

# Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality?

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## Abstract

Tramadol is a centrally acting analgesic agent used in the treatment of mild to moderate pain. It has a low affinity to opioid receptors and inhibits the reuptake of norepinephrin and serotonin producing an analgesic action by blocking nociceptive impulses in the spine. Although 21 drug-combined fatalities including tramadol have been reported, only two fatal overdoses in adults with tramadol alone have been reported to date. We report four additional lethal intoxications, assess the toxicity of tramadol, the detection method and the possible interaction with other central nervous system (CNS) depressants, particularly benzodiazepines. Similarities between tramadol and buprenorphine are discussed, and a possible cytochrome P450-based interaction between tramadol and benzodiazepine is considered. To our knowledge, this relationship has never been reported in the literature.

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## 1. Introduction

Tramadol hydrochloride (Ultram<sup>®</sup>, Contramal<sup>®</sup>, Zamudol<sup>®</sup>, Topalgic<sup>®</sup>), is a centrally acting analgesic agent (Fig. 1) used in the treatment of mild to moderate pain [1]. It has been approved for use in the United States since 1995 and in France since 1997. It has a low affinity to opioid receptors and inhibits the reuptake of norepinephrin and serotonin making a significant contribution to analgesic performance by blocking nociceptive impulses in the spine. Its analgesic effect is partially blocked by naloxone, but totally blocked by yohimbine. Tramadol is rapidly absorbed orally and has a distribution volume of 3 l/kg. Following a 100 mg oral dose, a peak concentration of approximately 0.3 mg/l is detected 2 h post-dose. After a single bolus infusion of 100 mg tramadol, concentrations in plasma can be immediately detected. Elimination is slow and characterized by an elimination half-life of 5–6 h [2]. Tramadol is metabolized to an active desmethyl

derivative (*o*-desmethyltramadol) and several inactive compounds (Fig. 1). *o*-Desmethyltramadol shows higher affinity for the  $\mu$ -opioid receptors and has twice the analgesic potency of the parent drug. It has been shown that the hepatic *o*-demethylation of tramadol is carried out by the isoenzyme cytochrome P4502D6 (CYP2D6). The gene encoding for CYP2D6 is known to show polymorphism [3] and the existence of different alleles result in functionally different enzymes. This is the basis of large inter-individual differences of the metabolism of those drugs requiring CYP2D6 to be eliminated from the body. More than 30 drugs are substrates of CYP2D6, including drugs with a narrow therapeutic range. In the case of tramadol, poor metabolizers of sparteine/debrisoquine (affecting about 5–10% of Caucasians) are virtually unable to demethylate it to its pharmacologically active metabolite, *o*-desmethyltramadol. Therefore, poor metabolizers may exhibit either an absent or at least a weaker analgesic efficacy after i.v. tramadol administration [4]. Adverse effects include seizures and respiratory depression. Tramadol dosage should be adjusted according to the severity of the pain and the individual sensitivity of the patient. Standard therapeutic doses are 50 mg orally, 50–100 mg by injection and

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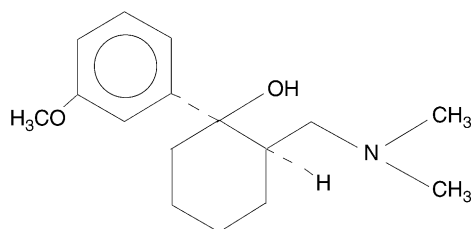


Fig. 1. Chemical structure of tramadol.

100 mg rectally. The total daily dose should not exceed 400 mg. Therapeutic blood levels in adults range from 0.1 to 0.3 mg/l.

## 2. Case reports

### 2.1. Case #1

A 36-year-old man, without history of depression, was found dead in his bed with bloody vomit near his head (Table 1). An empty package of Lexomil<sup>®</sup> (bromazepam) was near the body and a box of Skenan<sup>®</sup> (morphine chlohydrate) was also found in the rubbish-bin. Forensic examination revealed a slight decomposition and no evidence of violence was noticed. No other medication were found around. Toxicological screening revealed an unexpected and very elevated post-mortem tramadol level in femoral blood (134 mg/l) and a toxic bromazepam level (0.867 mg/l).

### 2.2. Case #2

A 42-year-old man was found with cardiorespiratory arrest in his office, in the toilet. He died during transport to the emergency intensive care unit. Forensic examination found no evidence of cardiac abnormalities but signs of asphyxia were observed. Toxicological screening found a toxic tramadol blood concentration of 0.880 mg/l and a toxic bromazepam blood level of 0.801 ng/ml. However, two other drugs were present, meprobamate and zopiclone, at therapeutic level.

