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# Fatal unintentional intoxications with tramadol during 1995–2005

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**Abstract**

Tramadol is an extensively used centrally acting analgesic and is considered a safe drug devoid of many serious adverse effects of traditional opioids. However, recently, toxicity and an abuse potential of tramadol have been reported. This study examined fatal unintentional tramadol intoxications among Swedish forensic autopsy cases between 1995 and 2005. All fatal intoxications were selected, in which toxic concentrations of tramadol (>1 μg/g femoral blood) had been detected, and where the forensic pathologist considered the intoxication unintentional and the fatal outcome at least partly explained by tramadol. Toxicology analyses, police reports, autopsy protocols and medical records were scrutinized. A total of 17 cases (eleven men and six women) of fatal unintentional tramadol intoxications were identified. For these cases the median age was 44 years (range 18–78 years) and the median tramadol concentration was 2.0 μg/g (range 1.1–12.0 μg/g). Other pharmaceutical substances, illicit drugs or ethanol were detected in addition to tramadol in all of these cases. In fact, intoxication with multiple drugs was considered the cause of death in 10 (59%) cases. However, in seven cases tramadol was the only substance present in toxic concentrations. A history of substance abuse was identified in 14 (82%) subjects and a present tramadol abuse in 8 (47%). These results suggest that fatal intoxications with tramadol may occur unintentionally and that subjects with a history of substance abuse may be at certain risk. Precaution is therefore warranted when prescribing tramadol in such patients.


*Keywords:* Tramadol; Intoxications; Fatal outcome; Autopsy

## 1. Introduction

Tramadol is a centrally acting analgesic, which was first introduced in Germany in 1977. It has become the most prescribed opioid worldwide [1]. In Sweden, tramadol has been available since 1995 and has a widespread use [2].

Tramadol is composed of a racemate of the two enantiomers (+)-tramadol and (−)-tramadol [3] and is converted to N- and O-demethylated metabolites by CYP2B6/CYP3A4 and CYP2D6, respectively [4,5]. The pain relief is mediated by weak opioid receptor agonism and inhibition of serotonin and noradrenaline reuptake, mechanisms that are attributable to tramadol and the active metabolite, O-desmethyltramadol [6]. The (+)-enantiomer of O-desmethyltramadol has higher affinitiy for the opioid μ-receptor than the (−)-enantiomer and both enantiomers of tramadol [6]. Furthermore, the (+)-enantiomer of tramadol preferentially inhibits serotonin reuptake and the (−)-enantiomer is the most potent inhibitor of noradrenaline reuptake [6].

Tramadol is generally said to be devoid of many serious adverse effects of traditional opioid receptor agonists, such as the risk for respiratory depression [7,8] and drug dependence [7,9]. Based on the latter, the abuse potential of tramadol is considered to be low or absent [1,10–12], which is in contrast to other opioids. Hence, tramadol is the only clinically available non-scheduled opioid [13]. Tramadol abuse and tramadol related fatalities have nevertheless been reported recently in postmarketing surveillance and in case reports [14].

Forensic autopsies have been shown to constitute a unique source for the identification of drug-related deaths [15]. Using forensic materials, Clarkson et al. [16] reported that tramadol might be a significant contributor to lethal intoxication when taken in excess with other drugs that depress central nervous

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functions, such as analgesics, muscle relaxants and antidepressants.

Based on this, we decided to investigate fatal unintentional tramadol intoxications and possible risk factors in such intoxications using Swedish forensic autopsy data.

## 2. Methods

The National Board of Forensic Medicine is responsible for forensic toxicology and forensic pathology investigations in Sweden. When certifying death physicians are obliged to report all suspected and certified unnatural fatalities to the police. In most of these cases, the police will request a forensic autopsy. During autopsy, blood from the femoral vein, when available, is collected and analysed as regards presence of pharmaceutical and illicit drugs and ethanol at the Department of Forensic Genetics and Forensic Toxicology. The diagnosis of a fatal intoxication is based on the toxicology results, autopsy results and information in the police reports and other available relevant documentation. Moreover, manner of death is determined by the forensic pathologist in three categories; unintentional, intentional (suicide or homicide) or undetermined manner of death. Suicide is considered whenever any expression of intent of the decedent is found, e.g. expressions of farewell, hopelessness or great stress, desire to die, efforts to prepare for death or to avoid being rescued, previous suicide attempt or suicide threat and history of stressful event/significant losses or of serious depression/mental disorder [17]. Unintentional manner of death is considered when the forensic pathologist does not find any sign of intent. The manner of death remains undetermined if neither intentional nor unintentional manner of death can be established.

