



Case report

Fatal overdose of tramadol and alprazolam

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Abstract

A 30-year-old woman, with history of depression, was found dead after the ingestion of an unknown quantity of Xanax (alprazolam), Tramal (tramadol) and alcohol. At the autopsy only a slight decomposition and a diffuse visceral congestion were noticed. Biological samples obtained at autopsy were analysed to detect the presence of alprazolam, tramadol and alcohol. Blood concentrations of alprazolam, alcohol and tramadol were 0.21 mg/l, 1.29 g/kg and 38.3 mg/l, respectively. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Alprazolam (Xanax) is a triazolobenzodiazepine derivative (Fig. 1a), mainly used as an anxiolytic and antidepressant, but also efficient in the treatment of agoraphobia, panic attacks and panic disorders. Daily doses of 0.75–4 mg are effective for generalized anxiety, while daily doses of 6–9 mg have been used for phobic and panic disorders. Side effects include drowsiness, confusion, hypotension, tachycardia, palpitations and nightmares. Therapeutic plasma levels of alprazolam range from 0.005 to 0.05 mg/l, toxic concentrations range between 0.1 and 0.4 mg/l [1]. Few overdoses were described with blood concentrations ranging from 0.12 to 0.39 mg/l [2]. The highest reported postmortem blood concentration of alprazolam was 2.1 mg/l [3].

Alprazolam is metabolized by oxidation and conjugation. The principal metabolites are α -hydroxyalprazolam, 4-hydroxyalprazolam and α ,4-dihydroxyalprazolam. Both

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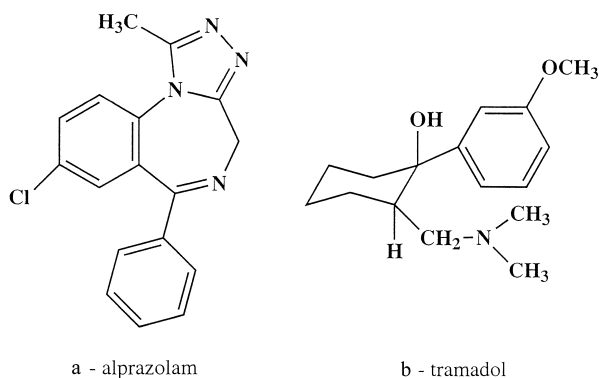


Fig. 1. Molecular structures of alprazolam and tramadol.

metabolites are pharmacologically active with approximately 66 and 19% the potency of parent drug, respectively.

Tramadol (Tramal) is a centrally acting analgesic used for the treatment of moderate to severe pains (Fig. 1b) with a low affinity for opioid receptors. It binds to the μ -opioid receptors and inhibits serotonin and norepinephrine reuptake, making a significant contribution to the analgesic action by blocking nociceptive impulses at the spinal level [4]. Tramadol is metabolized to an active desmethyl derivative (*O*-desmethyltramadol) and several inactive compounds. *O*-desmethyltramadol shows higher affinity for the μ -opioid receptors and has twice the analgesic potency of the parent drug.

Side effects include seizures and respiratory depression. Usual therapeutic doses are 50 mg orally, 50–100 mg by injection and 100 mg rectally. Total daily dose does not exceed 400 mg. Therapeutic blood levels in adults range from 0.1 to 0.3 mg/l [5]. Several drug-combined fatalities including tramadol have been described (concentration of tramadol ranging from 0.03 to 22.59 mg/l) [6]. No death was attributed only to tramadol intoxication until now, except in one case concerning a 6-month-child with blood concentration of tramadol of 2 mg/l [1].

2. Case history

A 30-year-old woman, with history of depression, was found dead in her residence. Several packages of Tramal (four empty bottles of 10 ml each containing 100 mg of tramadol for oral administration) and Xanax as well as an empty bottle of wine were found in the kitchen. At autopsy, except for a slight decomposition and a diffuse visceral congestion, neither morphological changes nor evidence of violence were noticed. Femoral blood, liver, bile and gastric contents were sampled for toxicological analysis. In our case, only 1 ml of urine was found and collected which has been used up in preliminary tests.

Table 1
Tissue distribution of tramadol, alprazolam and α -hydroxyalprazolam in the present case

Specimen	Tramadol	Alprazolam	α -hydroxyalprazolam
Peripheral blood	38.3 mg/l	0.21 mg/l	non-detected
Bile	44.0 mg/l	0.27 mg/l	0.12 mg/l
Liver	27.6 mg/kg	0.23 mg/kg	<0.005 mg/l
Gastric contents (100 ml)	130 mg	2.73 mg	non-detected

3. Toxicological analysis and results

Preliminary tests (immunoassays and colour tests) indicated the presence of benzodiazepines and cannabinoids in urine. Tramadol, *N*-desmethyltramadol, *O*-desmethyltramadol, alprazolam and cotinine were detected in the blood by gas chromatography–mass spectrometry (GC–MS) screening after acid or basic extraction and acetylation [7,8]. In gastric contents, tramadol, alprazolam and cotinine were detected.

