Forensic Science International 290 (2018) 111–120

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Fatal zolpidem poisoning due to its intravenous self-injection: Postmortem distribution/redistribution of zolpidem and its predominant metabolite zolpidem phenyl-4-carboxylic acid in body fluids and solid tissues in an autopsy case

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ARTICLE INFO

Article history:
Received 19 April 2018
Received in revised form 28 June 2018
Accepted 30 June 2018
Available online 6 July 2018

Keywords:
Zolpidem
Zolpidem phenyl-4-carboxylic acid
Postmortem distribution/redistribution
Intravenous injection
QuEChERS method
LC–MS–MS

ABSTRACT

We experienced a curious fatal case, in which a male in his 20s self-administered zolpidem intravenously. The victim was found dead lying on floor of his apartment room, with a tourniquet band and new injection marks on his right forearm. Nearby the body, a medical disposal syringe containing small-volume solution dissolving crushed zolpidem tablets was found. The postmortem interval was estimated at about two days.

The direct cause of his death was judged as asphyxia due to the aspiration of stomach contents into the trachea and bronchi. The specimens dealt with were body fluids and solid tissues including femoral vein blood, right and left heart blood, pericardial fluid, urine, bile, stomach contents, the brain, lung, heart muscle, liver, spleen, kidney, pancreas and skeletal muscle. For the extractions of zolpidem, zolpidem phenyl-4-carboxylic acid, deuterated internal standards zolpidem-d_7 and zolpidem phenyl-4-carboxylic acid-d_4, a modified QuEChERS method was used, followed by the analysis by liquid chromatography–tandem mass spectrometry. Because this study included various kinds of human matrices with quite different properties, the standard addition method was most preferable to overcome the matrix effects and recovery rates, and also did not need to use blank human matrices for validation experiments. The concentration of zolpidem and its phenyl-4-carboxylic acid metabolite in various specimens tested were generally extreme higher than those of reported fatal cases, supporting that the victim had died of intravenous zolpidem injection. The concentrations of zolpidem in femoral vein blood and right and left heart blood specimens in the present case were 9.55, 28.5 and 46.9 μg/mL, respectively, which far exceeded estimated fatal levels. The present study also showed the postmortem distribution/redistribution of zolpidem and its phenyl-4-carboxylic acid metabolite in 15 body fluid and solid tissue specimens including stomach contents. Although a number of published literatures dealt with zolpidem poisoning cases due to oral ingestion of the drug, this is the first report on fatal intravenous zolpidem injection case and postmortem distribution of zolpidem and its predominant metabolite.

1. Introduction

Zolpidem (*N*,*N*,6-trimethyl-2-(4-methylphenyl)-imidazo[1,2-*a*] pyridine-3-acetamide) is an imidazopyridine derivative which has selective affinity to the benzodiazepine receptors [1–4], although its structure is quite different from that of benzodiazepine group. The drug is nowadays being used as a hypnotic agent for short-term treatment of insomnia throughout the world. Especially in forensic area, zolpidem poisonings have been frequently encountered in misuse and abuse cases including suicides, though fatal cases were relatively rare [2]. Moreover, zolpidem also often becomes the focus of interest as “date rape drug” [5].

Very recently, an autopsy case of a male in his 20s involved in the overdose of zolpidem due to intravenous self-injection was experienced at our department. In this article, we present the distribution of zolpidem and its phenyl-4-carboxylic acid

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https://doi.org/10.1016/j.forsciint.2018.06.044
0379-0738/

metabolite in 15 body fluids and solid tissues including stomach contents obtained from the cadaver at autopsy. To our knowledge, although there are five reports dealing with the non-lethal intravenous zolpidem injection cases [6], this is the first report on fatal intravenous zolpidem self-injection case and postmortem distribution/redistribution of zolpidem and its phenyl-4-carboxylic acid metabolite in various specimens. A number of previous literatures described postmortem determination of zolpidem from body fluid(s) and/or solid tissue(s) in poisoning cases [7–14], but the matrices tested were blood, plasma, urine, stomach contents and/or sporadic solid tissue(s) only [7,9,10], while we have presented the distribution/redistribution of zolpidem and its main phenyl-4-carboxylic acid metabolite [1] from blood specimens from three different locations, bile, pericardial fluid, stomach contents and eight solid tissue specimens in this study.

2. Case history and autopsy findings

A male in his 20s was found dead in spine position, lying on floor of his apartment room. He had been employed at a hospital as a medical staff. One day, because he did not come to work for a couple of days, his colleagues contacted his parents to inform them about his absence. Soon after that, the victim's mother visited his apartment room and found the deceased. The victim was wearing a surgical goun with a tourniquet band wrapped around his right forearm. In his room, nearby the body a medical disposal syringe containing a small volume of an unknown solution, opened packages of medicines, many various tablets were also found; sodium valproate 200 mg (196 tablets), clomipramine hydrochloride 50 mg (170 tablets), amitriptyline hydrochloride 25 mg (1 tablet), imipramine hydrochloride 25 mg (29 tablets), eszopiclone (content per tablet-unknown, 74 tablets), quazepam 15 mg (2 tablets), suvorexant (content per tablet-unknown, 5 tablets), zolpidem tartrate 5 and 10 mg (each 10 tablets), levomepromazine maleate 25 mg (20 tablets), duloxetine (content per tablet-unknown, 4 tablets) and flunitrzepam 1 and 2 mg (108 and 138 tablets, respectively) were found.

