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RESEARCH ARTICLE

PATHOLOGICAL EFFECTS OF TRAMADOL ON LUNG TISSUE IN THE CADAVER REFERRED TO LEGAL MEDICINE ORGANIZATION OF TEHRAN 2008-2013

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ABSTRACT

Introduction: 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 lungs 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 acute 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 16 spss.
Findings: A total of 49 patients were examined in this study. 39 dead (79.5%) of men and 10 body (20.5%) were women-owned. Most common age groups in the study were 24 to 34 years old (41%), were reported. There were significant difference between Lung microscopic spread among different ages, sex, positive and negative toxicology tests stomach contents, urine, blood, tissue and vitreous. Most common pathological change was in lung edema and Atelectasis. Aspiration and pneumonia signs was seen only in patients over 40 years old.
Conclusion: Tramadol poisoning among young people is increasing. In this study, the majority of patients had acute poisioning with tramadol, it can be concluded that the majority of changes in tissue obtained is as a result of acute tramadol, respectively incidence of atelectasis and edema and alveolar bleeding in the lung were most pathological findings.

INTRODUCTION

Tramadol is an opioid analgesics as one of the widely available. Despite the adverse effects of tramadol poisioning, including cardiac arrest, advanced hepatitis, kidney failure and serious complications resulting from it, few studies have been done in this case. Tramadol is a synthetic opioid used to treat moderate to severe pain with central effects.(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 bodies of the following changes were recorded:

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

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In a study in 2007 by Tjäderborn and colleagues unintentional poisoning and fatal tramadol forensic Sweden in 1995 and 2005 were studied. A total of 17 (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.

In fact, in ten cases (59%) of multiple drug poisioning 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. (3,4,5) In study in 2012 was carried out by Mr Häkkinen *et al*., In Finland from 2000 to 2008, for the age group 14 to 44 years that the most critical age for drugs in Finland. In this study, poisoning by weak opioids, codeine 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) (6) In a study in mice, acute intoxication with tramadol in the 0> 25mg / kg compared to the control group, lead to pathological changes in the lungs 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 lung tissue has been reported. (7,8)

Unfortunately, despite the prevalence of tramadol, in communities especially Iran, histological studies of lung complications caused by 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 lung tissue of death using tramadol.(9)

MATERIALS AND METHODS

This cross-sectional study with a simple statistical method (the number) Using demographic indices of death and toxicology reports registered with existing lung pathology, through observation, in the case of the forensic examination of the bodies 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 is other cause of death except poisioning by tramadol in case they test negative in biological fluids (urine or blood or stomach) or not to include the recent history of tramadol in clinical case history sheet. As well as those with a history of smoking or drugs or stimulants or other drugs were also were excluded.

Ethical Considerations

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

Findings

In this study. A total of 49 cadavers were selected and evaluated based on inclusion and exclusion criteria listed.

In terms of gender, out of 49 dead 20% were female, 80% were male, 76.6% were under 34 years old. (Table 1) Their average age was 26 years old with 24-year view. All patients used tramadol for first time.. In terms of marital status, 33 were single (67%) and the rest were married (%33). In terms of employment, 16% were students which in itself is remarkable. 84% of cadavers in less than 24 hours and only 3 patients (6%) were examined at a distance of more than two days.

Meanwhile, 24 people died in the home (49%) and 11 patients (22.5%) died out of the house and 14 (28.5%) died in hospital. Out of 49 dead, 57% were referred outside the hospital to the dissection salloon and 43% of them died in the hospital. Among the dead, 33 patients had cardiopulmonary arrest, 6 patients had acute respiratory distress symptoms and 10 had a loss of consciousness.

Among Macroscopic findings of the lung, most common findings was elastic consistency and pulmonary edema (In 55% of deaths) in Microscopic findings of the lung, 41 case was abnormal %, 34 was atelectasis, 32% pulmonary edema and 22% had a hemorrhage in the alveoli. 5% of dead were eligible to aspiration and 11% had symptoms of pneumonia, all of which were seen in people over 40 years old. In examining the toxicity of the liver and gallbladder, only 24% showed positive for tramadol. In examining the stomach contents, (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.

