

Pathological Findings of Tramadol on Liver Tissue in the Cadaver Referred to Legal Medicine Organization of Tehran 2008-2013

Alizadeh-Ghamsari A¹, Dadpour B¹, Najari F^{2*}

¹ Department of Clinical Toxicology, Mashhad University of Medical Sciences, Mashhad, Iran

² Department of Forensic Medicine and Toxicology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article Type:
Original Article

Article History:
Received: 3 Dec 2015
Revised: 27 Dec 2015
Accepted: 12 Jan 2016

Keywords:
Tramadol
Poisoning
Hepatic Necrosis
Pathology

ABSTRACT

Background: Tramadol is a synthetic opioid used to control chronic pain and pain after surgery. However, many cases of poisoning and dangerous side effects have been reported. In order to discover the causes of death in forensic medicine is usually examine tissue samples taken from the body, although the results of toxicology tests generally give us more information, but identifying the pathological effects of Tramadol on the internal organs, especially the livers can be very helpful.

Methods: In this cross-sectional study, information on the history, the autopsy report and toxicology testing of patients who died due to poisoning Tramadol were studied. In this study, all of the information already provided by the use of particular forms collected and then analyzed using computer software SPSS.

Results: A total of 49 cadavers were examined in this study. There were 39 dead (80%) of men and 10 of (20%) women. Most common age groups in the study were 24 to 34 years old (41%), 15 to 24 years old (39%), were reported. There were significant difference between liver microscopic spread among different ages, history of Tramadol, positive and negative toxicology tests stomach contents, urine, blood, tissue and vitreous. Most common pathological changes were in liver, degenerative changes and inflammatory cell infiltration in patients who under 35 years old.

Conclusion: In this study, the majority of patients had acute poisoning with Tramadol, it can be concluded that the majority of changes in tissue obtained was as a result of acute Tramadol, respectively incidence of atelectasis and edema and alveolar bleeding in the liver were most pathological findings. In reviewing toxicology, Tramadol are also present in the stomach contents, urine, gall bladder, liver and blood were positive, the result of stomach contents will be most helpful for us.

Copyright©2016 Forensic Medicine and Toxicology Department. All rights reserved.

► *Implication for health policy/practice/research/medical education: Pathological Findings of Tramadol on Liver Tissue*

► *Please cite this paper as: Alizadeh-Ghamsari A, Dadpour B, Najari F. Pathological Findings of Tramadol on Liver Tissue in the Cadaver Referred to Legal Medicine Organization of Tehran 2008-2013. International Journal of Medical Toxicology and Forensic Medicine. 2016; 6(2): 59-64.*

*Archive of SID***1. Introduction:**

Tramadol has weak agonist effects on receptor m (Mu) and the effects of serotonin reuptake inhibition and inhibitory effects on the release of noradrenaline, which ultimately leads to pain in the spinal cord. Tramadol are mentioned as an alternative for patients who are not good candidates for receiving narcotic analgesics (1). Use of Tramadol for the first time was approved for public in 1977 in Germany, in America since 1995 and in France since 1997 and in 2004 in Iran (2).

In a study in Ireland in 2007, the serious complications such as heart failure and severe liver failure, which ultimately led to the death of patients have been studied. Two cases presented that the only reason for his death was announced net Tramadol. In autopsy examination of the cadaver of the following changes were recorded:

1. Alveolar hemorrhage (bleeding in the air sacs);
2. Acute renal tubular necrosis;
3. Perry Central liver ischemia (3).

Tjaderborn and colleagues in 2007 studied on unintentional poisoning and fatal Tramadol forensic Sweden between 1995-2005. The results of this study showed 17 patients (eleven men and six women) have been identified from unintended poisoning and fatal Tramadol. For these cases, the average age was 44 years (range 18 to 78 years) and the average concentration of Tramadol was 2 micro/ml (4).

