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Two Fatal Cases of Caffeine Poisoning

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A caffeine overdose is most likely to result from the consumption of nutritional supplements or caffeine pills. Herein, we describe two fatal cases of caffeine intoxication. Case 1: A Japanese man in his 30s was found dead, with two bottles of water and unopened tablets for motion sickness near his body. Caffeine concentrations were 99.6 μg / mL in the cardiac blood and 169.1 μg / mL in stomach contents. Case 2: A Japanese man in his 40s was found dead, with an empty bottle of caffeine and six empty boxes of Travelmin（a motion sickness medication）in a trash can. Caffeine concentrations were 79.6 μg / mL in the cardiac blood and 876 μg / mL in the stomach contents. Fatal caffeine poisoning is comparatively uncommon, but it has recently been increasing due to the easy availability. For the prevention of caffeine overdoses, there should be heightened public awareness of the potential dangers of a caffeine overdose.

Keywords: caffeine, poisoning, fatal, LC/MS, GC/MS

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INTRODUCTION

Caffeine（1,3,7-trimethylxanthine）is classified as a weakly basic natural alkaloid with a molecular weight of 196.21 g / mol and is contained in coffee, chocolate, cocoa, black tea, green tea, and many other products. It is one of several methylxanthines known to have pharmacological effects including central nerve stimulation, cardiac stimulation, the relaxation of smooth muscles such as bronchi, and diuresis. Caffeine moderately stimulates the central nervous system to awaken, reduce fatigue, and stimulate cognitive activity. The range of the safe administration of caffeine is relatively wide, and it is unlikely that poisoning will be caused by coffee [1]. After water, coffee is the most popular beverage and is consumed worldwide in daily amounts of roughly 1.6 billion cups [2].

Caffeine is one of the drugs most readily available to the general public. It is often used to relieve drowsiness and reduce anxiety and fatigue. Caffeine stimulates the nervous system by blocking the effects of the neurotransmitter adenosine, but high doses of caffeine may have unpleasant and even dangerous side effects [3]. Intentional poisoning by caffeine consumption has recently become comparatively common. When consumed in relatively insignificant doses, the side effects of caffeine are milder, but when a high dose is ingested, this methylxanthine alkaloid becomes profoundly toxic and can result in death [4]. Several reports of caffeine overdoses have been published despite the rarity of caffeine intoxication. Here, we report two cases of fatal caffeine intoxication.

CASES

Case 1

A Japanese man in his 30s was found dead outside a church by some tourists. On a nearby bench, there were two bottles of water, unopened tablets of Semper QT (a medication for motion sickness), and a bag with his wallet and a pessimistic note. Semper QT contains d-chlorpheniramine maleate and scopolamine hydrobromide. There was some vomit under a bench a short distance away from where the man was discovered (Fig. 1a).

Case 2

A Japanese man in his 40s did not arrive at work on Monday morning as expected, and he was found dead on the floor of his apartment house that afternoon. There was an empty bottle of caffeine (100 tablets) and six empty boxes of the motion sickness medication Travelmin (36 tablets) in a trash can, and 18 empty boxes of Travelmin (108 tablets) in another trash can. Travelmin contains diphenhydramine salicylate and diprophylline. A mortar and pestle, a soup bowl with some white powder, and an unopened bottle of caffeine (100 tablets) were on a table in the room where the man was found (Fig. 1b).