The results are registered in two forensic nationwide databases [18]. The cause of death is registered using the International Classification of Diseases codes, ninth revision (ICD-9).

### 2.1. Selection

All forensic autopsy cases, in which tramadol was detected during forensic toxicology analysis were identified. Cases investigated during 10 years after registration of tramadol in Sweden (15 September 1995–14 September 2005) were selected. Based on the assessment of the forensic pathologist, only unintentional tramadol intoxications were included. A femoral blood concentration of tramadol exceeding 1 μg/g was defined as toxic and tramadol was then considered to have contributed to the fatal outcome [19]. The relative contribution of tramadol as compared to other detected substances was assessed by the forensic pathologist. Only cases in which tramadol had a major or contributory role in the fatality were included in this study.

All available documents on each case, including autopsy protocols, toxicology analyses, police reports and in some cases medical records, were scrutinized. The following parameters were registered: sex, age, medical history, history of substance abuse, tramadol prescriptions, toxicology analysis results and autopsy results.

### 2.2. Analytical methods

Blood concentrations of tramadol and O-desmethyltramadol were detected and quantified using a previously described gas chromatography technique with nitrogen detection [20]. In brief, an alkaline extract was made by extracting 1.0 g of femoral blood with butylacetate after the addition of 1 M trisbuffer (pH 11). After 10 minutes of extraction and subsequent centrifugation, the extract was injected into a DB-5 column. The chromatography was done with a Hewlett-Packard GC 5890, series II instrument coupled to nitrogen–phosphorous detector. Standard curves were used for quantification by adding known amounts of tramadol to drug-free blood and plotting the area response ratio for drug and internal standard versus the concentration of the drug. In each run, internal controls were used to achieve high quality and similar results over time. The method limit of quantification for tramadol was 0.2 μg per gram (1995–2000) and 0.1 μg per gram (2000–2005) blood. The inter assay coefficient of variation varied during the study period between 6.1–11.3%. The between run accuracy varied between 94 and 104%.

Sales statistics for the study period were retrieved from the National coorporation of Pharmacies, Sweden (Apoteket AB).

## 3. Results

During the 10-year study period 49 700 forensic death investigations, which included toxicological analyses, were undertaken. Of these, tramadol was detected in 837 (2%) cases. The registered cause of death was intoxication in 297 (36%) cases. Of these, tramadol was considered to contribute to the death in 148 (50%) cases. In 17 (11%) of the 148 cases the fatality was judged as unintentional. Seventy three (49%) cases were classified as intentional and for 58 (39%) cases the manner of death was undetermined. During the study period a total of 124.5 millions defined daily doses (DDDs) of tramadol were sold in Sweden [2], which implies an incidence of unintentional fatal tramadol intoxications of 0.14 per million DDDs sold (1 case per 7.3 million DDDs).

Key demographic and clinical characteristics of the 17 fatal unintentional intoxications with tramadol are presented in Table 1. Of the 17 cases, 11 (65%) involved men and 6 (35%) involved women. The median age was 44 years (range 18–78 years). The median femoral blood concentrations of tramadol and O-desmethyltramadol were 2.0 (range 1.1–12.0) and 0.3 (range 0.1–1.1) μg/g, respectively.

In all cases, other substances were detected in addition to tramadol and in 16 cases (94%), substances acting on the CNS were found. Most commonly, opioids (nine cases, 53%), bensodiazepines (eight cases, 47%), substances acting on serotonergic systems (eight cases, 47%) and/or ethanol (seven cases, 47%) were detected. Of the substances acting on serotonergic systems, four cases involved selective serotonin reuptake inhibitors (SSRI), two cases involved tricyclic antidepressants (TCA) and two cases involved other antidepressants. Illicit drugs were detected in four (24%) cases. Tramadol was, however, the only substance present in toxic concentrations in seven cases. In 10 (59%) cases multiple drug intoxication was assessed as the cause of death.

In 12 cases of the unintentional tramadol intoxications the source of tramadol was known. In seven (58%) of these, the drug had been prescribed to the subject. Two (17%) subjects had obtained tramadol from their partner and two (17%) subjects were suspected to have purchased the drug illegally.

