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An autopsy case of triazolam overdose

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Abstract: We present a case of fatal triazolam poisoning. Quantitative analysis using liquid chromatography-mass spectrometry revealed that the concentrations of triazolam were 72ng/ml, 120ng/ml, 12ng/ml and 12,190ng/g in the femoral venous blood, heart blood, urine and stomach contents respectively. We concluded that the cause of death was due to triazolam overdose.

Key Words: triazolam, poisoning, liquid chromatography-mass spectrometry.

Triazolam, a triazolobenzodiazepine hypnotic agent, is widely used for the management of insomnia [1]. It is a short acting hypnotics with a half-life of 1.8-3.9 hrs [1-4] and relatively safe in low prescribed doses [5], but there are a few reports of the fatal cases [6-12]. Here we report a case of death due to the toxicity of triazolam.

Case report

A Japanese male in his seventies was found dead in his room. Subsequent investigation by the authorities revealed that the deceased had been receiving therapy for insomnia and had been prescribed drugs. A lot of empty packets were also observed in a dust can.

The deceased was 163 cm in height and 62.6 kg in weight. No external evidence of violence was found. The heart weighed 461g, contained 270ml of blood without coagulum. The brain weighed 1270g and was slightly edematous. The left and right lungs weighed 619 and 734g, respectively, and were severely congested.

There were approximately 150 ml of stomach contents, containing foodstuffs. There were no notable changes, other than congestion in the other organs. A drug screening test using a TriageTM (Biosite Diagnostic Inc, San Diego, USA) panel was positive for benzodiazepines. Postmortem samples of heart blood, femoral venous blood, urine and the stomach contents were collected for toxicological investigation.

Toxicological analysis was performed using liquid chromatography-mass spectrometry (Quattro micro® API mass spectrometer in combined with 2695 alliance system®, Waters, Milford, MA, USA) [13]. Its operation and the preparation of the samples were in accordance with the manufacturer's specifications. Quantitation of ethanol was performed using head-space gas-chromatography.

Results and Discussion

Triazolam was identified by toxicological examination and the concentrations in each postmortem specimen are presented in Table 1. No other drugs or ethanol were detected in the blood and urine.

The concentrations of triazolam in fatal cases, its therapeutic range and toxic level are summarized in Table 2 [1-5, 8-12]. In the present case, the concentration of triazolam in the blood (72ng/ml) was within fatal levels. Since a relatively large amount of unabsorbed drug components remained in the stomach, it was apparent that the victim died during the absorption phase of triazolam following oral ingestion. As shown in Table 1, the concentration of triazolam in the heart blood was about 1.67 times higher than in the femoral blood. This may be due to the concentration gradients in the absorption phase

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Table 1: Triazolam concentrations in each sample in the present case (ng/ml).

Specimen	Triazolam
Heart blood	120
Femoral venous blood	72
Urine	12
Stomach contents	12190 (1.8)*

*Figure in parentheses represents the total amount of drug in the stomach (mg).

Table 2: Blood and urine concentrations in fatal triazolam alone poisoning cases, and therapeuric range and toxic level of triazolam (ng/ml).

No	Age	Blood	Urine	Reference
1	31-71	10-40 (4 cases)	-	[8]
2	79	110	-	[9]
3	33	73.9 (Heart)	741	[10]
4	77	120 (Heart), 91 (peripheral)	24	[11]
5	57	90-153 (Heart), 62 (Femoral vein)	45	[12]
Therapeutic range		2-20	-	[1-5]
Toxic level		> 40	-	[5]

Table 3: The value of absorption rate constant (Ka) in short acting benzodiazepine (triazolam and bromazepam) and other hypnotics (zopiclone).

Drug	Absorption rate constant (Ka) (hr^{-1})	Reference
Triazolam	14.71	[2]
Bromazepam	4.14	[15]
Zopiclone	4.20	[16]

between the portal and the peripheral vein [12].

In the present case, there are two factors that influence the toxico-physiology, from the viewpoint of pharmacokinetics. The first factor concerns the value of absorption rate constant (Ka) of triazolam. In general, peak drug concentration and the time of peak blood concentration following oral ingestion depends on the Ka value of the drug [14]. Peak drug concentration is increased and the time of peak blood concentration is shortened when the drug has a high Ka value [14]. The Ka value of triazolam is extremely higher than that of other short acting benzodiazepine and hypnotic drugs, as shown in Table 3 [2,15,16]. This means that triazolam is rapidly absorbed, and its concentration in blood increases more rapidly immediately following ingestion, compared to other short acting benzodiazepine and hypnotic drugs. The second factor is the reduction of triazolam clearance by age [17,18], since the reduction of CYP3A expression, the main metabolic enzyme of the triazolam, has been observed in elderly people [17-19]. This also results in high peak blood triazolam concentrations [18,19]. These rapid and higher increases of triazolam blood concentration enhance the sedative effects due to depression of the central nervous system [5]. These pharmacological properties of triazolam may be affected to toxico-physiology in the present case.

We have also estimated the victim's total amounts of ingestion of triazolam, using values of the distribution volume (Vd) for triazolam (1.1-2.7 L/kg) [1], the victim's body weight and femoral blood level. The minimum calculated amount of triazolam was approximately 4.9 mg. In this case, however, the ingested amount of triazolam may have been larger than the estimated amount, because there was a large amount of unabsorbed drug left in his stomach. The total ingested dose of triazolam was the sum of the above value and the dose left in the stomach. We therefore estimated that he had ingested at least 6.7 mg of triazolam.

From the autopsy findings and the results of the toxicological examination, we conclude that the victim died due to an overdose of triazolam, soonly after ingestion.

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