In other study, in ten cases (59%) of multiple drug poisoning was intended as the cause of death. However, in seven cases, Tramadol was the only substance present in toxic concentrations. History of substance abuse in 14 cases (82%) were detected and recent history of abuse of Tramadol in 8 patients (47% women) were identified. The results showed that Tramadol fatal poisoning may have occurred unintentionally and people

with a history of substance abuse may be at greater risk and so when Tramadol in these patients, caution is required (5).

In study in 2012 was carried out by simonsen *et al*, in Finland from 2000 to 2008, 14 to 44 years, age group was the most critical age for drugs poisoning. In this study, poisoning by weak opioids, codeines and Tramadol were identified and linked to suicide. The average concentration of Tramadol and O-desmethylTramadol poisoning was 5.3 and 0.8 mg/L (5).

In a study in mice, acute intoxication with Tramadol in the 0>25 mg/kg compared to the control group, lead to pathological changes in the livers and infiltration of inflammatory cells into alveolar hemorrhage and pulmonary edema congestion and edema in 95% and 80% of the mice, while in the control group received normal saline only normal liver tissue has been reported (6).

In a study in 2014 by simonen *et al*, in Finland forensic in 2010 to 2011, abuse of Tramadol in the age group above 60 years were rare. In this study it was shown that Tramadol abuse and fatal poisoning has been focused in men 20 to 49 years old (8).

Unfortunately, despite the prevalence of Tramadol consumption in Iran, histological studies of liver complications caused by it, have not been done, therefore, in view of the importance of the issue and also identify possible preventive effects of pathological in deaths from poisoning or Tramadol, we decided to do pathological study on liver tissue of death using Tramadol.

2. Materials and Methods:

This routine data base study with a simple statistical method (the number) using demographic indices of death and toxicology reports registered with existing liver pathology, through observation, in the case of the forensic examination of the cadaver referred Tehran in 2008-2013 and finally data was analyzed using software 16 SPSS.

Inclusion criteria. Positive test of Tramadol in biological fluids (blood or urine or stomach) and recent history of clinical use of Tramadol.

Exclusion criteria. There was other cause of death except poisoning by Tramadol in case

Corresponding author: Najari F, MD. Assistant Professor, Department of Forensic Medicine and Toxicology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: fares.hospital@yahoo.com

Archive of SID

They test were negative in biological fluids (urine or blood or stomach) or not to include the recent history of Tramadol in clinical case history sheet. Also other patient with a history of smoking, stimulants drugs were excluded. In this study is used from exactly Fisher test.

All cadavers were studied with the consent and approval of the organization and the preservation of personal data files to determine the cause of death.

3. Results:

In this study, all sent cadaver to forensic dissection hall of Tehran during the years 2009-2013 were studied with a diagnosis of definite cause of death as acute poisoning Tramadol. A total of 49 cadavers were selected and evaluated based on inclusion and exclusion criteria listed.

In terms of gender, out of 49 dead, 10 (20%) were female, 39 (80%) were male, (80%) were under 35 years old (Table 1). Their average age was 26 years old with 24-year view.

In terms of marital status, 33 (67%) were single and the rest were married. 8 (16%) were students which in itself is remarkable.

41(84%) of cadaver in less than 24 hours and only 3 (6%) cadaver were examined at a distance of more than two days.

Meanwhile, 24 (49%) people died in their home and 11 (22%) death occurred out of the house and 14 (29%) death were in hospital. Out of 49 deaths, 28 (57%) were referred outside the hospital to the dissection saloon and 21 (43%) of them died in the hospital, all of whom had a history of recent use of Tramadol.

Among the dead, 33 (67%) patients had cardiopulmonary arrest, 6 (3) patients had acute respiratory distress symptoms and 10 (20%) had a loss of consciousness.

