Online publication ahead of print, AJMHS Vol 70, 2026

Drowning under the Influence of Flunitrazepam and Ethanol, an Autopsy Case

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Abstract

An autopsy case of drowning involving flunitrazepam and ethanol is presented. Quantitative toxicological analysis of femoral venous blood revealed flunitrazepam and 7-aminoflunitrazepam concentrations of 0.013 μg/mL and 0.192 μg/mL, respectively, along with ethanol at 2.39 mg/mL. Findings of drowning were confirmed by the autopsy and subsequent examination. We concluded that the cause of death was drowning under the influence of flunitrazepam and ethanol.

Keywords: flunitrazepam; ethanol; drug interaction; drowning

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INTRODUCTION

Flunitrazepam, an N-methyl-2'-fluoro analogue of nitrazepam, is prescribed for the treatment of insomnia (1). As a benzodiazepine, this drug acts as a central nervous system depressant (2). Fatalities in cases with ingestion of ethanol have been reported (2-4), as the pharmacological effects of flunitrazepam are potentiated in combination with ethanol (2,5,6). Here, we report a fatal case of drowning under the influence of flunitrazepam and ethanol.

CASE REPORT

A Japanese woman in her fifties (height, 150 cm; weight, 45 kg) was found dead in the sea. She had been prescribed flunitrazepam for the treatment of insomnia. Autopsy findings indicated slight contusions on the limbs and forehead, but these were not considered contributory to the cause of death. Her heart weighed 260 g and contained 130 mL of dark-red blood with coagula. Her brain weighed 1372 g and showed neither pathological findings nor injuries. The left and right lungs weighed 444 g and 496 g, respectively, and were edematous. Pleural effusions were observed in the left (110 mL) and right (100 mL) pleural cavities. The stomach contained 250 mL of a blue-green, muddy substance with a moderate amount of foodstuff. Internal examination revealed no diseases. White, frothy fluid was observed in the trachea and bronchi. Except for congestion, no notable changes were evident in other organs. Drug screening conducted using the IVeX-screenTM panel (Bio Design, Tokyo, Japan) yielded no positive results. Postmortem samples of blood, urine, bile and cerebrospinal fluid (CSF) were collected for toxicological investigations.

Toxicological analysis was performed using liquid chromatography tandem mass spectrometry [7]. In brief, liquid chromatography separations were carried out using EkspertTM UltraLC 100-XL (Sciex, Framingham, MA, USA). An L-column2 ODS (1.5 mm × 150 mm, 5.0-µm particle size; Chemicals Evaluation and Research Institutes, Tokyo, Japan) was used with the mobile phase comprising solvent A (5% methanol containing 10 mM ammonium formate) and solvent B (95% methanol containing 10 mM ammonium formate) with a flow rate of 0.1 mL/min. A QTrap® 4500 tandem mass spectrometer (Sciex) was used to obtain the mass spectra. Quantification of ethanol was performed using headspace gas chromatography.

RESULTS AND DISCUSSION

Benzodiazepines are one of the most common pharmacological contributors to drowning (8), and the combination of ethanol and drugs, including benzodiazepines, is also a significant risk factor in cases of drowning (9). In the present case, slight injuries were observed but were not considered contributory to the cause of death. Characteristic findings of drowning such as morphological findings in the lungs, pleural effusion and foam in the trachea were evident from autopsy.

Flunitrazepam, caffeine and metabolites of those substances were identified from toxicological analyses. Table 1 shows the concentrations of these substances in postmortem samples, along with currently accepted lethal, toxic and therapeutic ranges (10). Desmethyl-flunitrazepam, 7-aminoflunitrazepam and 3-hydroxyflunitrazepam are all metabolites of flunitrazepam (11). Since the standard substance of 3-hydroxyflunitrazepam was unavailable, only qualitative analysis was performed. Relatively high concentrations of ethanol were also detected in blood (2.39 mg/mL) and urine (2.81 mg/mL) samples. Due to the rapid metabolism of flunitrazepam and postmortem bioconversion, 7-aminoflunitrazepam represents an important marker of flunitrazepam ingestion (4). A relatively high concentration of ethanol was detected in the present case, and the 7-aminoflunitrazepam concentration was also relatively high. The combined use of ethanol and flunitrazepam was considered to have resulted in impaired psychomotor performance, decision making, hazard perception and an inability to take sufficient risk-avoidance actions. Potentiation of the pharmacological effects of flunitrazepam when combined with ethanol is attributed to increased intake as a result of interactions during gastrointestinal absorption, based on a finding from a recent study (12).

As desmethyl-flunitrazepam is known to have pharmacological activity (11), we have to take into its pharmacokinetics. In the present case, desmethyl-flunitrazepam was not detected in blood, so the pharmacological role in the present case was considered minimal.

The IVeX-screenTM panel yielded negative results at autopsy. This may be due to the 7-aminoflunitrazepam concentration in urine (0.161 μg/mL) being below the limit of detection (>100 μg/mL) for this panel (13).

In the present case, postmortem blood concentrations of caffeine and theophylline, a metabolite of caffeine, were below the therapeutic ranges, and were thought to have been derived from earlies intake of beverages such as tea or coffee. These substances were considered relatively unlikely to have contributed to her death.

We estimated the total amount of ingestion in this case using toxicokinetic factors (1). Using the distribution volume (flunitrazepam: Vd = 0.4–0.8 L/kg; ethanol: Vd = 0.43-0.59 L/kg), body weight of the victim, and the level of flunitrazepam and ethanol in femoral blood, we estimated that the woman had ingested at least 29.3 mg of flunitrazepam and at least 46.2 g of ethanol.

Based on the autopsy findings, the results of toxicological examinations and the subsequent investigation by the authorities, we concluded that the cause of death was drowning under the influence of flunitrazepam with ethanol.

Table 1. Concentrations of each drug and metabolite in postmortem samples

	venous blood	left heart blood	right heart blood	portal blood	urine	bile	CSF	therapeutic range *	toxic range	lethal range *
flunitrazepam	0.013	0.017	0.013	0.005	0.003	0.007	0.004	0.005-0.015	0.05	0.11-0.74
7-aminoflunitrazepam	0.192	0.233	0.168	0.356	0.161	1.785	0.061	-	-	
3-hydroxy flunitrazepam	N.D.	N.D.	N.D.	N.D.	+	+	N.D.	-	-	-
desmethylflunitrazepam	N.D.	N.D.	N.D.	N.D.	0.007	0.030	N.D.	-	-	-
caffeine	1.003	1.141	0.930	0.961	1.418	1.788	1.060	2-10	15-20	80-180
theophylline	0.309	0.340	0.290	0.304	0.044	0.553	0.233	5-20	20	50

* Therapeutic and lethal ranges are cited from the reference [10].

- : no data, + : detected, N.D. : not detected

Acknowledgement: None declared.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

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