Two Fatal Intoxications Due to Tramadol Alone

Autopsy Case Reports and Review of the Literature

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Abstract: Since tramadol was marketed, it has been widely prescribed as a pain killer because of its relatively safe profile among opioids.

Nevertheless, intoxication can occur: overdose can lead to fatal outcomes mostly in association with other drugs, via the potential interaction with serotonergic antidepressant medications, as well as the potential for increased central nervous system (CNS) depression.

Fatal outcomes only attributable to tramadol are a rare entity. In this case report, 2 fatal cases are described due to tramadol stand-alone intoxication with peculiar characteristics.

In case 1, gas chromatography - mass spectrometry analysis detected tramadol in all specimens (32 μg/mL in the heart blood, 23.9 μg/mL in the femoral blood, 3.3 μg/mL in the bile, and 1.4 μg/mL in the urine). No other CNS depressants were detected by toxicological analysis.

In case 2, gas chromatography - mass spectrometry analysis detected tramadol in all specimens (7.5 μg/mL in the heart blood, 5.8 μg/mL in the femoral blood, and 18 μg/mL in the urine). No other CNS depressants were detected by toxicological analysis.

Review of the literature was performed to clarify the actual knowledge on this topic.

Key Words: forensic pathology, tramadol, overdose, poisoning, intoxication, postmortem, autopsy, suicide

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Tramadol is a centrally acting opioid analgesic usually prescribed for moderate to severe pain. Its efficacy is comparable with codeine and meperidine. Its analgesic effect is partially blocked by naloxone and totally blocked by yohimbine.[1]

Tramadol has been used for almost 3 decades in Europe and was approved for marketing in the United States in 1995. It is widely prescribed by physicians because it is considered a safe drug devoid of many adverse effects of traditional opioid drugs such as respiratory depression and drug dependence. In fact, it has only a weak affinity for μ-opiate receptors and it mainly exerts its analgesic effect by inhibiting monoamine (norepinephrine, 5-hydroxytryptamine) reuptake.

The most common reported adverse effects are dizziness, nausea, constipation, and headache.[2]

Tramadol overdoses frequently cause central nervous system (CNS) depression, nausea/vomiting, tachycardia, and seizures; symptoms generally resolve within 24 hours and accidental ingestions in children are well tolerated.[3]

Tramadol-related deaths are generally referred to an association of the drug with other CNS depressants. Fatal outcomes only attributable to a tramadol overdose are a rare entity.[4] With regard to that, we report 2 autopsy cases of fatal intoxication due to tramadol alone.

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CASE REPORTS

Case 1

A 48-year-old man was found dead in the bed of a rehabilitation center where he was a resident. He was an ex-addict, under house arrest. Furthermore, he was taking tramadol against Pott disease–related pains (no other information was available about dose and therapy regimen). The afternoon before his death, he found out that his twin sister had been struck by cancer and was deeply affected by the news.

Forensic autopsy was performed 48 hours later.

External examination of the body showed only bilateral multiple little scars on the forearms from previous acupunctures; there was no sign of a violent confrontation before the death. The subsequent internal examination showed bilateral pulmonary edema; the heart weighted 450 g, the right lung weighted 890 g and the left one 680 g, and the bladder was distended by urine; no pill was found in the stomach.

Organ and body fluid samples were taken for further histological and toxicological analysis.

The histological examination showed pulmonary edema and did not reveal signs of acute hepatic failure; no preexisting disease contributing to or causing the deaths was identified.

Case 2

A 17-year-old adolescent boy was found dead in his bed by his parents. The boy was known to have relational difficulties with his girlfriend who left him. Relatives declared that the boy was assuming tramadol against pains of a nonspecific origin (no other information was available).

Forensic autopsy was performed 24 hours later.

External examination of the body showed no injuries, and the autopsy revealed just pulmonary edema; the heart weighted 290 g, the right lung weighted 640 g and left one 544 g, and the bladder was distended by urine; no pill was found in the stomach.

Organ and body fluid samples were taken for further histological and toxicological analysis.

The histological examination showed pulmonary edema and did not reveal sings of acute hepatic failure; no preexisting disease contributing to or causing the deaths was identified.

TOXICOLOGICAL ANALYSIS

Systematic toxicological analysis was performed on the postmortem samples to investigate for illegal and prescribed drugs and for alcohol.

Screening for the presence of illegal and prescribed drugs (opiates, cocaine and metabolites, cannabis, amphetamines and methylenedioxy derivatives, methadone, barbiturates, and benzodiazepines) in urine and whole blood was performed using immunoassay methods (cloned enzyme donor immunoassay).

To perform the cloned enzyme donor immunoassay analysis, the blood was treated with acetonitrile to precipitate and to separate the corpuscular part; then, the acetonitrile was allowed to evaporate at room temperature and then was added an equal

volume of phosphate buffer. The aforementioned method gave negative results for all substances listed.

