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Risk for Aspiration of Foods by Benzodiazepine with Ethanol: An Autopsy Case

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Abstract

A fatal case involving hypnotics with ethanol is presented. Quantitative toxicological analysis revealed that the concentrations of etizolam, bromazepam and ethanol in the femoral blood sample were 0.079 μg/mL, 0.164 μg/mL and 151 mg/dL, respectively. Relatively high concentration of etizolam (14.8 μg/mL) and bromazepam (18.7 μg/mL) were detected from the stomach contents, which meant that 3.4 mg of etizolam and 4.3mg of bromazepam remained in the stomach. Autopsy revealed impact of foodstuffs in pharynx and bronchus. Ethanol decreases the lower esophageal sphincter pressure. And co-ingestion of psychotropic drugs may reinforce the suppression of the CNS function. We concluded that the cause of death was due to aspiration of foodstuffs under the drug intake with ethanol. Ethanol with drug intake have a synergistic effect and it may induce aspiration of food.

Keywords: etizolam, bromazepam, massive ingestion, ethanol, forensic toxicology

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INTRODUCTION

Etizolam is a thienotriazolodiazepine derivative, similar chemical structure to brotizolam, which is used as a sedative-hypnotic drug (1,2). It is often abused and observed in combined use with ethanol or other drugs (3-6). Bromazepam is a benzodiazepine derivative, used as an antianxiety agent (1). Although optimal doses of etizolam or bromazepam are generally considered quite safe, however, fatalities have been reported in case of multiple drug use or use with ethanol (2-9).

Here we report a fatal case of etizolam and bromazepam with a combined use of ethanol, and discuss the usefulness of detailed examination by the autopsy for preventive measures.

CASE PRESENTATION AND AUTOPSY FINDINGS

A Japanese female in her thirties (height, 166cm; weight, 47 kg) was found dead in a sitting position at her house. Subsequent investigations by the authorities showed that the victim was seen quite drunk, and she was taking medication for depression, and a few dozens of empty packets of antidepressants were found at home. Autopsy findings indicated slight contusion of the lower limb, but these were not considered contributory to the cause of her death. Internal examination revealed impact of foodstuffs in pharynx and bronchus (Fig. 1 A, B). The heart weighed 254 g and contained 140 mL of blood without coagulum. The brain weighed 1289 g and was slightly edematous. The left and right lungs weighed 761 g and 928 g, respectively, and were edematous with severe congestion. The stomach contained a dark brownish fluid (230 mL) with foodstuffs. Signs of congestion were notable in other organs. A drug screening test of urine using a TriageTM (Biosite Diagnostic Inc, San Diego, CA) panel was negative. Postmortem blood (femoral vein and portal vein), bile and stomach contents samples were collected for toxicological investigation.

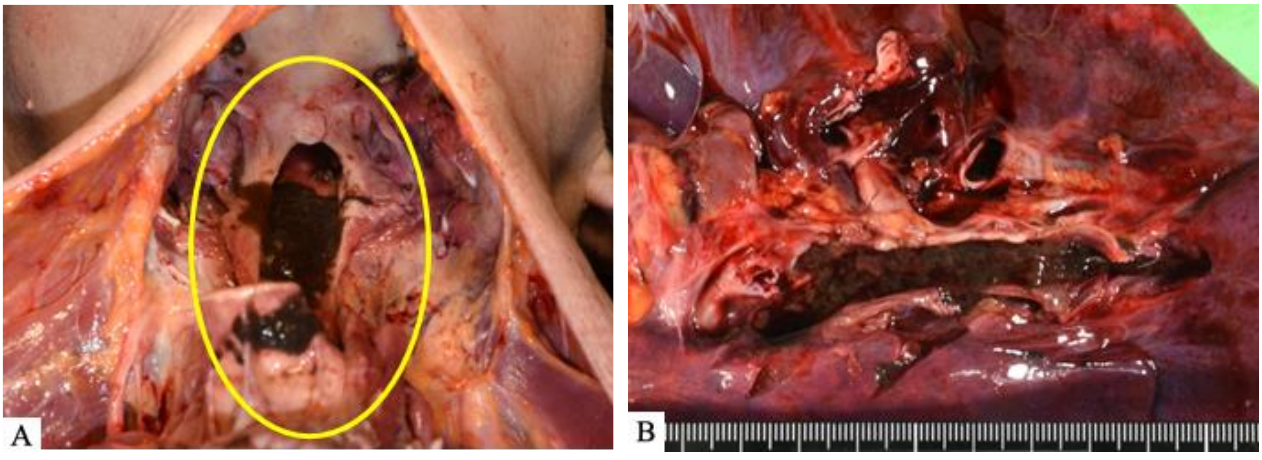

Figure 1 A, B. Autopsy findings of the respiratory tract. A. Foodstuffs in pharynx, and B. Foodstuffs in the bronchus