Among Macroscopic findings of liver, the most common findings in men were firm consistency and in women was cream color. (Figure 1). In Microscopic findings of the liver, 28 (%57) of dead was abnormal; therefore the most microscopic pathologic finding in men and female was degenerative change in hepatocytes, followed by infiltration of inflammatory cells all of hepatic necrosis and steatosis were seen in men. Degenerative changes of hepatic cells was uncommon in above 35 years old and alone necrosis pericentral of liver was not

Table 1: The frequency of deaths by tramadol in terms of Sex and different liver macroscopic findings in cadaver referred to Legal Medicine Organization in 2008-2013.

	Sex	Women	Men	frequency	frequency percent
Liver finding					
Normal finding		4 (8%)	17 (35%)	21	43%
Degenerative changes of Hepatic cells		4 (8%)	12 (25%)	16	33%
Inflammatory cells		0 (0%)	5 (10%)	5	10%
steatosis		0 (0%)	2 (4%)	2	4%
Necrosis pericentral of Liver		0 (0%)	3 (6%)	3	6%
Necrosis and steatosis		0 (0%)	2 (4%)	2	4%
Total		8 (16.5%)	41 (83.5%)	49	100%

Table 2: Prevalence of deaths of tramadol in terms of, age and Liver microscopic finding of in cadaver referred to Legal Medicine Organization in the Years 2008-2013.

Age	15-24	25-34	35-44	+45
Liver finding				
Normal finding	19%	20%	6%	4%
Inflammatory cells	3%	3%	1%	3%
steatosis	16%	17%	5%	1%
Necrosis pericentral of Liver	2%	4%	2%	0
Degenerative changes of Hepatic cells	19%	16%	4%	4%
Total	59%	60%	18%	12%

seen in above 35 years old. Also, all of deaths had nothing to do Tramadol history in the past. All of the deaths in our study used Tramadol in order to suicide and died following complications. In history, cause of death has been cardiopulmonary arrest 33 (67%), convulsion 24 (49%), decreased level of consciousness 23 (47%) and acute respiratory failure 6 (12%).

In examining the toxicity of the liver and gallbladder, only 12 (24%) showed positive for Tramadol. In examining the stomach contents, 32 (65%) were positive for the presence of Tramadol.

In blood toxicology study, among the total samples, only one sample was positive for the presence of Tramadol without a history of use.

4. Discussion:

This study investigates that between the sex and macroscopic changes in liver tissue in cadaver. There was significantly difference (p value $<0.05\%$) between them, while in other researches was not mentioned that. In our study the majority of deaths from Tramadol was in range from 15-34 years old with an average 26 years old. While in simonen and colleagues study the average

age was 44 years, by reason less education people and more access to this drug in our country (5).

In terms of gender, out of 49 dead, 39 (80%) were men and 10 (20%) were women and significant correlation was seen between recent use of Tramadol and gender (p value <0.003) the results is consistent to results of other studies(5,8). Cause of death among poisoned has been different including; cardiopulmonary arrest 33 (67%), convulsion 14 (49%), decreased level of consciousness 23 (47%) and acute respiratory failure 6 (12%). In a study by Matthiesen *et al*, in 1997, the most common cause of death was neurological symptoms (.because of late timing in starting of CPR in our patient.(11)

Among microscopic findings, between degenerative changes of hepatic cells, sex, and age significant relationship was found, meanwhile alone pericentral necrosis was not found above 35 years (p value $<0.03\%$). Degenerative changes of hepatic cells was seen most under 35 years (p value <0.04) which were not mentioned in other studies only. In a study, clarot F. *et al*, reported the same changes in mice too(13). But the

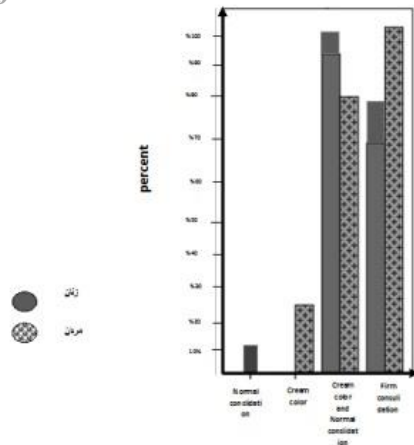


Fig. 1. The frequency of deaths by tramadol in terms of sex and different liver macroscopic findings in cadaver referred to Legal Medicine Organization in 2008-2013.

incidence of these complications is much more in people (in our study).

