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Case Report

An Autopsy Case of Drowning Under the Influence of Etizolam: A Case Report

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ABSTRACT

A fatal case of drowning under the influence of etizolam is presented. Quantitative toxicological analysis revealed etizolam concentrations of 0.50 µg/mL and 0.068 µg/mL in femoral venous blood and urine, respectively. According to the autopsy findings, the results of toxicological examinations, and the investigation by the authorities, it is concluded that the cause of death is drowning under the influence of etizolam.

1. Introduction

Benzodiazepines are prescribed as hypnotics worldwide. Etizolam, a thienotriazolodiazepine derivative, has been used as a sedative-hypnotic drug [1]. Benzodiazepines are one of the most common causes of drowning due to their impairment of psychomotor functions [2]. This report is a case of drowning under the influence of etizolam.

2. Case Presentation

Foreign findings

The body of a 70-year-old Japanese woman (height, 153 cm; weight, 49 kg) was found on the coast near her house. The deceased had her clothes on, with a few long sleeve shirts layered, and a pair of pants and socks. No visible damage was found on the clothes. The subsequent investigation by the authorities revealed that the deceased had been prescribed drugs to treat neurosis. Several empty packets of etizolam were found in her

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room. A medico-legal autopsy revealed slight external injuries to her face. In detail, abrasions were observed on the forehead and right cheek, and bruises were found on the bilateral temporal region.

Domestic findings

Bruises had a slight subcutaneous hemorrhage. The weight of the heart was 284 g and contained 140 mL of non-coagulated blood. The weight of the brain was 1200 g and was slightly atrophic. The left and right lungs weighed 505 g and 581 g, respectively, and appeared edematous with ballooning. Effusions were observed in the left and right pleural cavities of 40 mL and 100 mL, respectively. The stomach contained a grayish-white liquid (120 mL) containing foodstuffs. The trachea contained white, frothy fluid (Figure 1). Internal examination of other organs revealed no disease or injuries.

Biological and toxicological examination

Postmortem femoral blood, urine, and stomach content samples were used for biological and toxicological investigations. Lungs, liver, and kidneys were collected for the diatom test. Femoral blood was tested for C-reactive protein (CRP) concentration and hemoglobin A1c (HbA1c) level. Urine was used for drug screening tests using IVeX-Screen M-1® panel (Bio Design, Tokyo, Japan).

All samples were used for toxicological analysis. Toxicological analysis was performed by liquid chromatography-tandem mass spectrometry [3]. Briefly, liquid chromatography separations were carried out using EkspertTM UltraLC 100-XL (Eksigent part of AB 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 a 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 (AB Sciex) was used to obtain the mass spectra.

For femoral blood and urine, quantification of ethanol was performed using headspace gas chromatography.

3. Results

In the present case, bruises had subcutaneous hemorrhages, indicating that they were formed antemortem. The degree of the hemorrhage was slight, and no internal findings were related to the injuries except for subcutaneous hemorrhage, therefore, it was decided that the injuries were unrelated to the cause of death. The injuries were presumed to be due to mild or abrasive force, with tumbling at the shore as a possibility.

C-reactive protein (CRP) concentration in the blood was below 0.1 mg/mL, and HbA1c level was 5.1%, both within the normal range.

The diatom test yielded positive results for the lungs, liver, and kidneys. Drug screening test yielded negative results (Figure 2). Toxicological analysis identified etizolam and acetaminophen in each sample. Table 1 presents the concentrations of these substances in postmortem samples, along with currently established lethal, toxic, and therapeutic levels [4]. Ethanol was not detected in any postmortem samples.

4. Discussion

The concentration of etizolam in blood was within the lethal range [4], but the concentration in urine was much lower. This is likely because etizolam is mainly metabolized by the liver and is almost eliminated via non-renal pathways, with urinary excretion of etizolam representing less than 0.3% of the dose [5]. The immunochromatographic drug screening test using a urine sample failed to detect etizolam in the present case, probably due to the low level of urinary excretion.

Psychotropic drugs, including etizolam, is vital in drowning [2]. Etizolam is a thienotriazolodiazepine derivative that is prescribed in various Asian and European countries [5]. Absorption of etizolam following ingestion is rapid, its maximum concentration is reached within 0.5–2 hours for ordinary use [5]. Etizolam has anticonvulsive properties, attenuates conflict behaviors, and has muscle relaxant effects [1]. due to

Table 1. Concentrations of Etizolam and Acetaminophen in the tested samples (µg/mL).