Table 1 prevalence of deaths of tramadol in terms of age, and Lung microsocopic finding of in cadaver referred to Legal Medicine Organization in the Years 2008-2013

Age **Lung finding**	15-24	25-34	35-44	+45	**Frequency**
Normal finding	3	4	1	0	8
Edema and Alveolar heamorage	3	3	0	1	7
Atelecta zia	3	2	1	1	7
Edema and Atelectazia	3	3	1	0	7
Edema and Evidence of pneeumonia	2	1	0	0	3
Alveolar heamorage,Atelectazia	2	1	0	0	3
Edema	4	2	0	0	6
Alveolar heamorage	1	0	0	0	1
pnemonia	0	0	2	3	5
Avidence of Aspiration	0	0	1	1	2
Total	21	16	5	6	49

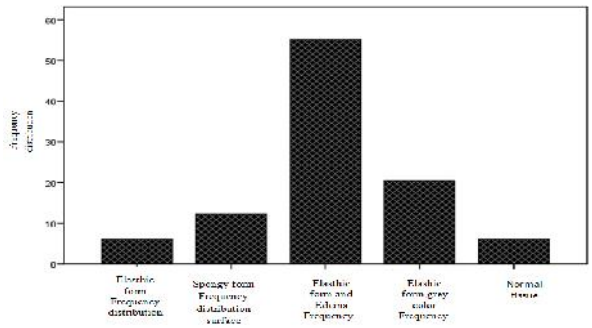

Figure 1 Comparison of frequency of deaths from of tramadol in terms of different lung macroscopic findings in cadaver referred to Legal Medicine Organization in 2008-2013

Table 1the frequency of deaths by tramadol in terms of Sex and different Lung micoroscopic finding in cadaver referred to Legal Medicine Organization in 2008-2013

sex Lung finding	women	men	frequency	Frequency percent
Normal finding	1	7	8	(%16)
Edema and Alveolar heamorage	2	5	7	(%!4)
Atelecta zia	1	6	7	(%14)
Edema and Atlectazia	1	6	7	(%14)
Edema and Evidence of Pneumonia	1	2	3	(%6)
Alveolar heamorage	0	1	1	(%2)
Edema	2	4	6	(%12)
Alveolar heamorage, Atelectazia	1	2	3	(%6)
pnemonia	1	4	5	(%11)
Avidence of Aspiration	0	2	2	(%5)
Total	10	39	49	(%100)

DISCUSS

This study the majority of deaths from tramadol was 39 males from 25-34 years old with an average 26 years old. A significant correlation (P-value <0.05) was found between age and acute poisoning..

In terms of gende, out of 49 dead , 80% men and 20were women ans significant correlation was seen between recent use of tramadol and gender (P value <0.003) .the results is consistent to resutls of other studies. Cause of death has been cardiopulmonary arrest (67%), convulsion (49 %), decreased level of consciousness (47%) and acute respiratory failure (12.%). But in a study by T. matthiesen T. wohermann in 1997, the most common cause of death was neurological symptoms. (10,11,12)

There was significant correlation between the studied variables in lung microscopic findings with acute poisoning of tramadol(Pvalue</004%) meanwhile the most pathologic finding was seen under 34 years old,. 100% of patients who has pneumonia and aspiration signs were over 40 years of age likewise this finding were not mentioned in other studies.

So deaths more common among men with tramadol and had nothing to do tramadol history in the past. Between recent use of tramadol and gender significant correlation was found. (P <0.003) Most of the dead in our study used tramadol acute to abuse to suicide and died following complications.

In reviewing toxicology, blood, urine and tissues, and gallbladder and stomach contents, there was singficant correlation between recent use of tramadol and possitive toxicology and all had p-value <0.05.

In this study, with most deaths caused by tramadol was 25-34 years old in males. Any of them didn't have the history of Tramadol use or other disease in the past, and significant relationship between age and tramadol was seen. (P <0.05) So use and subsequent poisoning reported deaths and complications in men in this age range. In a study, Mr. Samaka reported the same changes in mice too. But the incidence of these complications is much more in people (in our case)(16,17)

Final result

Given the prevalence, tramadol is known as the most popular analgesic around the world that are now readily available to the public (1-3) and according to its fatal and dangerous symptoms after taking such symptoms and loss of consciousness and cardiac arrest, prolonged hospitalization for poisoning it (18) and also 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 poisioning 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.(23)

Problems and Limitations

The problems and limitations of the study include lack of kidney and brain samples for all of them and also uncertainty as careful dosage of tramadol consumed could not compare with other articles.

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