one subject simultaneous used tramadol was listed.

As a result, limited numbers of subjects 16.3 % were taking the drug and also the use of irr itants wasn't observed in any of the samples. There was no significant relationship betwee n the History of drug abuse and Pathological changes in the examined organs. There was n o significant relationship between the drug ab use and pathological changes weren't observ ed. (P-value>0.05)

Symptoms before death as cardiopulmonary arrest, convulsions, dyspnea, gastrointestinal symptoms and reduced level of consciousnes s and Pupil size were separated. Most sympto ms are seen as cardiopulmonary arrest with (67.3%), seizures (49.2%), decreased level of consciousness (46.9%) and dyspnea (12.2%) and gastrointestinal symptoms were observed among deceased. mydriatics pupils were rep orted in 16.3% of the dead who have no histo ry of tramadol use that the finding was contra ry to the findings of the study. In a study con ducted by, T.matthiesen T.wohermann (1997) the most common symptoms before death was neurological symptoms. (16) Also, in a s tudy in Isfahan, Izadi and et al (2010) mentio ned that the most common symptoms of tram adol poisoning were loss of consciousness. (1 5) Among the study variables, there was a sig nificant relationship between microscopic pat hology of the brain in order (51%) brain ede ma and 6.1%) had evidence of hypoxic injury . (P-value=0.04)

There was no significant relationship betwee n the Macroscopic findings of the lung and re cent history of drug or tramadol use and …an d also, there was no significant relationship b etween Microscopic findings in the recent his tory of tramadol.(P- value=0.72)

Microscopic examination of the liver was the most common of the 16 patients (32.7%) ha d degenerative changes of hepatocytes. There was significant relationship between the path ological findings in liver and blood and urine toxicology, tissue, gallbladder stomach cont ents for tramadol that all had p-value<0.05 .

There was not significant relationship Macro scopic and microscopic findings in all and st udy variables. In macroscopic examination of heart, only one subject (2%) increased the si ze of the heart, along with slight narrowing o f the coronary arteries and 38 of subjects (77. 6%) remaining abnormal findings weren't ob served. In Microscopic examination of heart pathology, 4subjects (8.2%) atherosclerosis, 2subjects (4.1%) had inflammatory cells, sub arachnoid hemorrhage and Hypertrophy and atherosclerosis were simultaneously. None of changes were not significantly were related with tramadol use in dead people.

There was significant relationship between th e pathological findings in There was significa nt relationship between the pathological findi

ngs in toxicological examination of blood uri ne and tissues, and gallbladder and stomach c ontents and toxicology tramadol positive sign ificant relationship between current consump tion can be seen that all was p-value <0.05. I n this study the in toxicology studies there w as significant relationship between positivity of samples and heart and liver pathological c hanges. In a paper case report form was desig ned by B.debacher and F.renaryly and et al (2 010) between two dead subjects due overdos e of tramadol that with qualitative and quanti tative toxicology testing of urine and blood s amples were compared, only one of the samp les were positive and tramadol level has been reported as fatal.(17)

In this study we did not have access to a smal l amount of tramadol samples to be compare d.

RESULTS

According to the wide consumption of trama dol as the most widely used sedative around t he world which is now easily accessible (1-3) and according to dangerous and fatal sympto ms after the consumption such as loss of cons ciousness and cardiac arrest and prolonged h ospitalization following poisoning were repor ted (5) and also in this study the most of the death signs before the death were Cardiac arr est and loss of consciousness and its complic ations have formed. Considering the poising followed by use of tramadol was important. As it was seen in the files of the death due to poisoning by tramadol, death was the most pr evalent in young men. Therefore, Prevention of self-consumption and care after poisoning with tramadol is obviously important. After t he death also, the most diagnostic aid deceas ed biological samples with drug toxicity was first stomach contents and then urine samples . Pathological changes in organs like the liver and the brain has been seen that most of the pathological findings, we will examine these organs.

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