A case of drowning whilst under the influence of brotizolam, flunitrazepam and ethanol

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SUMMARY
A case of drowning involving brotizolam, flunitrazepam and ethanol ingestion was presented. Quantitative toxicological analysis showed that the concentrations of brotizolam, 7-aminoflunitrazepam (a metabolite of flunitrazepam) and ethanol in the femoral blood were 0.025μg/ml, 0.094μg/ml and 0.29mg/ml, respectively, and these drugs were also detected in the stomach contents. We concluded that the cause of death was drowning whilst under the influence of combined use of brotizolam, flunitrazepam and ethanol.

Key words: brotizolam – flunitrazepam – ethanol – drowning

Případ utopení pod vlivem brotizolamu, flunitrazepamu a etanolu

SOUHRN
Je prezentován případ utopení po požití brotizolamu, flunitrazepamu a etanolu. Kvantitativní toxikologická analýza ukázala, že koncentrace v krvi ze stehenní žíly u brotizolamu byla 0,025 μg/ml, 7-aminoflunitrazepamu (metabolit flunitrazepamu) 0,094 μg/ml a etanolu 0,29 mg/ml. Tyto látky byly detekovány v obsahu žaludku.
Lze usuzovat, že v daném případě bylo příčinou smrti utopení, způsobené vlivem kombinovaného užití brotizolamu, flunitrazepamu a etanolu.

Klíčová slova: brotizolam – flunitrazepam – ethanol – utopení

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Benzodiazepines are commonly detected in many medico-legal autopsy cases (6). They are widely used as sedative and/or hypnotic agents, since they are characterized as having a wide therapeutic index with a low risk of serious adverse reactions and toxicity (5). Proper evaluation of the psychomotor performance under the influence of benzodiazepine by itself or combined with ethanol ingestion is one of the problems in the fields of forensic practice. Here we report on a case of drowning whilst under the influence of brotizolam, a triazolothienodiazepine derivative (2), flunitrazepam, a N-methyl-2′-fluoro analogue of nitrazepam (3,4) and ethanol.

CASE HISTORY

A 75-year-old woman (height 141cm, weight 54.5kg) was found submerged in the bathtub of her house. She had been prescribed hypnotics. Autopsy findings indicated no evidence of external injury. The left lung weighed 318g and the right 421g, showed edematous, with approximately 70ml and 120ml of red-tinged effusion in the left and right pleural space, respectively. There was filled with frothy fluid in the trachea and bronchi. Histologically, the lung showed dilation of the alveoli with elongation of septa. No findings such as myocardial infarction or myocarditis were observed. The stomach contained 50ml of a brownish fluid with granules. Drug screening testing using a Triage™ (Biosite Diagnostic Inc, San Diego, USA) panel was negative. Postmortem samples including femoral blood and stomach contents were collected for toxicological examination and kept at -20°C until analysis.

MATERIALS AND METHODS

Toxicological analysis was performed using a GC-MS system (QP-2010 Plus, Shimadzu, Kyoto, Japan). Identification and quantification of each drug was performed by the slightly modified method of the previous report (8). Quantitation of ethanol was performed using head-space gas-chromatography.

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Table 1. Brotizolam and 7-aminoflunitrazepam concentrations in the sample, and their therapeutic and fatal levels.

Specimen	brotizolam (μg/ml)	7-aminoflunitrazepam (μg/ml)
Femoral venous blood	0.025	0.094
Stomach contents	1.51 (75.5 μg)*	58.6 (2.93mg)*
Therapeutic range	0.001-0.02 (13)	0.005-0.015 (13)
Fatal range	0.01 (12)***	> 0.16 (5)**

* Each figure in parentheses represents the total amount of drug in the stomach.
** Combined total levels of flunitrazepam and 7-aminoflunitrazepam.
*** Case report; combination of six drugs and alcohol poisoning.

RESULTS AND DISCUSSION

Toxicological analysis identified brotizolam and 7-aminoflunitrazepam, a metabolite of flunitrazepam. Table 1 shows the quantitation of brotoizolam and 7-aminoflunitrazepam in the victim's blood and stomach contents and also summarizes their therapeutic and fatal levels (5,12,13). The 0.29 mg/ml of ethanol was detected in the blood. Although 7-aminoflunitrazepam was identified, no flunitrazepam was detected in any sample. This may have been due to postmortem bioconversion of flunitrazepam to 7-aminoflunitrazepam (11), and therefore the presence of 7-aminoflunitrazepam was an important marker of flunitrazepam usage (4,7). The victim's femoral blood concentrations of brotizolam and 7-aminoflunitrazepam were 0.025 and 0.094 μg/ml respectively. The estimated antemortem blood concentration of flunitrazepam was 0.10 μg/ml, calculated from 7-aminoflunitrazepam data in the femoral blood. These concentrations were within toxic levels, but not fatal levels (5,13). The negative result of Triage™ test may be due to the low sensitivity for thienodiazepine (brotizolam) (9) and 7-aminoflunitrazepam (10).

Flunitrazepam is a central nervous system depressant that may cause drowsiness, hangover, fatigue, dizziness and ataxia (1), and additive effects may occur when other central nervous system depressant such as brotizolam or ethanol are co-administered (1). In the present case, flunitrazepam, brotizolam and ethanol were detected concurrently in the blood. Therefore, additive psychomotor impairment would have occurred, and would have led to loss of consciousness. From the autopsy findings and the results of the toxicological examination, we concluded that death was due to the drowning whilst under the influence of brotizolam, flunitrazepam and ethanol intoxication. The present case indicates that we should consider the effects of drugs on psychomotor performance in case of drowning.

The peak concentration of flunitrazepam is reached three hours following the administration of recommended dose (14). In this case, it was apparent that the victim died during the absorption phase following oral ingestion, based on the detection of the quite high concentrations and large amounts of drugs in the stomach. By using forensic toxicokinetic factors, we have also estimated the victim's total amounts of ingestion of brotizolam and flunitrazepam. Using values of the distribution volume (Vd) for brotizolam (0.4-0.8 l/kg) and for flunitrazepam (3.4-5.5 l/kg) (2,3), the victim's body weight and femoral blood levels, the calculated amounts of brotizolam and flunitrazepam were 0.55-1.1mg and 18.5-30.0 mg, respectively. The total ingested dose of each drug is the sum of the above value and the dose left in the stomach. We therefore estimated that she had ingested at least 0.62 mg of brotizolam and 21.4 mg of flunitrazepam.

CONCLUSION

The cause of her death was drowning whilst under the influence of brotizolam, flunitrazepam and ethanol, and it is estimated that she died within three hours following ingestion of at least 0.62 mg of brotizolam and 21.4 mg of flunitrazepam.

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