MATERIALS AND METHODS

Sample preparation

Whole blood and stomach contents of each case were collected at autopsy and kept frozen at −80℃ until analysis. The extraction for narcoleptics, ataractics, and agrichemicals performed using Extrelut NT-3 polyethylene columns (Merck, Darmstadt, Germany). Briefly, ammonium chloride/ammonia buffer (pH 9.5) was added to the blood sample, and the mixture was loaded onto Extrelut NT-20 columns. After 15 min, the mixtures were eluted from the columns using methylene chloride/isopropanol (85:15 v/v). The solvent was distilled and then dissolved in methanol. The stomach contents were mixed with distilled water and acetonitrile. Anhydrous sodium sulfate/anhydrous sodium acetate (4:1 v/v) was added to the mixture, and the supernatant after centrifugation was filtered using Captiva ND^{Lipids} (Agilent Technologies, Santa Clara, CA, USA). The eluants were evaporated under a stream of nitrogen gas, and the residue was dissolved in acetonitrile for the liquid chromatography/mass spectrometry (LC/MS) analysis.

Caffeine extraction was performed using Extrelut NT-20 columns. Briefly, samples were diluted with distilled water (sample/distilled water, 1:100 v/v). An internal standard (IS) solution (diazepam-d5)

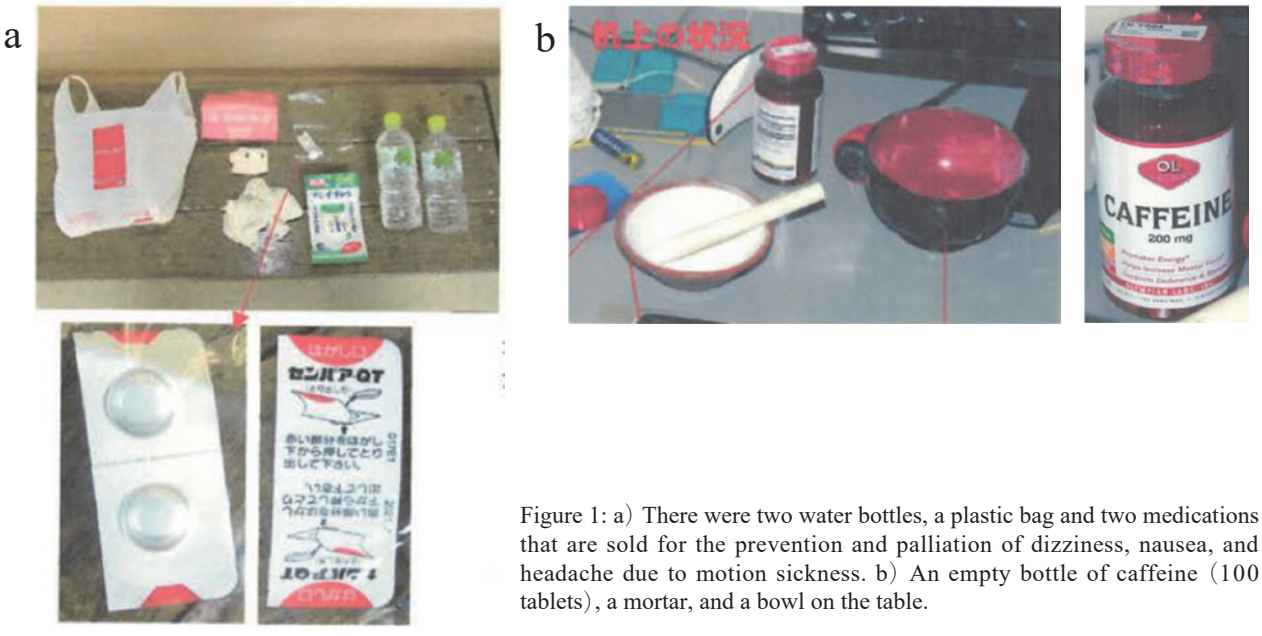

Figure 1: a) There were two water bottles, a plastic bag and two medications that are sold for the prevention and palliation of dizziness, nausea, and headache due to motion sickness. b) An empty bottle of caffeine (100 tablets), a mortar, and a bowl on the table.

was added to each sample. Caffeine and the IS solutions 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 the 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.