An amount of 130 mg and concentrations of 38.3 mg/l, 44.0 mg/l and 27.6 mg/kg of tramadol were measured by gas chromatography–nitrogen-phosphorus detector (GC–NPD) in the gastric contents and peripheral blood, bile and liver, respectively after basic liquid–liquid extraction with chloroform–isopropanol (9:1, v/v). Benzodiazepine quantification by gas chromatography–electron capture detector (GC–ECD) using a procedure based on that described by Ulrich and Sager [9] indicated that 0.21 mg/l of alprazolam was present in the blood (Table 1). Quantification of α -hydroxyalprazolam was also performed by GC–ECD.

Further analysis performed by GC–MS after solid-phase extraction and methylation with iodomethane indicated that 17 ng/ml of 11-nor-tetrahydrocannabinol (11-carboxy-THC) was present in the blood. Finally, the presence of ethanol (1.29 g/kg) and 1-propanol were indicated by gas chromatography–flame ionization detector (GC–FID) analysis [10].

4. Discussions and conclusions

Only a few overdoses due to alprazolam alone have been reported until now with postmortem blood concentrations ranging from 0.12 to 0.39 mg/l [2]. McCormick et al. [11] presented two patients who attempted suicide with alprazolam by ingestion of 20–30 1-mg tablets and 60 1-mg tablets, respectively. These patients had markedly elevated serum concentrations, ten times greater than therapeutic doses, in the ranges of 0.25–0.55 mg/l and 0.20–0.30 mg/l, without significant alterations in vital signs or CNS depression.

The highest postmortem blood concentration of alprazolam described in the literature was 2.1 mg/l [3]. In our case, α -hydroxyalprazolam was not detected in the blood. The concentration of alprazolam in liver was 9.2 mg/kg (α -hydroxyalprazolam concentration

was 0.83 mg/kg), in bile it was 2.8 mg/l (1.3 mg/l of α -hydroxyalprazolam) and in the stomach contents only alprazolam was detected with a concentration of 13 mg in 110 ml.

Unlike several alprazolam associated fatalities, no fatal overdoses in adults with tramadol alone have been reported until now. Several fatalities including tramadol were described. Georinger et al. [6] reported 12 cases of tramadol-related deaths and four non-fatal intoxications involving tramadol. They revealed tramadol concentrations ranging from 0.03 to 22.59 mg/l. Three deaths were due to acute morphine toxicity, one was a doxepin overdose and six were multiple drug overdoses. The highest tramadol blood concentration (22.59 mg/l) was found in combined drug-intoxication (propranolol 3.9 mg/l, desipramine 1.00 mg/l and trazodone 3.70 mg/l).

Levine et al. [12] analysed tramadol distribution in four postmortem cases (none of them were attributed to tramadol intoxication) with heart blood concentrations ranging from 0.17 to 4.4. mg/l. Their results indicated concentrations in urine ten times greater than tramadol concentrations in blood and tissue specimens. The concentration of tramadol in the liver and kidneys, in relation to blood, failed to suggest sequestration of the drug in the analysed specimens.

In the present case, alprazolam blood concentration was 0.21 mg/l, which is above the usual therapeutic plasma levels (0.005–0.05 mg/l). Concentrations ranging from 0.12 to 0.39 mg/l were described in a few cases of suicidal overdoses [2] but, on the other hand, two patients with serum concentrations of 0.25–0.55 and 0.20–0.30 mg/l reported by McCormick et al. [11] did not demonstrate significant alterations in vital signs or CNS depression.

In our case, the tramadol blood concentration was 38.3 mg/l and exceeded at least 100-times the normal therapeutic range of 0.1–0.3 mg/l. The tissue concentrations measured seem to be compatible with the dose ingested and the tissue distribution is of the same order of magnitude as mentioned in the literature [12].

As concluded in other published report [6], this case illustrates that an overdose of tramadol can cause death especially when taken in combination with other CNS depressants such as alprazolam and ethanol. Moreover, the concentration of tramadol in the victim's blood was higher than the concentrations reported up to now. Nevertheless we can not ascribe the death only to tramadol because of high level of ethanol and alprazolam.

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