Case Report

A Case of Homicidal Poisoning Involving Several Drugs

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Abstract

Accidental or suicidal poisonings due to benzodiazepines have been previously reported. A case of fatal, homicidal poisoning with benzodiazepines, antipyretic analgesics (anti-inflammatory drugs), and beer is described here. In this homicidal poisoning, the drugs and beer were given to the decedent by his wife. Autopsy findings showed no clinically significant macroscopic findings except for slight postmortem change. Capillary gas chromatography coupled to mass spectrometry was employed to quantitate the drugs in biological fluids and stomach contents. Six drugs (brotizolam, triazolam, ibuprofen, dihydrocodeine, phenylpropanolamine, and chlorpheniramine) were identified and quantitated in blood, urine, and stomach contents. Although each drug was present in a very small quantity, the cause of death was determined to be the combination of these drugs and alcohol poisoning.

Introduction

Benzodiazepines are among the most widely prescribed hypnotic drugs in the world. Benzodiazepine overdoses usually induce mild to moderate central nervous system (CNS) depression and often death. The severity of the CNS depression or lethality is influenced by dose, age, personal health before ingestion, and by concomitant ingestion of other CNS depressants, including ethyl alcohol.

Many cases of lethal intoxication due to oral ingestion of benzodiazepine, which include overdoses or the co-ingestion of other CNS depressants, have been reported; one such well-known depressant is triazolam.

The present report describes the postmortem toxicological findings in a homicidal poisoning resulting from the ingestion of brotizolam (Lendormin®, Boehringer Ingelheim, Hyogo, Japan), triazolam (Halcion®, Pharmacia & Upjohn, Tokyo, Japan), antipyretic analgesics (Benza® block, Takeda Chemical Industrials, Osaka, Japan), and beer.

Brotizolam and triazolam are triazolothieno-diazepine and benzodiazepine hypnotic drugs with a triazolo structure (Figures 1 and 2), which have been shown in insomniac patients to exhibit a rapid onset of action, short elimination half-life (3.6–7.9 h and 2.4–5 h, respectively) and few associated side effects (1–4). There are differences in efficacy and tolerance (5). Unlike triazolam, deaths as the result of brotizolam overdose alone or in combination with other drugs have not been reported.

Case History

A 42-year-old man was found dead in a vacant lot. On the ground, near his abdomen, was a pair of shoes. An empty bottle of Benza block (ibuprofen/phenylpropanolamine hydrochloride/dihydrocodeine phosphate/chlorpheniramine maleate; dose per nine tablets, 450 mg/75 mg/24 mg/7.5 mg) was found in his breast pocket. Moderate signs of postmortem decomposition were present. According to the police report, the body was not found for 12 h. The police were suspicious that the abandoned corpse was not found earlier.

The autopsy was performed on the same day. At autopsy, postmortem bluish red and bright-red hypostasis on his back and front, which was the result of moving of the body, were found. No clinically significant macroscopic or microscopic lesions were found in the various organs examined except for visceral congestion. The cause of death was not due to cold temperatures. Postmortem blood, urine, and gastric contents were sampled and stored using plastic vials at -20°C in the dark until toxicological analyses.

Several days later, the police brought the man's wife to the station for further questioning. Subsequent investigation revealed that his wife had committed homicidal poisoning of her husband by having him ingest hypnotic drugs (Halcion and Lendormin). According to the confession of his wife, he had a slight cold. On a winter night, the man took a can of beer and antipyretic analgesics (Benza block) (amount unknown) to his car. Approximately 1 h later, he was given one Halcion tablet and four Lendormin tablets by his wife. Approximately 5 min after ingesting the hypnotic drugs, he went to sleep. The next morning, 10 h after leaving her husband, the woman went to the car and confirmed that he had died. Two days later, she took the body to a vacant lot.

Experimental Materials

A preliminary drug screening on blood and urine was performed with thin-layer chromatography (TLC) (TOXI-
LAB) and immunoassay (Triage™ Biosite Diagnostics, San Diego, CA and EMIT®, Syva, Palo Alto, CA). The EMIT d.a.u. assay of benzodiazepine was performed according to the manufacturer’s direction (6). In this assay, the cutoff concentration of 50 ng/mL was used to distinguish a positive from a negative sample. Toxicological analysis by liquid–liquid extraction and gas chromatography (GC) coupled to mass spectrometry (GC–MS) was therefore carried out to identify and quantify the individual substances present in the autopsy materials. A model 5890 series II Hewlett-Packard (HP, Palo Alto, CA) GC coupled with a model 5971 MS was used. Ethyl alcohol analysis was performed on blood and urine using headspace GC. A model 5890 series II HP GC equipped with a flame ionization detector and an HP 19395A headspace sampler.

Results and Discussion

The results of the quantitative analysis are shown in Table I. No other drugs or the internal standard were detected in autopsy samples by toxicological analysis. Screening of urine with the Triage panel detected only opiates. However, EMIT d.a.u. was positive for benzodiazepines and opiates. No particular opiates, such as 6-monoacetylmorphine, morphine, or codeine, were detected, which indicated that the positive result of the Triage panel was from dihydrocodeine. Ethyl alcohol was not detected in the blood. However, the ethyl alcohol concentration in the urine was 1.31 mg/mL. Using TLC, ibuprofen was tentatively identified in the blood.