### 2.3. Case #3

A 58-year-old man was admitted in emergency care unit after dizziness. He was comatose with hypothermia (34 °C). No biological or radiological abnormalities were noted. The patient subsequently died 2 days later after an irreversible coma. Autopsy revealed previous rib fractures and signs of asphyxia. Toxicological screening detected a tramadol toxic level (3.0 mg/l) and slightly supra-therapeutic alimemazine level (0.410 mg/l).

### 2.4. Case #4

A 24-year-old man was found dead in his residence and barbituric self poisoning was suspected. No violence was discovered and no evidence of crime was suspected. Toxicological analysis revealed a therapeutic phenobarbital blood concentration and a toxic tramadol level (1.9 mg/l).

## 3. Toxicological analysis: HPLC–DAD

Tramadol contains a weakly absorbing chromophore in its molecule, rendering UV detection above 220 nm unsuitable for the determination of its concentration in plasma samples [5]. Different methods for tramadol determination have been described, using gas chromatography (GC) with a nitrogen-selective detector (GC–NPD) [6] or GC–mass spectrophotometry (GC–MS) [7]. As previously described [8], we used a high-performance liquid chromatography with diode array detection method (HPLC–DAD).

The HPLC–DAD was used under the following conditions: flow rate 0.42 ml/min, acetonitrile concentration from 3 to 70% (v/v) in the phosphate buffer (pH 3.2). Each extract was injected into a C<sub>18</sub> BDS Column (3 μm × 100 mm × 3 mm, i.d.) via a HP 1050 autosampler (Hewlett-Packard).

Quantification of tramadol was performed according to the following procedure: to 1 ml blood (in duplicate) were added 4 ml NH<sub>4</sub>Cl buffer (pH 9.2), 50 μl of prazepam as internal standard and 4 ml dichloromethane hexane ethylacetate (5:4:1, v/v/v). The spectrophotometric detector was set at 200 nm. The limit of detection was 25 ng/ml for 1 ml of sample.

Table 1  
Case histories

Case	Gender	Age (years)	Circumstances of death	Blood concentration of tramadol (mg/l)
1	M	36	Found dead in bed	134.00
2	M	42	Found unconscious in the toilet	0.88
3	M	58	Loss of consciousness	3.00
4	M	24	Self poisoning with phenobarbital	1.90

Table 2  
Toxicological results

Case	Gender	Age	Blood concentration of tramadol (mg/l)	Other drugs detected	Amount of other drugs detected (mg/l)
1	M	36	134.00	Bromazepam Meprobamate Alcohol	0.867 2 0.22
2	M	42	0.88	Bromazepam Zopiclone Meprobamate	0.801 0.019 11.1
3	M	58	3.00	Alimemazine (trimeprazine)	0.410
4	M	24	1.90	Phenobarbital	12

#### 4. Results

Routine testing for volatile, therapeutic and abused drugs was performed on all cases. This includes:

- volatile blood and urine screening by headspace gas chromatography (GC-HS);
- qualitative blood and urine screening of barbiturates, tricyclic antidepressants;
- benzodiazepines, opiates, cocaine metabolite, sympathomimetic amines by fluorescence polarization immunoassay (FPIA);
- cannabinoids urine drug screening by FPIA;
- quantitative acetaminophen and salicylate determination of blood and urine by FPIA;
- digoxin determination of blood by FPIA;
- blood carbon monoxide detection by spectroscopy.

No volatile substances were detected in any of the cases. Tramadol blood quantitative determination by HPLC–DAD was performed in the four cases (Table 2).

#### 5. Discussion and conclusions

Although several drug-combined fatalities including tramadol have been described [9–14], only two fatal overdoses

in adults with tramadol alone have been reported to date [15]. Moreover, most of the associated drugs fatalities including tramadol have been reported with other central nervous system (CNS) depressants, particularly benzodiazepine [9–11,13,14]. In certain cases, benzodiazepine levels were in the therapeutic range or slightly higher. Review of the lethal tramadol intoxications in adults are summarized in Table 3 and later detailed.

Goeringer et al. [9] reported 12 cases of tramadol-related deaths involving tramadol. They reported tramadol concentrations ranging from 0.03 to 22.59 mg/l. All deaths were attributed to co-ingestion and not to tramadol alone. The highest tramadol blood concentration (22.59 mg/l) was found in combined drug-intoxication (propranolol, desipramine and trazodone). Levine et al. [10] analyzed tramadol distribution in four post-mortem cases but did not attribute death to tramadol intoxication.

Michaud et al. [11] reported a tramadol lethal intoxication with blood concentration of 38.3 mg/l, in association with alcohol at the concentration of 1.29 g/l.

Ripple et al. [12] reported a tramadol lethal intoxication but discovered multiple drugs with serotonin-effects. Tramadol level was 0.70 mg/l but death could not be attributed to tramadol only.