Specimen	Femoral Venous Blood	Urine	Stomach Contents	Therapeutic Range*	Toxic Range*	Lethal Range*
Acetaminophen	0.762	20.617	2.167	5-25	100-150	200-300
Etizolam	0.500	0.068	4.275	0.008-0.018	0.03	0.26

*Therapeutic, toxic, and lethal ranges are cited from the reference [4].

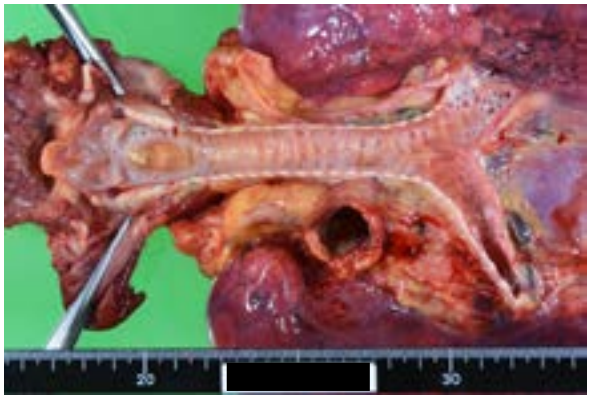

Figure 1. Frothy fluid contained in the trachea, for personal information protection, the numbers are concealed.

these pharmacological properties, the drug represents a risk factor for drowning via the resultant impairment of psychomotor functions [2]. Postmortem blood concentrations of etizolam in the present case were beyond the therapeutic range, therefore etizolam consumption may impair psychomotor performance by affecting cognitive function, coordination and balance. Since the blood concentration of acetaminophen was within therapeutic levels, that drug was considered less likely to have contributed to her death.

The total dose of Etizolam ingested by the victim was estimated using toxicokinetic factors [1, 5]. The calculated amount of etizolam using distribution volume (Vd: 0.7–1.1 L/kg), the victim's body weight, and femoral blood levels were within the range of 17.2–26.9 mg. Given the dose left in the stomach (0.53 mg), it was estimated that she had consumed at least 17.7 mg of etizolam.

5. Conclusion

Based on the autopsy findings, the results of toxicological examinations, and the investigations by the authorities, it is concluded that the cause of death in the reported case was drowning under the influence of etizolam.

Figure 2. IVeX-screen panel yielding negative results, including Benzodiazepine (BZD), for personal information protection, the numbers are concealed.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Kagawa University Faculty of Medicine (Code: Heisei22-030).

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Authors' contributions

Conducting the autopsy of this written case: Hiroshi Kinoshita, Tadayoshi Yamashita, and Sachiko Kawahara; Performing the examinations during autopsy, including the drug screening tests: Mostofa Jamal and Etsuko Tanaka; Conducting toxicological analysis by liquid chromatography tandem mass spectrometry: Etsuko Tanaka and Hiroko Abe; Contributing to the interpretation of the results: Shoji Kimura and Mitsuru Kumihashi; Drafting and revising the original manuscript: Sella Takei and Hiroshi Kinoshita. All authors contributed to creating the manuscript from the draft to the final text. All authors have approved the manuscript for publication and agree to be accountable for all aspects of the work.

Conflict of interest

The authors declared no conflict of interest regarding the publication of this paper.

References

[1] Baselt RC. Disposition of toxic drugs and chemicals in man. Seal Beach: Biomedical Publications; 2008. [Link]

[2] Ahlm K, Saveman BI, Björnstig U. Drowning deaths in Sweden with emphasis on the presence of alcohol and drugs - a retrospective study, 1992-2009. BMC Public Health. 2013; 13:216. [DOI:10.1186/1471-2458-13-216] [PMID] [PMCID]

[3] Kinoshita H, Tanaka N, Takakura A, Kumihashi M, Jamal M, Ito A, et al. Flunitrazepam in stomach contents may be a good indicator of its massive ingestion. Romanian Journal of Legal Medicine. 2017; 25(2):193-5. [DOI:10.4323/rjlm.2017.193]

[4] Schulz M, Schmoldt A, Andresen-Streichert H, Iwersen-Bergmann S. Revisited: Therapeutic and toxic blood concentrations of more than 1100 drugs and other xenobiotics. Critical Care. 2020; 24(1):195. [DOI:10.1186/s13054-020-02915-5] [PMID] [PMCID]

[5] Fracasso C, Confalonieri S, Garattini S, Caccia S. Single and multiple dose pharmacokinetics of etizolam in healthy subjects. European Journal of Clinical Pharmacology. 1991; 40:181-5. [DOI:10.1007/BF00280074] [PMID]