Although EMIT d.a.u. immunoassays for benzodiazepine were positive, Triage panel gave a negative response. Edinboro

![Figure 1. Main metabolites of brotizolam in humans.](https://www.jatjournal.com/figure1.jpg)

![Figure 2. Main metabolites of triazolam in humans.](https://www.jatjournal.com/figure2.jpg)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Brotizolam (ng/mL)</th>
<th>We 964*</th>
<th>Triazolam (ng/mL)</th>
<th>α-OH-Triazolam</th>
<th>Ibuprofen (ng/mL)</th>
<th>Dihydrocodeine (ng/mL)</th>
<th>Phenylpropanolamine (ng/mL)</th>
<th>Chlorpheniramine (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood (ng/mL)</td>
<td>10.4</td>
<td>ND</td>
<td>ND</td>
<td>–</td>
<td>3000</td>
<td>130</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Urine (ng/mL)</td>
<td>ND</td>
<td>42</td>
<td>ND</td>
<td>173</td>
<td>1700</td>
<td>3590</td>
<td>320</td>
<td>70</td>
</tr>
<tr>
<td>Stomach contents (g)</td>
<td>30</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>80800</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* We 964 is the brotizolam metabolite hydroxylated in the methyl group at the 9 position.
† Not tested.
‡ Not detected.
§ A peak with relative retention time equal to phenylpropanolamine was observed, but the qualifying ion ratio failed.
¶ A peak with relative retention time equal to chlorpheniramine was observed, but the qualifying ion ratio failed.
and Poklis (7) reported discordant benzodiazepine results by EMIT d.a.u. assay and Triage panel. They reported that, of 63 specimens testing positive for benzodiazepines by the EMIT d.a.u. assay, only 52 (82%) were also positive by Triage panel. The overall positive and negative result agreement between Triage and EMIT d.a.u. was found to be 85%. However, our discordant result was due to the difference in cutoff value. In the present case, the cutoff value of EMIT d.a.u. for benzodiazepine was 50 ng/mL using calibrator A, whereas the cutoff value of Triage for benzodiazepines was standardized at 300 ng/mL (8).

The pharmacological actions of brotizolam are similar to triazolam with a sedative-hypnotic action together with anti-convulsant, muscle-relaxant, and anti-aggressive properties (9). Several investigators have studied the metabolism of brotizolam in humans and experimental animals (1,10) and showed that brotizolam is readily absorbed from the gastrointestinal tract and is eliminated in the urine as conjugated with sulfuric and glucuronic acid. Although the brotizolam intake usually does not exceed 0.5 mg, in one study, after a single oral dose of 1.0 mg to four subjects, the maximum plasma concentration detected was 19.2 ng/mL at 2-h postdose (1). In the present case, the blood brotizolam concentration was lower than these values; however, brotizolam was found in the stomach contents.

In humans, the major metabolites of brotizolam are the hydroxylation products that are hydroxylated in the methyl group at 9-position (We 964) and hydroxylated in the 6-position (We 1061) (Figure 1) (1). Bechtel (1) reported that after the ingestion of 0.5 mg of brotizolam, healthy volunteers excreted 27% as We 964 and 7% as We 1061 in urine. Unmetabolized brotizolam in the urine was less than 1% of the ingested dose up to 8 h after administration. In the present case, unmetabolized brotizolam and We 1061 were not detected in the urine.

After a single oral dose of 0.25 mg, triazolam was not detectable in blood by GC–MS-electron impact analysis. The most sensitive and specific analytical technique available at present is GC with an electron capture detector. Generally, urine is screened for the presence of the α-OH triazolam and/or the 4-OH triazolam of triazolam metabolites. α-OH Triazolam is the major urinary metabolite and has a longer plasma elimination half-life than triazolam. In our case, α-OH triazolam was detected in urine but not 4-OH triazolam.

A possible explanation for the blood concentration of benzodiazepine and the relatively low urine concentrations of benzodiazepine metabolites is the rapid death. The contributions of brotizolam and triazolam in the present fatality were difficult to evaluate. The blood dihydrocodeine concentration of 0.13 μg/mL may well have been a contributing factor. Bal et al. (11) reported a triazolam drug-interaction death with 16 ng/mL triazolam and 0.137 μg/mL dihydrocodeine. Ibuprofen has a similar CNS depressant effect (12), and toxic screening methods have had varying ability to detect other involved drugs, especially benzodiazepines (13). Therefore, like dihydrocodeine, the blood ibuprofen concentration of 3 μg/mL may well have been a contributing factor. Joynt (14) reported that it seems impossible to determine the precise blood-triazolam concentration that is certain to cause death.

It was not detected in immunological screening only by Triage panel. The reported data strongly suggest that it is important not to overlook the presence of benzodiazepine during routine toxicological screening.

Acknowledgments

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References


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