

## Two Fatal Cases of Caffeine Poisoning and a Review of the Literatur

Junko FUJIHARA<sup>1)</sup>, Toshihiro YASUDA<sup>2)</sup>, Kaori KIMURA-KATAOKA<sup>1)</sup>, Masanori HASEGAWA<sup>3)</sup>, Satsuki KURATA<sup>4)</sup>, Haruo TAKESHITA<sup>1)</sup>

<sup>1)</sup> Department of Legal Medicine, Shimane University Faculty of Medicine, Izumo, 693-8501, Japan

<sup>2)</sup> Division of Medical Genetics and Biochemistry, Faculty of Medical Sciences, University of Fukui, Eiheiji-cho, 910-1193, Japan.

<sup>3)</sup> Criminal Investigation Laboratory, Shimane Prefectural Police Headquarters, Matsue, 690-0038, Japan

<sup>4)</sup> Kurata Clinic, Matsue, 690-0001, Japan

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Caffeine is commonly used as a stimulant, and fatal caffeine overdoses are increasing. In the present study, two case reports showing a fatal blood concentration of caffeine were reported and compared to previously published case reports.

Case 1: A 19-year-old female was found dead in her room. It was speculated that she ingested 84 tablets (100 mg) of a sleep-inhibitor product. The caffeine levels in her cardiac blood and stomach were 116 µg/ml and 619 µg/ml, respectively. There was no macroscopic indication of any natural or unnatural cause of death.

Case 2: The condition of a 47-year-old male deteriorated suddenly. Hypothermia and excess sweating were observed. After vomiting several times, he lost consciousness. At autopsy, severe pulmonary edema was observed. His cardiac blood caffeine level was determined to be 171 µg/ml, which exceeds fatal blood caffeine levels. However, there is no evidence of his ingesting massive amounts of caffeine.

The blood caffeine concentration in previously reported fatal caffeine ingestions ranged from 33 to 350 µg/ml. The two present cases are within this range. The accumulation of data on blood caffeine concentrations and ingestion amounts is helpful to predict the intake amount of caffeine.

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Key words: caffeine, fatal, toxicology, symptom, poisoning

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Corresponding author: Junko Fujihara, Ph.D

Department of Legal Medicine, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan

Tel: +81-853-20-2157

Fax: +81-853-20-2155

E-mail: jfujihar@med.shimane-u.ac.jp

### INTRODUCTION

Caffeine, 1, 3, 7-trimethylxanthine, is a mild central nervous system stimulant and is widely used as a legal stimulant. Its pharmacological actions are central nervous system excitation, cardiac stimulation, skeletal muscle excitation, and diuretic action. Following oral ingestion, caffeine is rapidly absorbed from the gastrointestinal tract. Oral bioavailability is almost 100%, with peak plasma concentrations within 30-60 min of ingestion. Caffeine undergoes hepatic metabolism via N-demethylation, acetylation, and oxidation. The CYP450 1A2 isozyme is largely responsible for the N-demethylation of caffeine to paraxanthine [1].

Recently, incidents of caffeine poisoning are increasing due to the easy availability of sleep inhibitor products, “energy drinks” with high caffeine content, and dietary supplements available via health stores and online purchase [2]. Several case reports on death due to caffeine overdose have been published and the accumulation of data on blood caffeine concentrations and ingestion amounts is helpful to predict the intake amount of caffeine. In the present study, two case reports showing a fatal blood concentration of caffeine were reported and compared to previously published case reports.

### CASE HISTORY

#### Case 1

A 19-year-old female was found dead in her room. There were empty PTP sheets for 84 tablets of Estaron Mocha<sup>®</sup> (100 mg, anhydrous caf-

feine), which is sold as a sleep inhibitor, 6 empty PTP sheets for Sediel® (tandospirone citrate), and a RESTAMIN KOWA® tablet bottle containing an uncertain number of tablets on the carpeted floor (Fig. 1). According to investigation by the police, the victim had attended a mental clinic. She was autopsied to clarify the cause of death 3 days after her death.