As always in our laboratory, second level analysis was performed by gas chromatography - mass spectrometry (GC-MS) on blood, urine, and bile to verify the presence or not of exogenous substances.

For the GC-MS analysis, 1 mL of sample, along with the internal standard at known concentration, was added to 30 μL of β-glucuronidase at 40°C overnight (hydrolysis). Solid-phase extraction was then performed by using Bond Elut Certify extraction cartridge, 130 mg/3 mL Agilent Technology. The extraction liquid was brought to dryness in a nitrogen stream at room temperature and subsequently silanized with bis(trimethylsilyl) trifluoroacetile 50 μL for 45 minutes at 80°C.

The previous extraction procedure gave positive results for tramadol in both cases; we then performed the same extraction procedure without hydrolysis with tramadol hydrochloride, O-desmethyl-tramadol, and N-desmethyl-tramadol standards.

Tramadol hydrochloride, O-desmethyl-tramadol, and N-desmethyl-tramadol standards were obtained by Chemical Research 2000 Srl. Other reagents and solvents were Agilent Technologies, Carlo Erba, Helix Pomatia, and Sigma-Aldrich.

An Agilent Technology 6890N gas chromatograpy system with an HP 5973 mass selective detector and an HP 5 MS column (30 m × 0.25 mm internal diameter, 0.25 m film thickness) was used. The temperature program was 120°C for 5 minutes, 20°C/min up to 240°C held for 3 minutes, and 15°C/min up to 260°C held for 3 minutes, split-splitless injector at 290°C. Helium was the carrier gas flowing at 1 mL/min. Data were analyzed with gas chromatograpy–mass selective detector data analysis software.

The search of the substances was conducted in full scan by searching for 3 telltale ions: tramadol, 58-135-263; O-desmethiltramdol (ODT), 58-121-249; and N-desmethiltramdol (NDT), 188-135-249 (Library: Cayman Spectra Library SWGDRUG-PMWTOX3).

Method Validation

Analyses have been validated in accordance with the guidelines of Italian Society of Forensic Toxicologists. The detection selectivity of tramadol, ODT, and NDT was ensured by the retention time determination.

Calibration curves were elaborated for each compound. Each calibration point was analyzed in triplicate on 3 consecutive days. Standard deviation was calculated for each concentration. The calibration parameters were stable with regression coefficient (Pearson coefficient) always greater than 0.99 for each compound. Obtained data were used to detect the limit of quantification that was 0.1 μg/mL.

The internal standard used was 2.5 μg of scopolamine to a final concentration of 2.5 μg/mL (94-138-154 ions).

RESULTS

Case 1

Toxicological examinations, performed on peripheral (femoral) blood, bile, and urine, tested negative for psychoactive drugs and alcohol.

The GC-MS analysis detected tramadol in all specimens; tramadol concentrations were 32 μg/mL in the heart blood, 23.9 μg/mL in the femoral blood, 3.3 μg/mL in the bile, and 1.4 μg/mL in the urine; O-desmethyl-tramadol concentrations were 0.2 μg/mL in the femoral blood and 8 μg/mL in the urine; N-desmethyl-tramadol was not detected.

No other CNS depressants were detected by toxicological analysis.

Case 2

Toxicological examinations, performed on peripheral (femoral) blood and urine, tested negative for psychoactive drugs and alcohol.

The GC-MS analysis detected tramadol in all specimens; tramadol concentrations were 7.5 μg/mL in the heart blood, 5.8 μg/mL in the femoral blood, and 18 μg/mL in the urine; O-desmethyl-tramadol concentrations were 0.6 μg/mL in the femoral blood and 82 μg/mL in the urine; N-desmethyl-tramadol was not detected in the blood and was detected in the urine, but only in traces.

No other CNS depressants were detected by toxicological analysis.

DISCUSSION

After oral administration, tramadol is rapidly absorbed with a mean peak plasma concentration of 0.28 μg/mL to 0.31 μg/mL reached after approximately 2 hours after a single 100-mg dose.[5] Plasma protein binding is approximately 20%; tramadol is distributed in the body with a volume of distribution of 3 L/kg. Its mean therapeutic range is approximately 0.1 to 0.3 μg/mL.

Thirty percent of the drug is excreted through the kidneys in an unchanged manner; the remaining is metabolized in the liver by O-desmethyl-tramadol (CYP2D6 mediated) and N-desmethyl-tramadol (CYP3A4 mediated).[6] These primary metabolites may be further metabolized to 3 additional secondary metabolites.