Alcohol concentration was measured by the headspace method and GC-FID detector. Sample 0.2 mL were placed into sealed vials containing 0.2 mL internal standard solution of 0.2% 2-methyl-1propanol and incubated at 55°C for 15 minutes, then 0.3 mL of the gas phase was injected. The sample was analyzed using DB-WAX columns (GC-18A manufactured by Shimadzu Corporation), inner diameter 0.53 mm, length 30 m, thickness 1 μm. The Column temperature was maintained at 40°C (1 min hold) →100°C (10°C/min temperature rise). The Inlet temperature was at 200°C. Helium was used as a carrier gas at a flow rate of 1 mL/min.

LC/MS conditions for narcoleptics, ataractics, and agrichemicals

The qualitative analysis was performed using a Prominence ultra-fast liquid chromatography (UFLC) system (Shimadzu, Kyoto, Japan)/linear trap quadrupole (LTQ) (Thermo Fisher Scientific, Waltham, MA). Compounds were separated using Hypersil Gold™ columns (50 mm × 2.1 mm inner dia. and 10 mm × 2.1 mm inner dia.; Thermo Fisher Scientific). The column temperature was programmed at 40°C. The mobile phase consisted for methanol (A) and 10mM ammonium acetate (B). The gradient profile was as follows: 10% A hold for 2 min, further increased linearly to 94% A from 2 to 23 min. After 3 min, the mobile phase returned to 10% A, equilibrating for 4 min up to a total run time of 30 min.

GC/MS conditions for narcoleptics, ataractics, and agrichemicals

A qualitative analysis of narcoleptics, ataractics, and agrichemicals was also performed by gas chromatography-mass spectrometry (GCMS-QP2020, Shimadzu). Compounds were separated using a DB-5 MS column (30m × 0.25 mm inner dia.: Agilent Technologies). The column temperature was programmed initially at 60°C (2 min) to 320°C at 10°C/min, which was maintained for 10 min. The injector and ion-source temperatures were 260°C and 200°C, respectively. The MS detection was performed with electron ionization (EI).

GC/MS conditions for caffeine

Caffeine was determined by gas chromatography-mass spectrometry (HP 7890B/5977A GC/MSD, Agilent Technologies). Compounds were separated using a HP-5 MS column (30m × 0.25 mm inner dia.: Agilent Technologies). The column temperature was programmed at initial 50°C (1 min) to 100°C at 20°C/min and finally to 280°C at 10°C/min, which was maintained for 20 min. The injector and ion-source temperatures were 250°C and 230°C, respectively. MS detection was performed with EI. The m/z values 194 and 289 were monitored for caffeine and diazepam-d5 (IS), respectively, in the selected ion monitoring mode for quantification.

RESULTS

Case 1

The deceased was 172.0 cm and weighed 55.1 kg. There were slight abrasions and skin discolorations on the face, neck, and upper and lower limbs, and minor lacerations on the face and intramuscular bleeding on the neck. The major organ weights were as follows: brain 1450 g, heart 290 g, right lung 345 g, left lung 340 g, and liver 1320 g. Moderate to severe pulmonary edema was confirmed pathologically. The cardiac blood contained the sleep inducer/anticonvulsant nitrazepam, and the stomach contents contained zopiclone, a sleep disorder-improving agent. The caffeine concentrations were 99.6 μg/mL in the cardiac blood and 169.1 μg/mL in the stomach contents.

Case 2

The deceased was 169.0 cm and weighed 73.2 kg. Moderate decomposition was observed. The major organ weights were as follows: brain 1715 g, heart 300 g, right lung 790 g, left lung 770 g, and liver 925 g. Severe pulmonary edema was confirmed

pathologically. In addition, 0.46 mg/g of alcohol was detected in the right cardiac blood, and 0.14 mg/g was detected in the urine. The cardiac blood and stomach contents contained amoxapine, a therapeutic agent for depression/depressive state, and diphenhydramine, an antihistamine/sleep improver. The detected caffeine concentrations were 79.6 μg/mL in the cardiac blood and 876 μg/mL in the stomach contents, and those of diphenhydramine were 6.9 μg/mL in the cardiac blood and 175 μg/mL in the stomach contents.