Fig. 1. The 84 empty sheet for Estaron Mocha® tablets (100 mg, anhydrous caffeine) and 6 empty PTP sheet of Sediel® (tandospirone citrate) and unfinished RESTAMIN KOWA® tablet bottle.

## Case 2

A 47-year-old healthy male suddenly fell ill at midnight. Hypothermia and excess sweating were observed by his family. After vomiting several times, he lost consciousness. There is no evidence of his ingesting massive caffeine. He was taken to the hospital, and death was confirmed by a doctor. He was autopsied to clarify the cause of death 1 day after his death.

## MATERIALS AND METHODS

### Sample preparation

Whole blood and stomach contents were collected at autopsy and kept frozen at  $-80^{\circ}\text{C}$  until analysis. Caffeine extraction was performed using Extrelut® NT-20 (MERCK, Darmstadt, Germany). Briefly,

blood was diluted with distilled water (blood/distilled water, 1:100 v/v). An internal standard (IS) solution (diazepam- $d^5$ ) was added to each sample. Caffeine and the IS solution were mixed with an ammonium chloride/ammonia buffer (pH 9.5), and the mixture was loaded onto Extrelut® NT-20 columns. After 15 min, the caffeine and IS solution were eluted from the columns using methylene chloride/isopropanol (85:15 v/v). The eluants were evaporated under a stream of nitrogen gas, and the residue was dissolved in methanol.

### GC-MS conditions

Caffeine was determined by gas chromatography-mass spectrometry (6890N/5975C GC/MS, Agilent Technologies, Santa Clarita, CA, USA). Compounds were separated using an HP-5 MS cross-linked 5% diphenyl-95% dimethyl polysiloxane capillary column (30 m  $\times$  0.25 mm I.D., 1.00  $\mu\text{m}$  film thickness, Agilent Technologies). The oven temperature was programmed from initial  $50^{\circ}\text{C}$  (1 min) to  $100^{\circ}\text{C}$  at  $20^{\circ}\text{C}/\text{min}$  and finally to  $280^{\circ}\text{C}$  at  $10^{\circ}\text{C}/\text{min}$ , which was maintained for 20 min. The injector and ion-source temperatures were  $250^{\circ}\text{C}$  and  $230^{\circ}\text{C}$ , respectively. MS detection was performed with electron ionization (EI). The  $m/z$  194 and 289 were monitored for caffeine and diazepam- $d^5$  (IS), respectively, in the selected ion monitoring mode for quantification.

### Other assays

Urine was analyzed using Triage® DOA plus TCA (Biosite Diagnostics Inc., San Diego, CA, USA) for a pre-drug screening test. Ethanol concentrations in blood and urine were determined using a headspace gas chromatography-flame ionization detector according to our previous study [3]. The blood carboxy-hemoglobin (COHb) level in the cardiac blood was determined via a general method using AVOXimeter 4000 (AVOX; A-VOX Systems, International Technology Corporation, Edison, NJ, USA). The level of C-reactive protein (CRP) was measured using a Nycocard READER II (Axis-Shield PoC, Norway). These assays are routinely performed.

### Statistical analysis

Simple regression analysis was used to measure

the strength of the associations between caffeine intake amount and blood caffeine concentration. A *p* value of less than 0.05 was considered statistically significant. These analyses were conducted using the STATCEL2 program (OMS Publishing, Inc., Tokorozawa, Saitama, Japan).