A documented history of substance abuse was present in 14 subjects (82%). The substances abused were ethanol (three cases, 18%), pharmaceutical drugs (two cases, 12%), illicit drugs (two cases, 12%) and ethanol in combination with illicit drugs (eight cases, 47%).

The purpose of tramadol intake was generally difficult to assess. However, the available documents in eight cases suggested that large amounts of tramadol were taken to experience psychotropic effects or to reduce withdrawal symptoms. In two subjects an overdose was probably taken due to insufficient analgesia preceding the death. In one of these subjects an unclear tramadol prescription may have contributed to the large amount of tramadol taken.

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Table 1
Fatal unintentional intoxications with tramadol

| Case | Age (years) | Sex | Medical history | History of substance abuse | Tramadol prescription | Concentration of T (DT) | Concurrent drugs | Role of tramadol in intoxication assessed by forensic pathologist |
|---|---|---|---|---|---|---|---|---|
| 1 | 78 | F | Osteoporosis<br>Hypocalcaemia<br>Pancreatic insufficiency<br>Epilepsy<br>Liver cirrhosis | Yes | NA | 12.0 (0.5) | Codeine[a]<br>Mirtazapine | Contributory |
| 2 | 18 | M | – | Yes | NA | 12.0 (1.1) | Flunitrazepam<br>Amphetamine | Major |
| 3 | 56 | M | Asthma<br>COPD | NA | NA | 9.4 | Paracetamol[a,b]<br>Propoxyphene[a]<br>Ethanol | Contributory |
| 4 | 44 | M | Lower back pain<br>pancreatitis<br>Diabetes mellitus | Yes | Yes | 4.8 | Paracetamol[b]<br>Propiomazine | Major |
| 5 | 57 | M | NA | Yes | No | 3.3 | Paracetamol[b] | Major |
| 6 | 54 | M | Lower back pain | NA | Yes | 2.9 (0.5) | Amitriptyline<br>Sertraline | Major |
| 7 | 38 | M | Lower back pain<br>Dyssomnia<br>Social phobia | Yes | Yes | 2.7 (0.3) | Methadone<br>Mirtazapine<br>Morphine<br>Promethazine<br>Propoxyphene<br>Venlafaxine | Major |
| 8 | 67 | F | NA | Yes | No | 2.5 | Nitrazepam[a]<br>Ethanol[a]<br>Propiomazine | Contributory |
| 9 | 25 | F | Uteric cysts, bleedings<br>Pharmaceutical drug abuse | Yes | NA | 2.0 (0.3) | Alprazolam<br>Diazepam<br>Sertraline<br>Zopiclone | Contributory |
| 10 | 61 | F | Fractures<br>Pains<br>Anxiety<br>Chronic pancreatitis<br>Gastric ulcers<br>Colon irritable<br>Asthma<br>COPD<br>Hypertension | Yes | Yes | 2.0 | Mirtazapine[a]<br>Trimipramine[a]<br>Ethanol[a]<br>Hydroxizine<br>Paracetamol[b] | Contributory |
| 11 | 38 | F | Dyssomnia<br>Anxiety<br>Depression<br>Ovarian cysts | Yes | NA | 1.9 | Sertraline[a]<br>Propiomazine[a]<br>Ethanol[a] | Contributory |
| 12 | 18 | M | NA | Yes | NA | 1.8 (0.2) | Flunitrazepam<br>Sertraline<br>Amphetamine<br>GHB[c] | Contributory |
| 13 | 34 | M | Postsurgical pain | Yes | Yes | 1.7 (0.1) | Alprazolam[a]<br>Codeine<br>Diazepam<br>Ethylmorphine<br>Flunitrazepam<br>Levomepromazine<br>Morphine | Contributory |
| 14 | 46 | M | NA | Yes | NA | 1.2 | Alimemazine[a]<br>Diazepam[a] | Contributory |