Toxicological analysis using liquid chromatography tandem mass spectrometry (LC-MS/MS) was performed according to the previous report (10). In brief, the liquid chromatography separations were carried out using ekspertTM ultraLC 100-XL (Eksigent part of 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 of 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, Framingham, MA, USA) was used to obtain the mass spectra. Quantitation of ethanol was performed using headspace gas chromatography.

RESULTS AND DISCUSSION

The cardiac blood containing no coagulation and the congested organs indicated an acute death. From this, together with the contents in the respiratory tract and the highly congested and edematous lungs, the direct cause of her death was diagnosed as an asphyxia due to the impact of foodstuffs in pharynx and bronchus. Etizolam and bromazepam were identified by the toxicological examination. Table 1 shows the quantification for each drug in the victim's postmortem samples, along with the currently established lethal and therapeutic, toxic, and lethal levels (11). Ethanol was also detected from postmortem samples (151 mg/dL in blood and 217 mg/dL in urine, respectively), which indicated that she was at a moderately intoxicated status. The urine/blood ratio of ethanol concentration (urine/blood ratio = 1.44 > 1) (12) suggested that time has passed since she started drinking. Both etizolam and bromazepam remaining in the stomach contents, indicated that her death occurred in a relatively short time following drug ingestion. The drug concentrations in portal venous blood were higher than those in femoral venous blood. This would also support that she died at the absorption phase of these drugs.

Table 1. Concentrations found for each drug in the postmortem samples (µg/mL)

specimen	Femoral venous blood	Portal venous blood	Bile	Stomach contents	Therapeutic range *	Toxic range *	Lethal range *
etizolam	0.079	0.174	0.569	14.802	0.008-0.02	0.038	0.264
bromazepam	0.164	0.563	1.319	18.739	0.05-0.2	0.3-0.4	1-2

* Therapeutic, toxic, and lethal ranges are cited from the reference (11).

Although bromazepam concentration in femoral blood was within the therapeutic range, etizolam concentration was over 0.02 μg/mL (11), thus the blood levels of etizolam at the time of death should have been within the toxic range. A relatively large amount of unabsorbed etizolam (3.4 mg) remained in the stomach. We estimated that 2.6-4.0 mg of etizolam had already been absorbed, based on the pharmacokinetic parameters (1).

Aspiration of vomitus occurs in a patient with a decreased level of consciousness, and it has been reported that aspiration is observed in 29-50% of drug overdose cases (13). Ethanol reduces LES pressure (14,15), and it induces gastroesophageal reflux not only at high concentrations, but also at low concentrations (16,17). Furthermore, etizolam has a muscle relaxant effect, in addition to sedative effects (2). As a results of these pharmacological properties, we believe that the victim choked on the foodstuffs, caused by gastric reflux under the strong sedation by the combined use of ethanol and benzodiazepines. Combined use of ethanol and benzodiazepines are reported to cause fatal outcome (18), though it is often focused on the excessive sedative effects (19). However, we should reconsider the pharmacological effects and the risk of foodstuff aspiration. Based on the autopsy findings and the results of toxicological examination, we concluded the cause of death was due to aspiration of foodstuffs which was induced by co-ingestion of etizolam and brotizolam combined with ethanol.

Only a small number of data regarding the usefulness of portal venous blood sampling during autopsy are reported (10,20), and its usefulness has not been conclusive. The present case indicates the usefulness of sampling and quantification of drug concentration in the portal venous blood.

Conflicts of interest

The authors declare there are no conflicts of interest regarding the publication of this paper.

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Ethical approval

The use of the samples collected on autopsy and report on this autopsy case were approved by the Research Ethics Committee of Kagawa University Faculty of Medicine.

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