## RESULTS

### *Case 1*

The deceased was 171.0 cm in height and weighed 48.4 kg. Pale purplish red liver mortis was present on the posterior surface of the body. There were incisions 1.6 cm and 1.5 cm long and 0.3 cm and 0.5 cm deep, respectively, on the anterior region of the left forearm. Muscles and an uncut blood vessel were exposed within these incisions. Additionally, there were scars 1.7-3.5 cm x 0.1 cm in the middle the anterior region of the left forearm. These incisions are presumed to be made by recurrent suicide attempts. Little petechiae were observed on the palpebral conjunctiva and organs. Cyanosis was observed on the nails of both upper and lower limbs. Pleural effusion (440 mL) was present. The heart weighed 250 g, and there were no apparent lesions or arteriosclerosis of the coronary arteries. The cardiac blood was dark red and contained some coagulation. A transparent red serous fluid with fine foam was observed in the trachea and bronchi. An intestinal intussusception 4.5 cm long was observed 68.0 cm below the ligament of Treitz. Slight fatty liver was observed macroscopically. Organ weights were as follows: right lung 515 g; left lung 280 g; liver 1020 g; spleen 83.0 g; pancreas 70 g; right adrenal gland 5.7 g; left adrenal gland 8.0 g; right kidney 98.0 g; left kidney 115.0 g; uterus, ovaries and fallopian tubes 60 g; and brain 1375 g. Pathological observation revealed pleural thickening in the left lung.

Caffeine levels in the cardiac blood and stomach contents were 116 µg/ml and 619 µg/ml, respectively. A preliminary immunochemical urine screening with Triage® (Biosite, San Diego, CA, USA) was negative. No ethanol was detected in the blood or urine. The right and left cardiac blood COHb levels were 2.1% and 4.0%, respectively. The level of CRP in the blood serum was determined to be 8.2

mg/dL (reference value of < 0.5 mg/dL).

### *Case 2*

The deceased was 174.0 cm in height and weighed 65.7 kg. No injury or injection sites were found on the external surface of the body. Sudden death findings were observed: the cardiac blood was dark red, and numerous petechiae on the palpebral conjunctiva were recognized. Pulmonary edema was observed. Organ weights were as follows: right lung 1220 g; left lung 1045 g; liver 1560 g; spleen 107 g; pancreas 130 g; right adrenal gland 7.0 g; left adrenal gland 7.0 g; right kidney 150 g; left kidney 172g; and brain 1470 g. Pathological observation showed no pathogenesis.

The caffeine level in cardiac blood was 171 µg/ml. In this case, content was not collected because we did not suspect the poisoning. A preliminary immunochemical urine screening with Triage® was negative. No ethanol was detected in the blood or urine. The right and left cardiac blood COHb levels were 2.7% and 3.2%, respectively. The level of CRP in the blood serum was determined to be < 0.5 mg/dL.

## DISCUSSION

Caffeine is a mild central nervous system stimulant when ingested at a low dose (100 mg which is equivalent to a cup of coffee). Caffeine is well absorbed following oral administration, and clinical effects can be observed within 15 min [2]. The pharmacological effects of caffeine are central nervous system and cardiac stimulation. The poisoning symptom of caffeine at a high dose are vomiting, abdominal pain, and central nervous system symptoms such as agitation, altered consciousness, rigidity, and seizures. These poisoning symptoms are induced by adrenergic receptor stimulation (from cerebral limbic system). The cardiovascular effects include supraventricular and ventricular tachyarrhythmia [4].

The fatal acute oral caffeine dose is estimated to be 150-200 mg/kg body weight [5]. Caffeine blood concentrations of 80 µg/ml are considered lethal [6, 7]. In case 1, a blood caffeine level (116 µg/ml) higher than the fatal concentration was detected.

Table 1. Summary of case report of caffeine intoxication

Case	Sex	Age	Femoral blood Caffeine ( $\mu\text{g/ml}$ )	Heart blood Caffeine ( $\mu\text{g/ml}$ )	Caffeine intake	Reference
1	F	39	192		Uncertain amount of caffeine injection via syringe.	(1)
2	M	29	567		Uncertain amount of a bottle of caffeine pills	(1)
3	M	39	-	350	10-12 g caffeine anhydrous powder	(2)
4	M	54	173		100 caffeine tablets (100mg)	(4)
5	M	21	210		200 caffeine tablets (100mg)	(4)
6	M	31	153		100 caffeine tablets	(4)
7	F	47	200		100 tablets of letigen, adrug containing caffeine and ephedrine	(4)
8	M	52	-	47	30 caffeine tablets (100mg)	(11)
9	F	42	-	33	-	(11)
10	F	37	-	73	-	(11)
11	F	39	-	90	90 caffeine tablets (40mg)	(11)
12	F	43	-	320	Uncertain amount of caffeine tablets (200mg)	(11)
13	M	57	-	180	Uncertain amount of caffeine tablets (200mg)	(11)
14	M	44	-	80	Uncertain amount of caffeine tablets	(11)
15	F	50	-	300	Uncertain amount of caffeine tablets (200mg)	(11)
16	F	20		290	258 caffeine tablets (200mg)	(12)
17	F	Twenties		R:154.2 L: 48.4	Uncertain amount of sleepiness preventing tablets	(8)
18	F	19		116	84 caffeine tablets (100mg)	This study
19	M	47		171	Uncertain	This study

