Medicolegal implications of an autopsy case of hypothermia under the influence of flunitrazepam and quetiapine

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Abstract: Toxicological examination is an integral part of determining cause of death but must be considered in conjunction with other autopsy findings and the results of the investigation of the victim's surroundings. We present a fatal case involving a victim who had ingested flunitrazepam and quetiapine. Quantitative toxicological analysis revealed that the concentrations of 7-aminoflunitrazepam (a metabolite of flunitrazepam) and quetiapine in a femoral blood sample were 0.46 µg/mL and 0.48 µg/mL, respectively. However, her cardiac blood oxygen saturation met the criteria for hypothermia. These pathophysiological findings strongly suggested that the forensic diagnosis for her cause of death was hypothermia, rather than the direct effects of the drug as measured on toxicological analysis. From the autopsy findings, results of the toxicological examination, and investigation by the authorities, we concluded that the cause of death was hypothermia under the influence of flunitrazepam and quetiapine.

Key Words: flunitrazepam, quetiapine, hypothermia, oxygen saturation, cardiac blood.

INTRODUCTION

Flunitrazepam, an analogue of nitrazepam, is prescribed as a hypnotic [1]. It is often abused, and fatalities have been reported as a result of overdose or drug interactions with ethanol or other drugs [2-7]. Because flunitrazepam disappears rapidly from the blood by metabolism in the liver [4] or postmortem bioconversion [8], the presence of 7-aminoflunitrazepam is an important marker of flunitrazepam intake [3-7, 9]. Quetiapine is a dibenzothiazepine derivative, which is used as a neuroleptic agent in the treatment of psychosis [10].

Various types of death have occurred under the influence of these drugs [9]. Here we report a fatal case of hypothermia under the influence of flunitrazepam and quetiapine.

CASE REPORT

A Japanese woman in her twenties (height, 164 cm; weight, 67 kg) was found dead in a bathroom in her house in the middle of winter. The bathtub was empty, and there was no heating apparatus. She had been prescribed drugs for the treatment of a mood disorder, and a note written about her intention to overdose was found at investigation by the authorities. Autopsy findings indicated no evidence of external injury. The slight pink color of postmortem lividity was observed. The heart weighed 266 g and contained 490 mL of blood with a small amount of coagulum. The blood in the left cardiac chamber was bright red compared to that in the right cardiac chamber. The brain weighed 1220 g and was slightly edematous. The left and right lungs weighed 289 g and 346 g, respectively and were slightly reddish. The oxygen saturation of the blood in the left and right...
heart chambers was 68.3% and 19.7%, respectively, and the oxygen saturation ratio between the left and right heart blood was 3.47. The stomach contained a brownish, muddy-appearing liquid (240 mL). Approximately 470 mL of urine was collected in the bladder. An internal examination revealed no diseases. Signs other than congestion were not noted in other organs. A drug screening test using a Triage™ (Biosite Diagnostic Inc, San Diego, CA) panel was positive for benzodiazepines. Samples of postmortem blood, urine, and stomach contents were collected for toxicological investigation.

Toxicological analysis using a 6890N gas chromatograph (GC) combined with a 5973 MS mass spectrometer (Agilent Technologies, Santa Clara, CA) was performed by a method slightly modified from a previous report by Kudo et al. [11]. Quantitation of ethanol was performed using headspace gas chromatography.

**RESULTS AND DISCUSSION**

In the present case, findings of injury and comorbid diseases were excluded from the autopsy. Some findings at autopsy suggested that, in addition to overdose, hypothermia contributed to the victim’s death. The characteristic findings of hypothermia such as frost erythema and Wischnewski’s spot are known to be non-specific and occur with varying frequency [12]. A color difference between left and right heart blood is a common characteristic sign of hypothermic death, which is observed in approximately 95% of hypothermic death cases [13-15]. This finding seems to reflect the final balance of oxygen uptake and consumption in the dying process [16], and the blood in the left heart usually has a higher oxygen content than that in the right heart at autopsy in the case of hypothermia. Based on the oxygen saturation in the cardiac blood, the following diagnostic criteria for hypothermic death have been proposed: an oxygen saturation ≥36% in the left cardiac blood as the baseline criterion with the supplemental criteria of a difference in the oxygen saturation between the left and right heart blood ≥13% and an oxygen saturation ratio between the left and right heart blood ≥1.8, with a sensitivity of ≥86% and a specificity of ≥93% [15]. In the present case, the oxygen saturation in the left cardiac blood (68.3%), oxygen saturation gap between the left and right cardiac blood (48.6%), and oxygen saturation ratio between the left and right cardiac blood (3.47) fully met these criteria.