In the dust box of his room, empty packages and press through packages (PTP) of various medicines were also found, and corresponding medicines were sodium valproate (1 tablet), imipramine hydrochloride (10 tablets), eszopiclone (10 tablets) and zolpidem tartrate 5 mg and 10 mg (10 and 34 tablets, respectively); they were suspected to be used prior to his death.

In addition, there was an almost empty grape fruit juice package (1000 mL) at the sink of the kitchen.

Therefore, the police first suspected that he had died of multiple drug poisoning; neither any criminal evidence nor suicide note were found in his room.

His forensic autopsy was conducted at our department. The postmortem interval at the beginning of the autopsy was about 2 days. The male victim was 174 cm high and weighed 73.7 kg. Postmortem rigidity was relatively strong at all joints. Marked lividity accompanied by vibices was found on his anterior trunk consistent with the posture of the body. On the external examination, his face and neck were quite congested. Many small petechiae were observed at conjunctivae of both eyelids. There were severe cyanosis on the lips and every nail bed of both hands. On his face the right orbital area was swollen and discolored accompanied by a small laceration. There were many injection puncture marks along a vein in the front side of the right forearm, and a band-like pale area (about 2 cm in width) circling the proximal part of the forearm was found; the tourniquet band had already been removed at the time of autopsy. On the left forearm and right thigh, old burns-like scars (relatively wide area) were observed. In addition to the above findings, neither distinct wounds nor severe injuries were found on the surface of every part of the skin.

As internal findings, there was a brown fluid including massive stomach contents and small froth in the trachea and the bronchi. Both lungs were quite swollen and congested, showing that they were like "drowning lung"; the right lung weighed 751 g and the left lung 827 g. There were many small petechiae on the serous membranes of the lungs and kidneys, and also on the pericardium. A large volume of fluidal blood was present inside the heart. Almost all organs including the brain were congested. Except the above findings, there were neither pathological findings nor injuries by macroscopic observation.

Based on the above findings, the direct cause of his death was diagnosed as asphyxia due to massive aspiration of stomach contents into the trachea and bronchi. Such aspiration of stomach contents into the trachea plus bronchi and its occlusion of the airway are usually not thought to be observed for persons in a state of clear consciousness. This finding is likely due to lowered consciousness or drowsiness together with serious vomiting symptom provoked by intake of a large amount of sedative medicine(s), considering the injection marks on the right forearm; the indirect cause of death seemed to be drug poisoning.

Routine analysis of blood alcohol using gas chromatography showed no alcohol in heart blood and urine specimens. Immunochemical drug screening using the Triage Drugs of Abuse panel (Alere, Waltham, MA, USA) for the urine specimen showed a positive result for tricyclic antidepressant drugs. The NAGINATA screening for conventional drugs and toxic compounds in whole blood from the femoral vein using gas chromatography mass–spectrometry (GC–MS) [15] showed the presences of therapeutic levels of valproic acid (semiquantitative concentration: 0.364 μg/mL), nortriptyline (0.098 μg/mL), desipramine (0.125 μg/mL), amitriptyline (0.093 μg/mL) and imipramine (0.047 μg/mL), and lethal level of zolpidem (3.93 μg/mL).

The GC–MS screening was also tried for solution remaining in the syringe. The solution contained small amount of blood and white residue; the white residue was estimated to be crushed tablets including excipient(s). Although the screening showed the presence of large amounts of zolpidem and valproic acid in the solution even after appreciable dilution, the results of quantitative analysis were not thought to be reliable because of saturation of corresponding MS signals.

According to police investigation, it was found that he had long history (more than a couple of years) of a mental disease. He was diagnosed as depression, insomnia and suspected of drug-dependence at multiple clinics; flunitrazepam and zolpidem had been prescribed by psychiatrists very recently. Other medicines found in his room were not prescribed by the corresponding clinics, and suspected to be acquired through Internet by himself.

3. Materials and methods

3.1. Materials

Zolpidem, zolpidem phenyl-4-carboxylic acid, zolpidem-d_7, and zolpidem phenyl-4-carboxylic acid-d_4 (internal standards, ISs) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Other common chemical used were of the highest purity commercially available. Plastic centrifuge tubes with caps (5-mL capacity, 6 × 1.5 cm external diameter) and stainless beads (5 mm external diameter) for crushing solid tissues were purchased from TAITEC, Saitama, Japan. The QuEChERS dispersive solid-phase extraction (SPE) centrifuge tubes with caps (2-mL capacity), each of which contained 25 mg of end-capped octadecylsilane (C_{18EC}) and 150 mg of magnesium sulfate, and Captiva ND Lipids cartridges (3-mL capacity) were purchased from Agilent (Santa Clara, CA, USA).

Whole blood specimens from the femoral vein and the right and left atria, bile, pericardial fluid, urine, stomach contents and solid