There were empty PTP sheets for 84 tablets Estaron Mocha<sup>®</sup> containing 8.4 g of anhydrous caffeine (Fig. 1). A previous study reported that an intake of 50-100 tablets (100 mg/tab) reached a fatal blood caffeine level (80-100  $\mu\text{g/ml}$ ) (4). According to this study, the detected blood caffeine level (116  $\mu\text{g/ml}$ ) in case 1 corresponds the ingestion of about 100 tablets. Therefore, the victim is considered to have taken 84 tablets of anhydrous caffeine at the same time, and the oral caffeine dose is speculated to be 177 mg/kg body weight. No indication of any natural or unnatural cause of death was observed macroscopically. According to this result, the primary cause of death was determined to be caffeine intoxication caused by the ingestion of about 8.4 g of anhydrous caffeine. In this case, a higher CRP level was observed. Ishikawa *et al.* have reported that the CRP level was not elevated in a fatal caffeine intoxication case [10]. The elevated CRP level in this case may not be related to caffeine ingestion.

In case 2, the weight of the right and left lung was 1220 g and 1045 g, respectively. According to this finding, the cause of death was suspected to be pulmonary edema at the autopsy. Following the au-

topsy, the blood caffeine level was determined to be 171  $\mu\text{g/ml}$ , which exceeds fatal blood caffeine levels. Therefore, the primary cause of death was determined to be acute caffeine intoxication. However, there is no evidence of the subject's ingesting massive amounts of caffeine. Bioh *et al.* reported sweating, hypothermia, and acute pulmonary edema in a survival case of a massive dose (50 g) of ingested caffeine. Severe pulmonary edema is also reported in a case where a child ingested 2-3 g of caffeine. These symptoms are in good agreement with the autopsy findings of case 2.

The case reports of caffeine intoxication [1, 2, 4, 8, 11, 12] are summarized in Table 1. The blood caffeine concentration reported previously ranged from 33 to 567  $\mu\text{g/ml}$ . In most cases, the caffeine was ingested as tablets. In the case showing highest cardiac caffeine blood concentration, caffeine intake was lower than other cases [2]. In this case, caffeine was ingested as powder and was absorbed more efficiently than tablet. The cases reported by Holmgren *et al.*, clearly showed the relationship between ingested volumes and blood caffeine levels. According to this report, the amount of case 1

ingestion could be equivalent to 10 g of caffeine tablets [4]. In case 2, there is no evidence that the subject ingested a massive amount of caffeine. However, the blood caffeine concentration exceeds fatal blood caffeine levels. The data on case 2 is also similar to that from Holmgren *et al.* [4]. If the caffeine was ingested as a tablet, it is speculated that the victim of case 2 intook about 10 g of caffeine.

Fatal cases of caffeine ingestion are rare, but recently, case reports on caffeine-related fatalities are increasing. This is due to the easy availability of caffeine products and the increase in caffeine usage. A further increase in fatal caffeine cases is predicted. However, there are some cases, like case 2, in which the ingestion amount of caffeine is unknown. Generally, death due to poisoning is lacking in specific autopsy findings. The data accumulation of blood caffeine concentrations and ingestion amounts is helpful to predict the intake amount of caffeine and to determine the cause of death.

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