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Table 1 (*Continued*)

| Case | Age (years) | Sex | Medical history | History of substance abuse | Tramadol prescription | Concentration of T (DT) | Concurrent drugs | Role of tramadol in intoxication assessed by forensic pathologist |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Venlafaxine[a]<br>Ethanol[a]<br>Codeine<br>Mirtazapine | |
| 15 | 34 | M | Chronic lower back pain | NA | Yes | 1.2 | Propoxyphene[a]<br>Diazepam<br>Amphetamine | Contributory |
| 16 | 51 | M | Hepatitis C | Yes | Yes | 1.1 | Ethanol[a]<br>Paracetamol[b]<br>Propoxyphene | Contributory |
| 17 | 33 | F | NA | Yes | NA | 1.1 | Ethanol[a]<br>Alimemazine<br>Carbamazepine<br>Nitrazepam<br>Paracetamol[b]<br>Heroine[d] | Contributory |

*Abbreviations*: T: tramadol, DT: O-desmethyltramadol, COPD: chronic obstructive pulmonary disease, GHB: gamma hydroxybutyrate, NA: not available.
[a] Toxic drug concentration as described by Moffat et al. [19].
[b] Also known as acetamoniphen.
[c] Drug not quantified.
[d] Codeine, morphine and 6-acethylmorphine detected during postmortem analyses.

## 4. Discussion

In this study 17 fatal unintentional tramadol intoxications were identified during the 10-year study period. Considering the wide use of tramadol, unintentional fatal toxicity of this drug thus seems to occur rarely and tramadol might hence still be a safe alternative compared to other opioids. We estimated one unintentional tramadol intoxication per 7 million DDDs sold. According to our knowledge previous studies have not investigated the presence or absence of intention among the cases of tramadol intoxications. A comparable forensic US study concluded that despite increased detection of tramadol in forensic investigations, no corresponding increase occurred in the number of deaths solely attributable to tramadol [16]. This has been confirmed by the FDA [21] and the manufacturer Johnson & Johnson [11].

In agreement with two previous forensic studies [16,22] only a minority of the investigated cases of tramadol intoxications were attributable to tramadol alone. In this study, additional substances in toxic concentrations were found in 10 cases and all cases involved the detection of other substances. It has been suggested previously that tramadol may significantly contribute to the cause of death when taken in excess with other analgesic, muscle relaxant, and CNS depressant drugs. Potential interaction with serotonergic antidepressant medications, as well as the potential for increased CNS depression has been hypothesised as possible explanations [16]. Available data in this study do not suggest that serotonin syndrome occurred in any of the subjects, nor could CNS depression be established in any of the cases. However, in most cases no information was available on symptoms experienced by the subjects before death. None of the subjects died at hospital and the death occurred in most cases without any witnesses.

Our data suggest that unintentional fatalities related to tramadol are in a significant proportion (82%) related to a history of substance abuse. Moreover, in nearly half of the cases tramadol addiction was suspected. A few studies have previously reported that tramadol abuse occurs and that most patients have a history of substance abuse [11,21]. However, tramadol abuse is rare compared to that for other opiates [23] and the reported number of cases in the U.S. has declined despite increased drug exposure [11]. Hence, the general opinion among physicians is that tramadol is an unattractive substance of abuse and that tramadol abuse is not clinically relevant [12,10,7,24].

When interpreting the results of this study one should consider the strengths and weaknesses with the study. According to the instructions of the National Board of Forensic Medicine, all six departments of forensic medicine in Sweden use the same standardised routines during autopsy including blood sampling, and all toxicology analyses of samples taken during autopsy are performed at one central laboratory, the Department of Forensic Genetics and Forensic Toxicology. Data stored in the forensic databases is hence nationwide and uniform. The cases are, however, relatively few and the antemortal clinical information is limited. Consequently, the number of cases with a history of substance abuse, a present substance abuse and a prescription of tramadol might have been underestimated. Moreover, even though the assessment of the contribution of tramadol in the fatalities were made prospectively by the forensic pathologists, inter personal differences may exist. In addition, the criteria used to assess whether a fatality was unintentional might have differed somewhat between the six forensic departments involved in the study. However, we consider the information available in the Swedish forensic databases a valuable complement to traditional postmarketing data.

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In conclusion, this study suggests that fatal unintentional intoxications with tramadol may occur and that subjects with a history of substance abuse may be at certain risk. Precaution is therefore warranted when prescribing tramadol in such patients. However, fatal toxicity of tramadol seems to be rare considering the wide use of the drug. Moreover, in the cases of fatal unintentional intoxication other substances acting on CNS are often found. This might also increase the risk for fatal unintentional intoxications. More studies investigating tramadol abuse and fatal complications related to tramadol are warranted.

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