DISCUSSION

Caffeine is the most widely consumed psychoactive compound worldwide. In recent years, the risk of caffeine intoxication has increased due to the more widespread availability of analgesics, central nervous system (CNS) stimulant medications, and dietary supplements sold at neighbourhood shops, health stores, and e-markets [5]. In humans, the ingestion of 20 mg/kg caffeine is considered toxic, and caffeine blood concentrations >80 μg/mL are well known to be fatal [6]; >5–10 or 150–200 mg/kg is considered lethal [4, 7, 8].

Caffeine addiction is a major problem because it is widely used in mixtures with other drugs of abuse and can be ingested in large quantities by the body. Common toxic symptoms caused by caffeine are known to be adrenergic stimuli such as hypertension, tachycardia, mydriasis, sweating, fever, headache, dizziness, nausea/vomiting, dyspnoea, and convulsions. There are also reports of myotoxic symptoms such as myocardial infarction, myocarditis, fatal arrhythmia, and ventricular fibrillation [1]. The pharmacological effects of caffeine include stimulation of the CNS and cardiac stimulation and usually occur at plasma concentrations ≥15 mg/L [3]. Caffeine consumption in Japan has been increasing steadily, especially among children and young adults, since caffeine or caffeine-containing products such as coffee, energy drinks, and soft drinks are sold over-the-counter and can be purchased easily online. In general, fatal caffeine overdoses involve ingesting medications containing caffeine rather than consuming beverages or caffeine-containing food products such as chocolate, ice cream, frozen yogurt, pudding, and hot cocoa [9] and have been related to blood concentrations exceeding 80 mg/L [3].

In Case 1, 99.6 μg/mL and 169.1 μg/mL of caffeine were detected in the cardiac blood and the stomach contents respectively, and these were higher than the fatal concentration. The cause of death was thus determined to be caffeine intoxication coupled with an unhealthy overall condition. In Case 2's cardiac blood and stomach contents, the detected caffeine concentrations were 79.6 μg/mL and 876 μg/mL and those of diphenhydramine were 6.9 μg/mL and 175 μg/mL (other drugs detected were not quantitatively analyzed) respectively. The caffeine concentration in his blood was considered to have reached a nearly lethal dose but the blood alcohol level is indicated weak intoxication, not at a lethal level. In this case, it was extremely difficult to identify the cause of pulmonary edema, but caffeine poisoning is also known to cause pulmonary edema. Since diphenhydramine has anticholinergic and sedative effects, it is widely used as an anti-allergic agent, rhinitis drug, cold medicine, sleep-improving drug, and antiemetic drug. The toxic dose of diphenhydramine is 7.5 mg/kg, and the lethal dose is 20–40 mg/kg. Toxic symptoms appear at ≥1 μg/mL, and deaths have been reported at ≥5 μg/mL and above [10, 11]. The cause of death in this case was thus considered caffeine and diphenhydramine poisoning.

The number of drug accidents in Japan is increasing every year. There are many household products that contain poisonous substances, and the second most common source of poisonous substances is pharmaceuticals. It has been observed that severely ill patients who are transported to higher-order emergency medical facilities often have drug addiction. According to that report, about half of the poisoning-causing substances brought into tertiary emergency medical facilities are drugs/pharmaceuticals, and most of the drug poisoning is caused by taking large quantities of drugs in order to commit suicide [12]. In addition, in recent years in Japan, the abuse of illegal drugs such as narcotics and stimulants is spreading to the general public as well as minors and has become a serious social problem. Fatal caffeine poisoning is comparatively uncommon but has been increasing due to the easy availability

of caffeine products and usage. In order to prevent caffeine overdoses, the public should be educated about the potential dangers of consuming excessive amounts of caffeine.

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