Moore et al. [13] described the first isolated tramadol overdose fatality with a blood concentration of 15.1 mg/l.

Table 3  
Review of the literature

References	Number of lethal intoxications	Tramadol blood concentration (mg/l)	Death related to tramadol intoxication
Goeringer et al. [9]	12	0.03–22.59	0
Levine et al. [10]	4	0.27–6.5	0
Michaud et al. [11]	1	38.3	0
Ripple et al. [12]	1	0.7	0
Moore et al. [13]	1	20	1
Lusthoff et al. [14]	1	13	1 (tramadol alone)
Musshoff et al. [15]	1	9.6	1 (tramadol alone)
Our cases	4	0.88–134	2

Table 4  
Toxicological data of others drugs detected (mg/l)

Drug	Therapeutic levels	Toxic levels	Lethal levels
Bromazepam	0.080–0.170	0.25–0.50	–
Meprobamate	5–20	>50	>140
Alimemazine	0.050–0.400	>0.500	–
Zopiclone	0.010–0.050	>0.150	–

Lusthof and Zweipfenning [14] reported a suicide by tramadol overdose with a whole blood concentration of 13 mg/l where 7-aminoflunitrazepam was determined in a concentration too low to have contributed to death.

Musshoff et al. [15] described the first case of tramadol intoxication alone. Tramadol peripheral concentration was 9.6 mg/l and no other drugs, particularly benzodiazepine, were discovered.

According to the most recent data of the International Association of Forensic Toxicologists [16], therapeutic blood levels in adults range from 0.1 to 0.8 mg/l, toxic level was between 1 and 2 mg/l and lethal concentration was usually considered to be higher than 2 mg/l; which suggests that therapeutic, toxic and lethal levels of tramadol were relatively close. Other authors discovered drugs therapeutic, toxic and lethal levels are shown in Table 4.

In any of our cases, tramadol blood level was assessed by high-performance liquid chromatography with diode array detection and measured, respectively, at 0.88, 1.9, 3.0 and 134.0 mg/l. The concentration of 134 mg/l is the highest ever reported in the literature and is considered 62 times the toxic level. There is no indication to explain this concentration, though post-mortem redistribution could have played a role, it was not considered significant. In two of these four cases, we found a toxic co-ingestion of bromazepam. In three cases, we discovered an enzymatic inducer (meprobamate, phenobarbital) at infra-therapeutic or therapeutic concentration. Association between tramadol and benzodiazepine has frequently been described in the literature in fatal cases of intoxication involving tramadol. This association must raise questions regarding the risk of this association and eventually a decrease of the tramadol toxic level in this occurrence. However, benzodiazepines may decrease the incidence of seizures in tramadol overdose cases.

In three cases, the concentration of tramadol in the victim's blood was higher than the toxic concentration. Nevertheless, we cannot ascribe the death only to tramadol in any of these cases because of the co-detection of bromazepam at toxic concentrations. In the fourth case, tramadol was detected, but at a non-lethal concentration. In this case, multiple intoxication makes interpretation fuzzy.

As concluded by others reports [9,11–14], this paper illustrates that tramadol overdose, especially when taken in combination with other CNS depressants, such as benzodiazepines, can cause death, even at low dose. Although

excessive CNS depression due to the combination of buprenorphine and benzodiazepines is well known and related to a pharmacokinetic interaction between the drugs, tramadol and benzodiazepine interactions are not well documented. However, buprenorphine and tramadol present similarities [18,19]:

- both have a  $\mu$ -opioid receptors affinity;
- both are modulated by naloxone;
- both undergo extensive oxidative metabolism by P450 cytochrome;
- both have tissue distribution described as similar to those of morphine fatalities [15,20,21].

These data are confirmed by a recent study of 405 cases of non-lethal tramadol exposure which conclude that tramadol cause effects similar to opioid intoxication [22].

Therefore, these similarities suggest that tramadol could interact with benzodiazepine as buprenorphine does Ibrahim et al. [21], in a previous study, have reported that buprenorphine was a weak inhibitor of CYP3A [19] and suggested an additive or synergic effect of buprenorphine and benzodiazepines on the CNS. This hypothesis was based on the cytochrome P450 (CYP3A) mediated oxidative metabolism of benzodiazepines [17], which could be inhibited by buprenorphine.

To date, similarities between tramadol and buprenorphine have never been suggested, as well as cytochrome P450-based interactions between tramadol and benzodiazepine. However, the high frequency of benzodiazepine in tramadol fatalities is not purely random. This combined toxicity suggests a link between drugs. Finally, physicians should be aware of the potential toxic effects and use tramadol with caution when associated to benzodiazepines.

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