Toxicological analysis identified quetiapine, flunitrazepam, and its metabolite 7-aminoflunitrazepam in each sample. Table 1 shows these concentrations in her postmortem samples, along with the currently established lethal, toxic, and therapeutic levels [3, 4, 6, 17]. No ethanol was detected in the postmortem samples.

Although 7-aminoflunitrazepam was quantified in the blood, we could not detect flunitrazepam in the blood or urine. Evidence of flunitrazepam intake is usually supported by the presence of 7-aminoflunitrazepam in the blood [3-7, 9]. Her blood level of 7-aminoflunitrazepam at the time of death (0.46 µg/mL) was within the fatal range, which is distributed widely in cases without concurrent ethanol intake to be 0.27-1.27 µg/mL [3, 4, 6]. This would have depressed her level of consciousness. The volume of urine retained in the bladder (470 mL) also suggests that there was a relatively long interval between loss of consciousness and her death. Quetiapine is an atypical antipsychotic drug, which has sedative effects [18]. As the blood level of quetiapine was within the therapeutic range, central nervous system (CNS) depression was less likely to have directly contributed to her death. It seems that the victim died during the absorption phase following oral ingestion because a relatively large amount of unabsorbed flunitrazepam (1.42 mg) and quetiapine (58.6 mg) remained in the stomach. The present case also demonstrates the usefulness of the analysis of stomach contents, and flunitrazepam in the stomach contents is a good indicator of massive ingestion [7].

As hypothermic death was induced under the various condition, the diagnosis of fatal hypothermia can be made by not only by the autopsy findings, but also based on the circumstances of the victim’s surroundings [19]. It has been reported that risk factors for hypothermia include environmental and individual conditions [20]. The present case occurred in the middle of winter, and no heat source was present in the bathroom. Alcohol or CNS depressants such as benzodiazepines, tricyclic antidepressants, and chlorpromazine induce unconsciousness, which in turn decreases the ability for one to be able to move away from a cold environment and may also have direct effects on the heat regulation center in the hypothalamus [20].

Although the blood concentration of 7-aminoflunitrazepam was within a fatal range [3, 4, 6], the fact that the victim died during the absorption phase along with the significant pathophysiological findings

<table>
<thead>
<tr>
<th>Femoral blood</th>
<th>Urine</th>
<th>Stomach contents</th>
<th>Therapeutic range*</th>
<th>Toxic range*</th>
<th>Lethal range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunitrazepam</td>
<td>B.D.L</td>
<td>B.D.L</td>
<td>5.90</td>
<td>0.005-0.015</td>
<td>0.05</td>
</tr>
<tr>
<td>7-Aminoflunitrazepam</td>
<td>0.46</td>
<td>B.D.L</td>
<td>B.D.L</td>
<td>0.27-1.27 (without ethanol)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.48</td>
<td>14.8</td>
<td>244.0</td>
<td>0.1-0.5</td>
<td>1.0-1.8</td>
</tr>
</tbody>
</table>

B.D.L: below the detection limit. *Therapeutic, toxic and lethal range is cited from the reference [3,4,6,17].
of hypothermia strongly suggest a forensic diagnosis of hypothermia as the cause of death. Based on the autopsy findings, the results of the toxicological examination, and the investigation by the authorities, we concluded that massive intake of flunitrazepam led to her death by hypothermia, with some interval of unconsciousness.

**Conflict of interest.** The authors declare that there is no conflict of interest regarding the publication of this paper.

**References**