Unlike the other study, was not measurement of urine and blood quantitative level of Tramadol in this research and this is one of the advantages of our study compare of other researches

In reviewing toxicology, blood, urine tissues, gallbladder, and stomach contents, there was significant correlation between recent use of Tramadol and positive toxicology and all had p value <0.05 that in Mathieson, T and Baker B. studies were the same 9 (11, 12).

5. Conclusion:

Given the prevalence, Tramadol is known as the most popular analgesic around the world that is now readily available to the public. According to its fatal and dangerous symptoms after poisoning such as loss of consciousness, cardiac arrest, prolonged hospitalization for poisoning. In this study, the highest death into cardiac arrest and died after the symptoms have decreased level of consciousness type of subsequent complications, attention to Tramadol use poisoning are important.

As in the case of death for poisoning was seen with Tramadol, mortality in young males was most prevalent. More care for the elderly, in terms of risk of aspiration, which indicates a lack of defense mechanisms of prevention of these complications.

Therefore, prevention of intractable use of Tramadol and care after poisoning with Tramadol is obvious. After the death, the highest diagnostic aid will be biological samples with drug poisoning, first stomach contents and then urine samples.

6. References:

1. Grond S, Sablotzki A. Clinical pharmacology of Tramadol. *Clin Pharmacokin.* 2004;43(13):879–923.
2. Marchi AG, Messi G, Reniers S. Epidemiology of children poisoning: comparison between telephone inquiries and emergency room visits. *Vet Hum Toxicol.* 1992;34(5):402-4.
3. Hassanian-Moghaddam H, Kolahi AA. Tramadol intoxication/abuse: a new issue on high-access population. 6th Annual Congress of Asia Pacific Association of Medical Toxicology. Thailand; 2007.
4. Tjaderborn M, Jonsson AK, Hagg S, Ahlner J. Fatal unintentional intoxications with Tramadol during 1995-2005. *Forensic Sci Int.* 2007;173(2-3):107-11.
5. Simonsen KW, Edvardsen HM, Thelander G, et al, Fatal poisoning in drug addicts in the Nordic countries in 2012. *Forensic Sci Int.* 2015;248:172-80.
6. Cantineau A, Breurec JY, Baert A. Intoxications chez l'enfant. Aspects statistiques et économiques à partir des données du centre anti-poisons de Rennes pour l'année 1985. *Rev Pédiatr.* 1987;23(5):91-3.
7. Lam minpaa A. Hospitalizations due to poisoning in Finland in 1978–1984. *Clin Toxicol.* 1991;29:111-29.
8. Simonsen KW, Normann PT, *et al.* Fatal poisoning in drug addicts in the Nordic countries in 2007. *Forensic Sci Int.* 2011 Apr 15;207(1-3):170-6.
9. Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. *Ann Pharmacother.* 2005;39(6):1039-44.
10. Clarot F, Goulle JP, Vaz E, Proust B. Fatal overdoses of Tramadol: is benzodiazepine a risk factor of lethality? *Forensic Sci Int.* 2003;134(1):57-61.
11. Matthiesen T, Twohrmann T, Coogan H. The experimental toxicology of Tramadol: an overview in toxicology book. 2010;407-20.
12. Backer B, Renardy F, Denooz R. Quantification in post mortem blood and identification in urine of Tramadol and its two main. November/December 2010.

13. Clarot F, Goulle JP, Vaz E, Proust B. Fatal overdoses of Tramadol: is benzodiazepine a risk

factor of lethality. *Forensic Sci Int.* 2003;134(1):57–61.