The analgesic activity of tramadol is dependent on its main pharmacologically active metabolite O-desmethyl-tramadol, which has a higher affinity for the μ-receptors. The half-lives of tramadol and O-desmethyl-tramadol are 6.3 and 7.4 hours, respectively.[7]

In fatal intoxication, the interpretation of the probable cause of death relies on the measurement of xenobiotic concentration in blood; in fact, blood is the matrix of choice in toxicological analysis because there is a good correlation between blood concentration and the toxic effect. However, postmortem redistribution may affect the results and therefore the autopsy report. In fatal tramadol intoxications, femoral blood seems to be the specimen of choice for postmortem analysis because it is the least subjected to postmortem redistribution.[8]

Previous studies[9,10] showed that the concentration of tramadol in the liver and kidney, in relation to blood, fails to suggest sequestration of drug in the analyzed specimens; this is consistent with the reported volume of distribution of 3 L/kg.

The difference of concentrations between cardiac and femoral vessels is known as the cardiac-to-femoral blood ratio.[11] In our cases, the concentration of tramadol in the heart and femoral blood does not suggest any major differences (case 1, ratio of 1.34; case 2, ratio of 1.30); even if in the presented cases, organs (such as the kidney or liver) were not tested; our results are therefore consistent with the lack of sequestration of the drug in the organs and with its volume of distribution of 3 L/kg as widely reported in the literature.

Tramadol-related deaths have been generally reported when ingested with interacting drugs, via the potential interaction with serotonergic antidepressant medications, as well as the potential for increased CNS depression.[2,7,12–15]

Fatal intoxications only attributable to a tramadol overdose are a rare entity[4,7,9,15–20] and are listed in Table 1.

Costa et al[8] describe 15 cases of suspected fatal tramadol intoxications; their toxicological results, for the most part lower than those described in cases of lethal tramadol overdose, are not listed

TABLE 1. Review of the International Medical Literature (1997–2017)

Review of the International Medical Literature (1997–2017): Cases of Fatal Intoxication Due to Tramadol Alone

		Tramadol, μg/mL										
Authors/Year of Publication/Reference	**Sex/Age**	**Heart Blood**	**Peripheral Blood**	**Urine**	**Bile**	**Liver**	**Kidney**	**ODT Peripheral Blood**	**NDT Peripheral Blood**	**ODT Urine**	**NDT Urine**	**Ingested Tramadol Dose, mg**
Goeringer et al, 1997[7]	Female/38		2.5					0.1	0.2			
Lusthof and Zweipfenning, 1998[16]	Male/49		13									
Moore et al, 1999[17]	Female/23	19.7	15.1	110.2		68.9	37.5	6.8	5.7			
Musshoff and Medea, 2000[9]	Male/26	13.1	9.6	46	46.1	6.2	3.1					
Loughrey et al, 2003[18]	Male/67		3.7									
Clarkson et al, 2004[19]	Male/43		1.6									
	Male/28		7.9									
	Male/43		13.9									
De Decker et al, 2008[4]	Male/28		5.2			6.5	4.5		Positive			
Shadnia et al, 2008[15]	Female/24											5000
	Male/29											8200
De Backer et al, 2010[20]	Male/17		7.7	Positive				1.3	0.6			
	Female/75		48.3	Positive				2.4	10.1			
Gioia et al, (current)	Male/45	32	23.9	1.4	3.2			0.2		8		
	Male/17	7.5	5.8	18				0.6		82	Positive	

in Table 1 because the authors do not confirm or rule out the suspect of death by tramadol overdose after the completion of the toxicological analysis.

Generally, in fatal intoxication due to tramadol alone, the cause of death is a respiratory depression, even if acute hepatic failure has also been described.[18]

In case 1, tramadol central blood concentration exceeded the therapeutic range 106-fold and in case 2 exceeded this range 25-fold.

Case 1 presented high blood levels but lower urinary levels; on the other hand, case 2 reported lower tramadol blood levels and higher urinary levels, in association with very significant urinary levels of ODT metabolite.

Regarding the different bodily fluid distribution in the reported cases, it is possible to hypothesize the following:

- It could suggest a rapid death process in case 1 opposite to a slower one in case 2.
- Different distribution can be due to an increased previous intake of tramadol by case 2 with subsequent higher amount of the substance and its metabolites in urine.
- Different distribution may be also due to the fact that case 1 was in a rehabilitation center where the therapy is self-administrated: maybe the patient collected a big amount of pills, not assuming the prescribed therapy, and then took them all in 1 shot.

Considering the autopsy findings in both our cases, the results of toxicological analysis are consistent with the assumption of a fatal overdose due to tramadol alone. The manner of death is supposed to be suicidal in both cases because of the circumstantial information exposed previously.

Because of the absence of sings of acute hepatic failure at the histopathological examinations and the autopsy finding of pulmonary edema, confirmed by histology, respiratory depression may be considered the underlying pathophysiological mechanism of death in both cases. This is consistent with the literature that underlines respiratory depression as the most frequent cause of death in tramadol overdoses.

In conclusion, tramadol overdose is becoming a frequent cause of drug poisoning in recent years; our results confirm that tramadol in high dose can lead to death even in the absence of interacting drugs.

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